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ORIGINAL ARTICLE

Advanced malignant pleural mesothelioma: Experience in 42 patients

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Received for publication: 7 November 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

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doi:10.24875/j.gamo.M17000064

Gaceta Mexicana de Oncología. 2017;16(3):144-154

KEY WORDS
Malignant mesothelioma; Mortality; Risk factor

Abstract Malignant pleural mesothelioma is a rare, difficult to diagnose neoplasm with poor prognosis. To determine the prognostic factors for survival in patients with this disease at advanced stages (Stages III and IV), the medical files of 42 patients with this diagnosis were assessed, and factors known to be prognostic of poor survival were statistically analyzed. Age >60 years and serum albumin levels <3.5 g/dL were highly significant (p < 0.001). The presence of fever, dyspnea, weight loss >10%, and platelets >400,000/µL was highly significant (p < 0.01) and, finally, Eastern Cooperative Oncology Group performance status 3 or 4 and the presence of chest pain and cough were significant (p < 0.05). In contrast with reports in the literature, male gender, known exposure to asbestos, smoking, diabetes, leukocytosis, anemia, lactate dehydrogenase >500 IU/L in pleural fluid, presence of nodular pleural thickening on imaging studies, presence of pleural effusion >60%, mediastinal invasion, site of presentation, biphasic and sarcomatous lineage and forms of treatment showed no significant differences with regard to patient survival in our population. Mean survival was 8.1 months, with values ranging from 30 days to 1 year and 4 months. (creativecommons.org/licenses/by-nc-nd/4.0/).
INTRODUCTION AND BACKGROUND

Malignant pleural mesothelioma (MPM) can be defined as a neoplasm deriving from mesothelial cells, specifically from the mesothelial surface of the embryonic coelomic cavity that later will give origin to the pleura, the pericardium, the peritoneum, and the tunica vaginalis of testicle. There is general consensus, based on numerous studies, that considers this tumor as being originated by the inflammatory and foreign body reaction that is produced by the deposit of fibers of asbestos, a group of double-chain, metamorphic, fibrous minerals that show great flexibility and heat resistance, and they have therefore been used in a large amount of products.

The World Health Organization has declared all types of asbestos to be carcinogenic; since 2005, the European Union banned the use of all types of asbestos, with several countries having joined this initiative, for a total of just over 50.

Asbestos has been known to be a pleural mesothelioma causative agent since 1960; according to the United States Environmental Protection Agency, it comprises six types of minerals, all of them carcinogenic. Exposure to asbestos is known for entailing severe implications for health. Since 2005, the Rotterdam Convention includes all types of asbestos of the amphiboles group in Appendix III; however, the case of chrysotile has been more controversial and has not yet been included.

In Mexico, where 21 out of every 100 households have metal, cardboard or asbestos roofing, and one out of every 100 has cardboard, asbestos, reed, bamboo, or palm walls; there are still no laws banning the use of asbestos, especially chrysotile. In this country, there are 500 confirmed cases of MPM every year since 2010, although there may be two-thirds of patients. Characteristic cough is non-productive and in the decubitus position and is observed in 27-29% of patients. These symptoms and a history of risky exposure lead to suspect the diagnosis, and although confirmation should be by histopathology, some imaging studies are indispensable for staging and diagnostic-therapeutic approach.

On chest X-ray, the presence of pleural effusion, mediastinal ipsilateral shift or costal periosteal reaction can be observed; however, the most specific finding and, therefore, highly suspicious is diffuse pleural thickening with nodular images. Contrasted axial computed tomography (CT) scan with fine sections is the imaging gold standard for MPM staging. It is useful to determine pleural alterations, tumor extent and mediastinal invasion. Findings include pleural effusion, pulmonary volume decrease, chest wall invasion, costal involvement, fatty planes obliteration, nodular periarterial thickening, and direct extension to soft tissues. It is important mentioning that the pulmonary parenchyma regularly does not show masses. With a sensitivity of 90%, it has the disadvantage that it is poorly sensitive to assess mediastinal lymph node involvement. Magnetic resonance imaging is slightly superior to CT to assess MPM morphology and extension to the chest wall and transdiaphragmatic extension, and the study contrasted with gadolinium assesses tumor perfusion, vascularization, and angio permeability. It is important to stress that this study does not reliably detect the presence of distant metastasis. Positron emission tomography can be used for pre-operative staging; however, its main role is in treatment response and relapse emergence assessment, as well as distant metastasis detection. Although its sensitivity and specificity are low (specificity: 92% and sensitivity: 75%), a standard uptake value >2.0 can be used as a cutoff point to detect N2 disease, and false positives can be observed in tuberculosis pleuritis, empyema or in patients with previous history of pleurodesis.

Pleural fluid cytology is usually insufficient for diagnosis because, on the one hand, cellularity is not always obtained, and on the other, when it is obtained, cells can be mistaken with those originating from other malignancies such as adenocarcinoma or sarcoma. As an inconvenience, this method shows problems for diagnostic differentiation between benign and malignant mesothelial hyperplasia and is unable to demonstrate tumor invasiveness, which is considered essential for definitive diagnosis. Pleural fluid analysis...
can be highly helpful when hyaluronic acid levels >100 µg/mL are found, which is highly suspicious of MPM.

Mesothelioma definitive diagnosis should be established by biopsy-obtained tissue histopathological analysis; the biopsy can be obtained by puncture or surgery.

“Blind” biopsy by needle puncture, i.e., without the use of real-time imaging techniques, provides rather unsatisfactory results, since it combines the small size of the sample obtained with this system with lack of control on extraction site exact localization, and it is therefore practically not used and, instead, CT-guided puncture is currently carried out with a diagnostic effectiveness rate of 75% when the sample is >10 mm². On the other hand, diagnostic approach with surgically-obtained biopsy can be carried out with three main methods: Medical thoracoscopy, video-assisted thoracoscopic surgery, and thoracotomy. Although medical thoracoscopy can be performed with analgesia and sedation in the bronchoscopy room, its diagnostic effectiveness in mesothelioma with sarcomatous component is suboptimal and, therefore, in these cases it is better to obtain samples with any of the other two aforementioned surgical methods, with video-assisted thoracoscopic surgery being the technique of choice, since in addition to being a minimally invasive procedure, it is associated with the capability to better stage the tumor, especially in the mediastinal area, and even to perform pleurectomy and decortication procedures, although it is not always available in all centers. MPM histopathological diagnosis is usually difficult and even impossible with light microscopy examination, as it happens with the sarcomatous mesothelioma desmoplastic variety, which is indistinguishable from benign reactive pleural tissue. In all cases, special immunohistochemistry staining techniques are required for differentiation from neoplasms that appear very similar on microscopy. Differentiation between epithelioid-lineage MPM and adenocarcinoma (of the lung) involves the presence of epithelial markers for the former, especially calretinin, and absence of adenocarcinoma specific markers. A mesothelioma will never be positive for CD15, thyroid transcription factor-1 or estrogen receptor marker, with the former two being expressed in pulmonary adenocarcinoma and the latter in breast adenocarcinoma. With regard to malignant pleural sarcomatoid mesothelioma and squamous or transitional cell carcinoma, immunohistochemistry is based on sarcoma markers, especially p63, lack of expression, together with positivity for Wilms tumor antigen. It is important bearing in mind that the cytokeratin 5/6 marker, which is useful to differentiate mesothelioma from adenocarcinoma, is of no use for differentiation from squamous or transitional cell carcinoma, since both express it as well. Reactive mesothelial tissue is nearly indistinguishable from MPM and immunohistochemistry techniques are, therefore, also necessary. Markers for desmin are used to differentiate them since they are positive in mesothelial reactivity. On the other hand, the insulin-like growth factor II RNA-binding protein is present in MPM and does not mark for reactive mesothelial tissue (Table 1).

Staging systems proposed in previous decades tend to classify advanced state tumors more in detail and are usually based on researchers’ personal experiences. The oldest MPM staging method was proposed by Erick Butchart in 1976 with the scale that bears his name. Subsequently, in Harvard University Brigham and Women’s Hospital, David Sugarbaker developed a new scale using clinical and radiologic approaches. Subsequently, the International Mesothelioma Interest Group introduced a staging system in 1995 that was accepted in 2002 by the International Union Against Cancer (Union Internationale Contre le Cancer) and the American Joint Committee on Cancer. The new staging system takes the T (tumor), N (lymph node), and M (metastasis) factors into consideration. This is a complex classification system originally designed for patients assessed in surgery. Due to the diffuse presentation of the tumor, even with currently available imaging techniques, there are often difficulties to classify the T and N factors. Treatment is controversial with survival periods ranging from 16 to 24 months on average. During the 1st years of this century, each one of the specialized centers offered diverse options and different algorithms with options including chemotherapy, radiotherapy, immunotherapy, or combinations thereof for medical approach and pleurectomy/decortication, extrapleural pneumonectomy as surgical alternatives, but still without an international management standard. In 2009, the European Respiratory Society and the European Society of Thoracic Surgeons in 2010 determined that radical surgery can only be performed in the setting of clinical trials, with the use of decortication and pleurectomy being reserved to effusion palliation, whereas chemo- and radiotherapy should be adjusted to each patient’s characteristics. In 2013, the European Society of Medical Oncology and, in 2015, the National Comprehensive Cancer Network, based on the results of the scarce clinical trials, suggested that MPM Stages I to III with N1 and without contraindication for surgery can (with or without pre-operative chemotherapy) undergo extrapleural pneumonectomy, lymph node resection of at least three stations and diaphragm and pericardium ipsilateral resection. Patients with N0 might undergo pleurectomy and decortication. For Stages III with N2 or mixed histology, oncologic surgery procedures should only be performed within the setting of clinical trials or at centers with experience in this tumor. Finally, if tumor complete resection is not possible, the surgical procedure should be aborted, and palliation will consist in safe debulking and, if appropriate, pleurodesis. Patients with clinical Stage IV of the sarcomatous histological type, both clinically inoperable or in the post-operative period, may benefit from chemotherapy, with radiotherapy being left only as adjuvant treatment in the post-operati ve period of a successful resection surgery. Supportive and palliative measures as sole intervention are generally recommended at Stage IV, when patient conditions are poor or when no treatment is willingly accepted.

Objectives

In this work, we present the experience of 7 years in the management of MPM; we will analyze factors reported as being of poor prognosis for patient survival at any stage, and we will contrast them with observations in our group of patients at advanced stages.

Hypothesis

Survival in patients with Stages III and IV MPM will be affected by the same risk factors reported worldwide.
MATERIALS AND METHODS

A cross-sectional, retrospective study of patients diagnosed with MPM in the time period comprised from April 2008 to December 2015 was conducted at the Hospital Juárez de México. We assessed those variables that, according to the literature, were considered predictors in a retrospective longitudinal study.

<table>
<thead>
<tr>
<th>Table 1. Mesothelioma differential immunohistochemistry</th>
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<td><strong>Epithelioid mesothelioma versus adenocarcinoma</strong></td>
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<td>Breast carcinoma</td>
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<td>Sarcomatoid mesothelioma versus squamous cell and transitional cell carcinoma</td>
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<td>Mesothelioma versus Reactive mesothelial reaction</td>
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<td><strong>Antibody</strong></td>
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<td>Epithelial membrane antigen</td>
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<td>P53</td>
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<td>Glucose transporter-1</td>
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<td>Insulin-like growth factor-II RNA binding protein</td>
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Population
A total of 76 medical records were found with the MPM registry diagnosis, out of which 49 (64.5%) corresponded to males and 27 (35.5%) to females; of the 76 subjects, 7 had diagnosis registration mistakes, and 13 had no histopathology report or staging or obtaining them was not possible to, which left 56 patient files with MPM accurate diagnosis. Of these, 8 had incomplete medical records, and other 6 had no follow-up or were not deemed adequate for the study, which left 42 medical files that met the inclusion criteria, out of which 29 (69.1%) corresponded to males and the remaining 13 (30.9%), to females. The files were reviewed, and data were collected in case report forms. This material was analyzed by means of the Statistical Package for the Social Sciences 24.0 software. Variables were grouped in demographic, history, clinical presentation, laboratory, and imaging studies, diagnosis and treatment aspects, adding up to a total of 27. The Kaplan-Meier method was used for survival analysis, and univariate analysis for each one of these aspects determined their statistical significance, considered as such at a p < 0.05 (Figs. 1 and 2).

RESULTS

Survival
Mean survival in our population was 8.1 months, with a minimum of 30 and a maximum of 1 year and 4 months; the Shapiro-Wilk test, with W>p (0.96 > 0.16) demonstrated that data followed a normal distribution.

Demographic variables
A total of 37 patients came from the Megalopolis of Central Mexico (Mexico City, State of Mexico, Hidalgo, Morelos, Puebla, and Tlaxcala), 2 from Chiapas and Veracruz, and the remaining 3 from Querétaro; none of our cases came from Guanajuato. Mean age of our patients was 62.4 years, with a minimum value of 38 and a maximum of 85 years. Data distribution was corroborated to be normal with a W-value of 0.98 and a p value of 0.64 in the Shapiro-Wilk test. As a prognostic factor for survival, a cutoff point of 60 years was set, with a distribution of 59.2% above, and the remaining 40.8% below this value. Patients older than 59 years had a mean survival of 6 months versus 11.4 months for those younger than 60 years. The percentage of patients alive at 1 year in the older age group was 0%.

With a p < 0.0001, age was the most significant prognostic factor in our study. With an incidence of 2.23:1 in favor of the male gender, gender did not show differences in terms of mean survival, with 8.2 months for either gender, although, at 1 year, 21.4% of males remained alive in contrast with 8.3% of females; there were no statistically significant differences with regard to patient prognosis.

History
Only 12 patients (28.57%) acknowledged having a past history of exposure to asbestos, and survival in this group of patients was not also very different to that in those who did not acknowledge exposure to asbestos (7.8 vs. 8.5); in our group, it was not a significant factor that affected survival. History of tobacco consumption was found in 17 patients (40.5%), with a mean of 13.3 packs/year (min 3, max 23). Using a cutoff point of >10 packs/year for all 42 patients, smoking was analyzed as a poor prognosis factor, and with a difference slightly higher than 1 month for survival being found in favor of patients with no history of smoking or with <10 packs per year, this factor was not significantly different in our population’s patient survival. The incidence of diabetes mellitus in our population was 28.6%; however, there was no significant difference in survival of patients with or without this disease.

Clinical presentation
The Eastern Cooperative Oncology Group (ECOG)-developed performance status (PS) grade at diagnosis was different for each one of the performance grades, with the longest survival period being reached by Grade 1 with 11.3 months (min 3.5, max 16) and the shortest shown by Grade 3 with 5.9 months (min 1, max 13). Overall, those patients who were unable to be entirely responsible for their self-care (Grades 3 and 4) had a significantly poorer prognosis than those who at least were able to do it (Grades 0-2), with the survival of 6.5 and 10.2 months, respectively. In the classification of chest pain being present for the purposes of the study, we included the patients in whom this symptom occurred located in the hemithorax for at least 3 or more hours on a daily basis and ranged from blunt to impairing pain;
in more serious cases, pain was impairing and constantly present and only partially relieved by potent analgesics. Patients with chest pain accounted for 78.6% of our population and had a 7.3-month survival versus 11.3 months in those patients who did not experience pain. Pain was shown to be a symptom that significantly affected the prognosis.

The daily presence of episodes of temperature higher than 38.4°C lasting at least 1 h was documented in 8 patients (22.2%), with other causes for this sign being able to be ruled out, and, in 6 patients (75% of the group with fever), it followed an almost exclusively nocturnal pattern; in all 8 patients it was accompanied by chills and sweating. 28 patients did not experience fever and, in 6 patients, the presence or absence of this sign was not objectively documented. Absence of this sign practically doubled survival (8.5 vs. 4.3 months) and was a significant prognostic factor.

More than 90% of patients experienced dyspnea, and its absence, as in the case of fever, doubled survival, with a mean of 7.5 months for the group free of the symptom, and 14.8 for the group that did experience it.

Dry, persistent cough, which commonly required treatment with antitussives since diagnosis, was also a significant factor for poor prognosis; this factor was present in 83.3% of patients.

Weight loss occurred in 40 patients (95%), with average weight loss being 13.9% within the month before diagnosis. Overall, 35 patient had a weight loss higher than or equal to 10%, with mean weight loss of 15.0% versus 4.2% in the remaining 7 patients. With a difference of nearly 5 months in survival, weight loss was considered to be a factor significantly associated with poor prognosis.

Laboratory tests

White blood cell (WBC) count at diagnosis, or in case of any demonstrated infectious process, once the infectious process subsided, was 10.65 × 10³/µL on average, with 14 patients (33.3%) showing leukocytosis with a mean of 16.48 × 10³/µL (min: 10.4 × 10³/µL and max: 21.4 × 10³/µL), and this being a factor significantly associated with worse prognosis for survival.

Mean platelet count was 308 × 10³/µL, with 5 patients (11.9%) showing thrombocytopenia (mean: 110 × 10³/µL), 25 patients (59.5%) with normal platelet count (mean: 259 × 10³/µL), and 12 patients (28.6%) with thrombocytosis (mean: 493 × 10³/µL, min: 441 × 10³/µL, and max: 535 × 10³/µL), with the latter group showing a significant difference in terms of survival (9 vs. 9.4 months) in the groups with thrombocytopenia or normal counts. Therefore, in our population, thrombocytosis was a factor of poor prognosis for survival. In no case could the cause of these platelet anomalies be identified.

Mean hemoglobin in our population at diagnosis was 11.3 g/dL (min 8.8 g/dL and max 13.7 g/dL). There were 34 patients with levels <13 g/dL (mean 10.9 g/dL), while 8 patients have normal hemoglobin values, with a mean of 13.25 g/dL. There were no differences between both these groups in terms of survival; therefore, hemoglobin levels did not affect prognosis in our population.

Pleural fluid lactate dehydrogenase (LDH) levels in our population ranged from 265 IU/L to 1954 IU/L, with a mean of 1009 IU/L. With a cutoff point set at >500 IU/L, mean value in patients with low levels was 312.5 IU/L, whereas the group with high levels had a mean of 1407 IU/L, with survival differences of around 2.5 months; there was no significant difference regarding its prognostic value.

Normal albumin values were significantly associated with more than 2-fold survival levels than in case of hypoalbuminemia (9.8 vs. 4.5 months); mean serum albumin in our population was 3.7 g/dL (min 1.7 g/dL and max 5.7 g/dL), with a mean of 2.6 g/dL for the group with low albumin and 4.2 g/dL for the group with adequate albumin levels.

Imaging studies

Except for three patients, pleural thickening with nodular pattern was a consistent finding on chest CT, and in the vast majority on plain X-ray, without a relationship between its presence and prognosis being able to be established. Pleural effusion occurred in 37 patients (88%); however, it was massive (>60% of at least one hemithorax) in 13 patients (30.9%); pleurodesis was necessary in 20 patients (47.6%) and was carried out with povidone-iodine at bedside or transoperative in a biopsy procedure. Survival results were identical in the groups with and without massive effusion with 8.2 months. Mediastinal invasion was established in 39 patients (92.8%), but no prognostic difference could be established. There were also no significant differences with regard to the side of MPM involvement, although there was clear trend for development on the right side, which occurred in 65.8% of the patients with unilateral MPM.

Diagnosis

Plain X-ray and chest CT scan studies were performed in 100% of cases.

The diagnosis was histologically confirmed by means of open biopsy in 18 patients (42.9%) or CT-guided biopsy in the remaining 24 (57.1%). Of note, in 4 cases (9.5%) open biopsy occurred after a report of insufficient material for diagnosis with CT-guided biopsy, with the main indicators to decide this procedure being pleural thickness, site of location and patient general status. In our patient universe, nobody presented with clinical Stage I or II, and the prognostic impact was, therefore, studied in patients at both MPM most advanced stages: 7 patients (16.7%) at clinical Stage III with an 8.1-month mean survival showed no significant differences in comparison with 35 patients (83.3%) at clinical Stage IV with an 8.2-month survival.

With regard to histological lineage, malignant epithelioid pleural mesothelioma was the most common with 23 patients (54.8%), followed by sarcomatoid histology in 10 patients (23.8%) and mixed histology in 9 (21.4%). Neither the epithelial nor the sarcomatoid type showed survival differences in our population, with a survival mean of 8 and 7 months for the epithelial and sarcomatoid lineages, respectively (Table 2).

Antitumor treatment

Surgical antitumor treatment was contraindicated in all Stage IV patients. Among the 7 Stage III patients (all T3 N2 M0), surgical treatment was also contraindicated in those
with sarcomatous mesothelioma. Of the 4 patients with epithelioid or mixed mesothelioma, the N2 lymph node stage present in all of them contraindicated antitumor surgical treatment with pleurectomy and decortication, and the possibility of extrapleural pneumonectomy was therefore contemplated, with the procedure being contraindicated in the 2 patients with mixed mesothelioma owing to poor spirometric results.

Both patients with stage T3 N2 M0 epithelioid mesothelioma underwent surgical exploration with the purpose to perform extrapleural pneumonectomy, with initial exploration revealing complete resection was impossible, and the procedure was therefore aborted, and pleurodesis and debulking were performed in as much as it was safe.

As a logical consequence, if antitumor radiotherapy is considered as post-operative adjuvant treatment after any of both procedures that are specific for this entity, no patient was candidate to antitumor radiotherapy.

Of the 35 patients at Stage IV, 20 underwent palliative care owing to an ECOG PS of 3 or 4; the remaining 15, with ECOG PS of 0 to 2, were assessed for observation or chemotherapy initiation, with this treatment being administered in 8 cases. As for patients with sarcomatous lineage at Stage III (3 patients) or mixed histology (2 patients with medical contra indication for surgery), none underwent antitumor chemotherapy, either because they were maintained under observation (2 patients) or because they were maintained on palliative care (3 patients). Both patients who underwent surgical exploration received chemotherapy. The chemotherapeutic regimen administered in all cases was based on a combination of pemetrexed and platinum salts.

### Table 2. Lineage and staging for treatment in study patients

<table>
<thead>
<tr>
<th>Staging</th>
<th>N</th>
<th>M</th>
<th>Stage</th>
<th>Patients (%)</th>
<th>ECOG performance status</th>
<th>Histology</th>
<th>Epithelioid</th>
<th>Sarcomatous</th>
<th>Mixed</th>
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<tr>
<td>T</td>
<td>N</td>
<td>M</td>
<td></td>
<td>Patients (%)</td>
<td>0-2</td>
<td>3-4</td>
<td>n (% of stage)</td>
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<td>III</td>
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<td>II</td>
<td>III</td>
<td>IV</td>
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<td>23 (54.8)</td>
<td>10 (23.8)</td>
<td>9 (21.4)</td>
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</table>

ECOG: Eastern Cooperative Oncology Group.

### Symptom and Palliative Treatment

In those patients who experienced pleural effusion-associated dyspnea, drainage and/or pleurodesis with povidone-iodine was practiced, either at the moment of the open biopsy procedure or after diagnosis by placing the pleural drainage catheter at bedside. In addition, dyspnea that was not associated pleural effusion was managed with supplemental oxygen with nasal cannulas or different variants of masks. For the treatment of cough, when it was dyspnea or cyanosis-producing, benzonatate was resorted to; however, dextromethorphan, codeine, and dexamethasone were also used. Chest pain usually responded to combined analgesics; however, at more advanced stages, fentanyl-releasing patches were used, or when it was associated with dyspnea, morphine. Food supplements failed to stop weight loss; however, they caused for it to be less pronounced. Nausea, either secondary to the neoplastic process or to chemotherapy, was managed with metoclopramide and ondansetron. No patient received palliative radiotherapy. Patients who required pleurodesis (30.9%) due to pleural effusion, in spite of not having a significant increase in survival, did refer clinical and the quality of life improvement.

### Treatment-related Prognostic Factors

Most importantly, no type of treatment was superior to another with regard to patient survival. Upfront chemotherapy not associated with surgery yielded a 7.5-month survival; with palliative treatment, it was 8.8 months, and with observation, 7.4 months.
Mortality

Our patients’ survival was 8.1 months, with a range of 1 to 16 months. Factors affecting survival in our population, in order of importance, were age and serum albumin (p < 0.001) (Figures 1-2); platelet count, presence of fever, weight loss and dyspnea (p < 0.01), and WBCs, ECOG PS, chest pain, and cough (p < 0.05) (Table 3).

Factors that had no weight with regard to prognosis in our population were gender, exposure to asbestos, smoking, diabetes, hemoglobin levels, pleural fluid LDH, the presence of pleural nodules or mediastinal invasion, bila-

<table>
<thead>
<tr>
<th>Study variables</th>
<th>n (%)</th>
<th>x (min-max)</th>
<th>SD</th>
<th>Alive 6 months</th>
<th>Alive 12 months</th>
<th>p</th>
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<td>41.2%</td>
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<td>63.6%</td>
<td>27.3%</td>
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<td>69%</td>
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<td>25%</td>
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<td>17.9%</td>
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<td>7.9%</td>
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<td>4 (9.52)</td>
<td>14.8 (1-14-16)</td>
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<td>100%</td>
<td>100%</td>
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<tr>
<td>Cough</td>
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<td>7.5 (1-14)</td>
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<td>61.1%</td>
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<td>Weight loss</td>
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<td>&gt;10% weight</td>
<td>35 (83.33)</td>
<td>7.4 (1-13)</td>
<td>3.9</td>
<td>64.3%</td>
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<tr>
<td>&lt;10% weight</td>
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<td>12 (6-16)</td>
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<td>66.7%</td>
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<td>&gt;10,000/μL</td>
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<td>&lt;10,000/μL</td>
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<td>75%</td>
<td>25%</td>
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<td>Platelets</td>
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Table 3. Study variables statistical analysis (Continued)

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<th>n (%)</th>
<th>x (min-max)</th>
<th>SD</th>
<th>Alive 6 months</th>
<th>Alive 12 months</th>
<th>p</th>
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<td>&lt;400,000/μL</td>
<td>30 (71.43)</td>
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<td>76.7%</td>
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<td>Hemoglobin</td>
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<td>&lt;13 mg/dL</td>
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<td>37.5%</td>
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<td>71.4%</td>
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<td>Serum albumin</td>
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<td>12.8%</td>
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<tr>
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<td>19 (45.24)</td>
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<td>21.1%</td>
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<td>69.6%</td>
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<td>20%</td>
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<td>71.9%</td>
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<td>CT versus others</td>
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<td>CT alone</td>
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<td>30.4%</td>
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<tr>
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<td>9 (52.94)</td>
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<td>4.2</td>
<td>55.6%</td>
<td>0%</td>
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</tr>
</tbody>
</table>

SD: Standard deviation; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; WBC: White blood cell; LDH: Lactate dehydrogenase; CT: Computed tomography; PAL: Palliative.
terality or side, stage, lineage, and the different treatment modalities.

DISCUSSION

We present the experience on the treatment of MPM with a series of a similar number of subjects to those reported by other authors; however, our population was characterized for including predominantly American Indian ethnicity patients at Stages III and IV.

Gender and mean age distribution in our group was similar to those reported in the literature. Although age older than 60 years was a significant risk factor, male gender was not a poor prognosis factor in our study.

Another situation that draws the attention in our study is the small number of patients who referred having worked with or been exposed to asbestos, which differs from all existing literature. However, the causes can be multifactorial, and the considerably elevated latency time, lack of knowledge about substances handled at work, and the marked use of asbestos in structures as widely spread as asbestos sheets on household roofs might contribute to explain this apparent lack of exposure.

Smoking and diabetes, consistent with other studies, neither seem to influence on MPM patients’ survival. Mesothelioma synchronicity or lung cancer could not be determined in our population since no patient had both these conditions.

In other studies, the ECOG PS scale has been shown to be an index with prognostic value, with Grades 0, 1, and 2 being associated with higher survival, which is consistent with data obtained in our population.

Clinical presentation in our patients was similar to that described in previous publications; however, dyspnea and cough were present in 9 and 8 out of every 10 patients, respectively, which are figures much higher than those reported in the literature and that cannot be explained by the presence of infection, clinical stage, or comorbidities at diagnosis. Weight loss at diagnosis was also different in our population since 80% of patients lost 10% of their weight in 3 months versus 25% reported in the literature. Fever showed similar figures to those reported in the literature. The patient clinical presentation was fundamental to prognosis, and all clinical presentations were significantly related to patient prognosis.

Laboratory tests results were essentially shown, as in other studies, to be of prognostic importance; however, the fact that hemoglobin and pleural fluid LDH levels were not related to survival draws the attention; probably this was due to the number of individuals in one of the groups resulting from the division according to the cutoff point, or else to the disease advanced stage. One last factor that has not been prognostic, or has not been investigated in patients with MPM, is serum albumin, which, in our population, was a significant factor.

The involved hemithorax or the presence of bilateral involvement, massive pleural effusion and mediastinal invasion had no impact on survival as it could be expected, probably owing to the advanced stage of the disease in our patients, which rendered these factors being present in most patients, which in turn lowered the power for statistical comparison of the resulting groups, in addition to the lack of contrast with patients at earlier stages of disease.

As a finding that differs from reports in other studies, in our population, the type of MPM and the type of treatment had no impact on survival. This unusual situation might be due to the fact that all patients were at advanced Stages III and IV.

Patient survival was lower than that generally reported for MPM; however, it was consistent with the survival expected for Stages III and IV and, therefore, we believe that survival in our group of patients was adequate to that expected for advanced stages.

CONCLUSIONS

MPM is an aggressive condition that in our setting is lately diagnosed, with poor treatment response and adverse prognosis, especially at advanced stages, with the highest survival observed in these cases being 16 months. The three most influential factors on patient prognosis are age older than 60 years, patient clinical presentation, and presence of abnormalities in laboratory tests. At more advanced stages, lineage and type of treatment had no impact on patient survival in our population, which warrants the conduction of studies with larger samples and with earlier stages to corroborate this observation.

REFERENCES

Stage IB2 and IIB cervical cancer in young patients: Treatment results and management proposal

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Received for publication: 1 October 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

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doi:10.24875/j.gamo.M17000065

Gaceta Mexicana de Oncologia. 2017;16(3):155-161

Abstract

Introduction: Advanced cervical cancer (CC) remains a major health problem in our country, with an increasing percentage being diagnosed in young women. Objective: The objective of this study is to present an institutional experience with standard treatment in menstruating women with CC at stages IB2 and IIB, with complementary or rescue surgery being added in selected cases, as well as to propose some management alternatives for these patients. Materials and methods: Analysis of the cases of 45-year-old or younger stage IB2-IIB CC patients who received concomitant chemotherapy and radiotherapy with or without further surgery at the Oncology Department of the Hospital General de México. Results: Ninety-eight patients with a mean age of 37.1 years were treated. In 89 patients, there was follow-up data available, of which 63 (70.7%) had an average evolution of 30 months with no evidence of disease: 12/19 (63.1%) were at stage IB2 and 51/70 (72.8%) at stage II (p > 05). At stage IB2, only 4/8 adenocarcinomas (50%) had these results versus 8/11 (72.7%) squamous cell carcinomas (p > 05). At stage II, the figures were 8/11 for adenocarcinomas (72.7%) and 43/59 for squamous cell carcinomas (72.8%). With further surgery, the results were increased by 10.1%. Failure of established therapeutics was demonstrated in 17 patients (19.3%): 4 cases due to locoregional progression (23.5%) and 13 (76.4%) due to distant dissemination.

Conclusions: The results for stage IB2 were inferior to those for stages II, with most failures being related to distant metastasis. To prevent early menopause, exploring the use of neoadjuvant chemotherapy plus radical hysterectomy is recommended in younger patients. (creativecommons.org/licenses/by-nc-nd/4.0/).
INTRODUCTION

Cervical cancer (CC) is a health problem that represents the second malignancy in women worldwide, with more than 500,000 cases annually diagnosed and with more than 260,000 deaths every year. It is the female genital tract most common cancer and the one that causes the highest number of deaths\(^1,3\). While at the early stages, outcomes are highly encouraging, those obtained at advanced stages where radiotherapy is used as background treatment are accompanied by treatment failure ranging from 20% to 75%, according to the clinical stage of the disease\(^3,4\).

Although the advent of platinum-based radiosensitizing chemotherapy for the treatment of advanced stages improved previously obtained results with standard chemotherapy by up to 12%\(^4\), it has not had the desired impact for these stages, and hence, the efforts made by different authors to increase disease-free interval for these cases and 5-year survival without tumor\(^3,4,7-10\). While for CC, some authors recommend post-concomitant chemotherapy and radiotherapy (CCRT) consolidation treatment using platinum-based regiments\(^7-10\), and others suggest complementary surgeries\(^7,9,16\), or even the use of chemotherapy before rescue therapy in patients with tumor persistence or recurrence\(^7\), we are still awaiting for a therapy that allows for the results so far obtained in the treatment of this grievous disease to be ostensibly improved.

In Mexico, CC incidence and mortality figures are only surpassed by those of breast cancer among female cancers, and unfortunately, more than 60% of invasive cancers are diagnosed at advanced stages, which accounts for the nearly 4000 deaths recorded every year in our country\(^12,13\).

Although the age of disease invasive stages presentation is around 50 years\(^3,4\), recent studies show a trend toward presentation at younger ages. At least 15% of cases are estimated to be 40 years’ old or younger\(^14,15\).

A report deriving from the population that attends the Hospital General de México with 1217 patients\(^15\) showed a mean age of 51.9 years, with predominance for stage I with 353 cases (39%) and stage II with 340 (37%). Of the entire group, 23.7% were menstruating patients of 39 years of age or younger.

The results of CCRT standard treatment in menstruating patients with CC at stages IB2 and IIA2-IIIB of the International Federation of Gynecology and Obstetrics (FIGO)\(^1\) plus complementary or rescue surgery in those showing tumor persistence or risk factors for tumor recurrence or experiencing recurrence are shown in this publication. Some proposals are also made for advanced CC comprehensive management, especially when occurring in younger women, and conclusions are drawn on the subject.

MATERIALS AND METHODS

This was a retrospective, descriptive, observational study of medical records of the Hospital General de México “Dr. Eduardo Liceaga” Oncology Department clinical files during the period encompassed from January 2010 to December 2014, with those from patients with CC at FIGO\(^6\) clinical stages IB2 and IIA2-IIIB2, aged 45 years or younger, being selected to be studied. Data were obtained on age, histological varieties (squamous cell carcinoma or adenocarcinoma), established treatment, and results thereof.

The established primary standard therapy was CCRT, using external radiotherapy to the pelvis at 50 Gy doses in 5 weeks with external beam radiation therapy (EBRT) equipments (linear accelerators and less often cobalt 60) plus brachytherapy application at 30 Gy on average at the conclusion of EBRT, for a total of 80 Gy. In addition, concomitant chemotherapy was weekly administered during EBRT with cisplatin or carboplatin at standard doses for 5 cycles on average\(^14\).

At treatment completion, the patients were assessed by the treating radio-oncologist physician, who referred patients with suspected tumor persistence or progression, as well as those with risk for tumor recurrence due to highly bulky tumors and unfavorable histopathology (adenocarcinoma), and those that for some reason did not complete the brachytherapy established dose\(^16\).

These patients were considered for complementary surgery to be performed between 6 and 10 weeks after treatment completion with a mean of 8 weeks, with the procedures consisting in class II radical hysterectomy without pelvic lymphadenectomy or class III radical hysterectomy with lymphadenectomy at the surgeon’s judgment\(^3,4,16\).

Patients with tumor progression who were not eligible for rescue surgery were assessed to receive palliative chemotherapy with platinum-based regiments. The obtained results underwent statistical analysis with the Chi-square test and Fisher’s exact test when one of the cells had an expected value lower than 5, with 95% confidence intervals. The statistical package Info 6.04 was used. Confidence values lower than 95% were considered non-statistically significant (NS).

RESULTS

Clinicopathological aspects

During the analyzed period, 400 patients with advanced CC completed their treatment, of which 98 (24.5%) were at stages IB2, IIA2, and IIB, 23 (23.7%) at stage IB2, 5 (5.1%) at stage IIA2, and 70 (71.4%) at stage IIB. The average age of the group was 37.1 years; 80.6% had squamous cell carcinomas and 19.3% adenocarcinomas (Table 1).

Results of the concomitant treatment with radiotherapy and chemotherapy

Seventy-two patients (73.4%) completed their treatment without clinical or imaging evidence of tumor activity, whereas 26 (26.5%) showed tumor persistence, progression, or recurrence. Nine patients (9.1%) who completed their treatment without tumor activity were lost to follow-up during
the 1st month after treatment conclusion and were not considered for final results.

Final results assessment included 89 patients, of which 63 who received primary treatment (70.7%) spent from 12 to 62 months, with an average of 30, with no evidence of tumor activity. This number included 12 of 19 patients at stage IB2 (63.1%) and 51 of 70 (72.8%) at stages IIA-B (p = 0.3573) (Table 2). In addition, 12 of 19 (63.1%) had adenocarcinomas and 51 of 70 (72.8%) had squamous cell carcinomas (p = 0.5265; NS) (Tables 3 and 4).

Disease-free follow-up for the referred period by clinical stage according to histological type was as follows: For stage IB2, 4 out of 8 patients (50.0%) had adenocarcinomas and 8 out of 11 (72.7%) had squamous cell carcinomas (p = 0.3765; NS); for stages IIA2-B, 8 out of 11 (72.7%) had adenocarcinomas, and 43 out of 59 (72.8%) had squamous cell carcinomas (p = 0.7819; NS) (Tables 3 and 4).

Complementary and rescue surgery

Two patients with incomplete brachytherapy, 9 with tumor persistence, and one with recurrence were considered for surgical exploration after tumors limited to the pelvis susceptible to be extirpated became evident by clinical and/or imaging examination. Two cases with tumor persistence (16.6%) were unresectable since laparotomy revealed the presence of para-aortic metastases (one patient at stage IB2 with clear-cell adenocarcinoma and one with stage IIB squamous cell carcinoma).

Five class II hysterectomies without lymphadenectomy, 3 class III radical hysterectomies, and 2 pelvic exenterations (one anterior and one total) were carried out (Table 5). In 4 of the 10 patients with resection (40.0%), 3 with class II hysterectomy, and 1 with anterior pelvic exenteration; pathology final reports showed no residual tumor. Included reports are both patients with incomplete brachytherapy treated with class II hysterectomy, one with class II hysterectomy with cervical residual and one of the 2 patients with exenteration. The patient who underwent anterior exenteration had the previous report of squamous cell carcinoma tumor recurrence and the specimen reported chronic granulomatous disease.

Only in one of the 10 operated patients was their treatment failure. It was a stage IIB adenocarcinoma with tumor persistence at the cervix that was treated with class III radical hysterectomy, the specimen of which showed tumor residual at the cervix with extension to the uterine isthmus without any other adverse prognostic risk factors. The patient developed new tumor recurrence 7-month post-surgery and was lost to follow-up.

In the remaining 9 cases, a follow-up was achieved of between 13 and 61 months post-surgery, with a mean of 30 months without evidence of disease. This included 4 of 4 patients at stage IB2 and 5 of 6 at stage IIB (Table 2), and by histological lineage, 2 of 3 adenocarcinomas and 7 of 7 squamous cell carcinomas (Tables 3 and 4).

When the primary CCRT treatment results had further surgery results added, the overall figure with no evidence of disease, which initially was 70.7%, was observed to rise to 80.8%, which represented a 10.1% increase (p = 0.437; NS). For stage IB2, the figure increased from 63.1% to 84.2% (p = 0.2690; NS); for stage II, from 72.8% to 80.0% (p = 0.5451; NS); for adenocarcinoma, from 63.1% to 73.6% (p > 0.05), for squamous cell carcinoma, from 72.8% to 82.6% (p = 0.3255; NS) (Tables 2-4).

Treatment failure

In 17 of the 89 patients (19.1%) with follow-up data available, failure of the established treatment was demonstra-

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### Table 1. Clinicopathological aspects

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years*</td>
<td></td>
</tr>
<tr>
<td>15-20</td>
<td>6 (6.1)</td>
</tr>
<tr>
<td>21-25</td>
<td>8 (8.1)</td>
</tr>
<tr>
<td>26-30</td>
<td>13 (13.2)</td>
</tr>
<tr>
<td>31-35</td>
<td>11 (11.2)</td>
</tr>
<tr>
<td>36-40</td>
<td>30 (30.6)</td>
</tr>
<tr>
<td>41-45</td>
<td>30 (30.6)</td>
</tr>
<tr>
<td>Total</td>
<td>98 (99.9)</td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>79 (80.6)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>19 (19.3)</td>
</tr>
<tr>
<td>Total</td>
<td>98 (99.9)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
</tr>
<tr>
<td>Stage IB2</td>
<td>23 (23.4)</td>
</tr>
<tr>
<td>Stage IIA2</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>70 (71.4)</td>
</tr>
<tr>
<td>Total</td>
<td>98 (99.9)</td>
</tr>
</tbody>
</table>

*Younger age: 19 years; older age: 45 years; mean age: 37.1 years.

### Table 2. Treatment results by clinical stage

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Radiotherapy plus chemotherapy</th>
<th>Disease-free evolution*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Subsequent surgery**</td>
</tr>
<tr>
<td>Stage IB2</td>
<td>(a) 12/19 (63.1)</td>
<td>4/4 (100)</td>
</tr>
<tr>
<td>Stage IIA2-IIB</td>
<td>(b) 51/70 (72.8)</td>
<td>5/6 (83.0)</td>
</tr>
<tr>
<td>Total</td>
<td>(e) 63/89 (70.7)</td>
<td>9/10 (90.0)</td>
</tr>
</tbody>
</table>

*30 months on average. **In patients with tumor persistence or recurrence.
Statistical significance: (a) versus (b): p = 0.3573; (c) versus (d): p = 0.4714; (e) versus (f): p = 0.437.
Table 3. Treatment results: Adenocarcinoma

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Radiotherapy plus chemotherapy</th>
<th>Subsequent surgery**</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disease-free evolution*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IB2</td>
<td>(a) 4/8 (50.0)</td>
<td>1/1 (100)</td>
<td>(c) 5/8 (62.5)</td>
</tr>
<tr>
<td>Stage IIA-IIB</td>
<td>(b) 8/11 (72.7)</td>
<td>1/2 (50.0)</td>
<td>(d) 9/11 (81.8)</td>
</tr>
<tr>
<td>Total</td>
<td>(e) 12/19 (63.1)</td>
<td>2/3 (66.6.0)</td>
<td>(f) 14/19 (73.6)</td>
</tr>
</tbody>
</table>

*30 months on average. **In patients with tumor persistence or recurrence.
Statistical significance: (a) versus (b): p = 0.376; (c) versus (d): p = 0.602; (e) versus (f): p > 0.05.

Table 4. Treatment results: Squamous cell carcinoma

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Radiotherapy plus chemotherapy</th>
<th>Subsequent surgery**</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disease-free evolution*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IB2</td>
<td>(a) 8/11 (72.7)</td>
<td>3/3 (100)</td>
<td>(c) 11/11 (100)</td>
</tr>
<tr>
<td>Stage IIA-IIB</td>
<td>(b) 43/59 (72.8)</td>
<td>4/4 (100)</td>
<td>(d) 47/59 (79.6)</td>
</tr>
<tr>
<td>Total</td>
<td>(e) 51/70 (72.8)</td>
<td>7/7 (100)</td>
<td>(f) 58/70 (82.8)</td>
</tr>
</tbody>
</table>

*30 months on average. **In patients with tumor persistence or recurrence.
Statistical significance: (a) versus (b): p = 0.7819; (c) versus (d): p = 0.1909; (e) versus (f): p = 0.3255.

Table 5. Performed surgical interventions

<table>
<thead>
<tr>
<th>Surgery</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II hysterectomy</td>
<td>5 (41.6)</td>
</tr>
<tr>
<td>Class III hysterectomy</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Pelvic exenteration</td>
<td>2 (16.6)</td>
</tr>
<tr>
<td>Laparotomy and biopsy</td>
<td>2 (16.6)</td>
</tr>
<tr>
<td>Total</td>
<td>12 (99.8)</td>
</tr>
</tbody>
</table>

discussed. These patients were part of the group with tumor persistence, progression, and recurrence (17/26: 65.3%). This figure includes 6 of 13 patients (46.1%) with tumor persistence who showed progression, 5 of them with para-aortic metastases, and the patient with tumor persistence treated with radical hysterectomy that developed tumor recurrence and was lost to follow-up without further treatment. It also includes 11 of 12 with tumor recurrence (91.6%), 4 of 7 with adenocarcinoma (57.1%), and 13 of 18 with squamous cell carcinoma (72.2%) (Table 6), and by clinical stage, 1 of 4 (25.0%) at clinical stage IB2 and 5 of 9 (55.5%) at clinical stage IIB.

Tumor recurrence

Twelve patients developed tumor recurrence, which occurred between 7 and 28 months post-primary treatment, with a mean of 16 months. Eleven patients died with tumor activity, and only in one case, disease-free control was obtained; it was a patient with stage IIB squamous cell carcinoma who developed tumor recurrence 10-month post-primary treatment and underwent total pelvic exenteration. She had 24-month disease-free post-surgery control. Three patients developed locoregional progression and died without further treatment, and 8 had distant disease, 5 of them with loco-regional activity. Distant metastases location for the entire group is shown in Table 7.

Six of the 17 patients with treatment failure (35.2%) received palliative chemotherapy with platinum-based schemes, without treatment influencing on subsequent evolution.

DISCUSSION

The treatment of CC advanced stages, which are predominant in developing countries, remains an enormous challenge for institutions in charge of the management of this disease. Although the advent of chemotherapy came to globally improve the results obtained with radiotherapy as the treatment of choice, the eventual inaccessibility in developing countries to modern radiotherapy equipments and to drugs whose combination is being shown to improve the results reported with the use of CCRT are factors that contribute for CC to continue representing an important cause of death for women in countries such as ours.

The authors’ institution is a reference center for the population without social security, and only 30% of CC patients live in Mexico City; 60% of invasive cancers are diagnosed at advanced stages of the disease, without taking into account those that have already been treated outside the institution. Four-hundred eighteen patients out of 908 (46%) treated under the catastrophic expenses program of the Federal Government Ministry of Health were at FIGO stages IB2 and IIB, in which tumor persistence or recurrence between 15% and 23% has been reported with
standard treatment, as well as 5-year disease-free survival of 75.7% and 65.8%, respectively. We selected for the study menstruating patients at stages IB2-IIIB conventionally treated with CCRT owing to concerns deriving from reports that show that at least 15% of CC cases occur in younger women and to the desire to obtain information on treatment results in these patients, considering that 23.7% patients of CC attending the authors’ institution are 39 years old or younger.

In this series, 98 patients were part of a group of 400 who required standard CCRT treatment and that, having been classified at stages IB2-IIIB, were 45 years old or younger, with a mean of 37.1 years. With this therapy, tumor-free follow-up of 12-62 months, with a mean of 30 months, was achieved in 63 of 89 patients (70.7%).

For stage IB2, the figures were 12/19 (63.1%), including 4/8 adenocarcinomas (50%) and 8/11 squamous cell carcinomas (72.7%). For stage II, 51 of 70 (72.8%); 8/11 adenocarcinomas (72.7%) and 43/59 squamous cell carcinomas (72.8%). The figures referred for stage IB2 are lower than the value reported in the references (75.6%) inspite of follow-up not being at 5 years. Of note, only half of the patients in this study with a diagnosis of adenocarcinoma evolved with no evidence of disease for the referred period, a situation that should be, especially, taken into account to be corroborated or not in the future, once a larger number of patients with stage IB2 diagnoses is available, although adenocarcinoma accounts only for 11% of CC cases in our institution.

Twenty-six patients in the present series evolved with tumor persistence or recurrence, and 12 of them (46.1%) were candidates to complementary surgery with suspected or confirmed tumor persistence or to rescue surgery for tumor recurrence, with tumor-free follow-up figures being able to be increased by means of these treatments from 63.1% to 84.2% for stage IB2 (p = 0.2690; NS) and from 72.8% to 80.0% for stages II (p = 0.5451; NS).

The value of rescue surgery for patients in whom CCRT has failed is well documented, with some authors highlighting the usefulness of practising non-exenterative complementary surgeries in patients with suspected or confirmed central tumor persistence, and others, the convenience to consolidate CCRT conventional therapy with additional chemotherapies.

In this series, 10 of 12 patients with suspected tumor residue, persistence, or recurrence underwent complementary or rescue surgical procedures and treatment failure was observed only in one case with one patient with tumor persistence treated with class III radical hysterectomy developing tumor recurrence and being lost to follow-up in these conditions. Two pelvic exenterations were performed with disease control. The performed surgeries allowed for previously obtained results with CCRT to be improved by 10.1% (p = 0.437; NS). These results are consistent with those referred in the literature with similar therapeutic approaches.

Although in 4 of the 10 referred cases (40%) surgical specimens showing the absence of tumor residue was interpreted as a pathologic complete response to CCRT, the need or the convenience to carry out the referred surgical interventions was preoperatively documented. In some series, where a similar management approach has been used, pathologic complete responses of up to 60-67.4% have been reported.

Failure of the established therapy was demonstrated in 17 patients of 89 where follow-up data were available (19.1%), including 6 of 13 patients with tumor persistence who showed progression (46.1%) and 11 of 12 with tumor recurrence (91.6%) who had the same behavior. Four patients had uncontrollable locoregional tumor activity, and 13 developed the distant disease. Only 6 of the 17 patients (35.2%) received further oncologic treatment without objective results. The fact that 13 of the 17 treatment failures (76.4%) were due to distant dissemination should make us reflect on the convenience of consolidating our CCRT treatments with additional cycles of platinum-based chemotherapy, as some authors are recommending, as well as to administer 3-4 chemotherapy cycles before surgical exploration in patients who will undergo rescue surgery.

One problem that occurs at the authors’ institution is CC occurrence in younger patients, since 23.7% of the population attending the department with this diagnosis is 39-year old or younger, and a considerable proportion of these patients receive radiotherapy as basic therapeutic measure.

Standard treatment with CCRT in menstruating patients suppresses ovarian function in a sudden form, which results

### Table 6. Treatment failure

<table>
<thead>
<tr>
<th>Cause</th>
<th>Histopathology</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Tumor persistence</td>
<td>2/4 (50.0)</td>
<td>4/9 (44.4)</td>
</tr>
<tr>
<td>Tumor recurrence</td>
<td>2/3 (66.6)</td>
<td>9/9 (100)</td>
</tr>
<tr>
<td>Total*</td>
<td>(a) 4/7 (57.1)</td>
<td>(b) 13/18 (72.2)</td>
</tr>
</tbody>
</table>

*(a) versus (b): p = 0.6395.

### Table 7. Distant metastasis in 13 patients

<table>
<thead>
<tr>
<th>Site</th>
<th>n* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraaortic</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>Lung</td>
<td>4 (30.7)</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>2 (15.3)</td>
</tr>
<tr>
<td>Skeleton</td>
<td>2 (15.3)</td>
</tr>
<tr>
<td>Liver</td>
<td>1 (7.6)</td>
</tr>
<tr>
<td>Supraclavicular lymph nodes</td>
<td>1 (7.6)</td>
</tr>
</tbody>
</table>

*(a) patients with metastasis to 2 sites.
in premature menopause, vasomotor symptoms, loss of bone mineral density, tendency to overweight and to develop metabolic syndrome, diabetes mellitus, high blood pressure, and coronary disease; therefore, in these patients, the trial of management approaches that tend to preserve ovarian function is warranted. Although ovarian lifting away from radiation fields constitutes a logical solution for these patients, other options should be considered in countries like ours, where the radiation treatment demand often surpasses the offer of equipments available in our institutions. One of these options is the use of neoadjuvant chemotherapy with platinum-based schemes, just as recommended in some European clinics, and especially in Asian countries.

Neoadjuvant chemotherapy is intended to decrease tumor volume, to make originally inoperable neoplasms operable, and to eradicate or biologically alter micrometastases. Responses to platinum-based schemes are referred to range from 70% to 100%. Neoadjuvant chemotherapy offers a field worthwhile to explore.

CONCLUSIONS

- In our series, patient mean age was 37.1 years, 23.4% were classified at stage IB2, and 19.3% of the entire group had adenocarcinomas.
- Sixty-three of 89 patients (70.7%) with post-CCRT follow-up spent a mean of 30 months without evidence of disease, including 63.1% of patients at stage IB2 and 72.8% at stages II, as well as 63.1% with adenocarcinoma and 72.8% with squamous cell carcinoma.
- With the referred treatment, evolution was less favorable for stage IB2 adenocarcinomas, since only 4 of 8 patients (50%) with this diagnosis had tumor activity-free follow-up versus 8 of 11 (72.7%) with squamous cell carcinoma.
- The results were similar for both histological types at stage II: 8 of 11 (72.7%) for adenocarcinomas and 43 out of 59 (72.8%) for squamous cell carcinomas.
- With complementary or salvage surgery, follow-up global figures without evidence of disease were increased by 10.1%.
- Established treatment failure was observed in 17 cases (19.3%): 4 due to non-controllable locoregional progression (23.5%) and 13 (76.4%) due to distant dissemination.
- Although surgery improved the results obtained with CCRT by 10.1%, consolidating conventional treatment with chemotherapy schemes should be considered in the future to decrease local recurrence and distant metastasis figures.
- It is convenient to try different treatment approaches in menstruating patients at stages IB2-IIIB to avoid precocious menopause. Neoadjuvant chemotherapy with platinum-based schemes plus radical hysterectomy offers a field worthwhile to explore.

DECLARATION OF INTEREST

The authors declare not having any conflicts of interest.

REFERENCES


Pediatric cancer distribution in the State of Puebla

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Received for publication: 1 October 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

Abstract

Introduction: At present, in the world, there are approximately 360,000 children with cancer, many of them without social security in developing countries. Materials and methods: In this study, a retrospective analysis was performed of medical records from subjects younger than 21 years of age with cancer who live in extreme poverty and lack social security. The main purpose was to identify a pediatric cancer distribution pattern in the state of Puebla, Mexico, as well as sociodemographic characteristics and main types and incidences of disease. Results: A total of 406 medical records were reviewed; 4 years was the age with the highest rate of diagnosis, and male gender was predominantly affected. The most commonly found malignancy was acute lymphoblastic leukemia, followed by germ cell tumors and acute myeloblastic leukemia, with histiocytosis abnormal behavior also being found. Conclusions: These data are useful for health systems to detect municipalities with higher incidence and this way creates alerts for earlier diagnosis of the disease and thereby increases children survival.(creativecommons.org/licenses/by-nc-nd/4.0/).
INTRODUCTION

Cancer is one of the five leading causes of death worldwide. The World Health Organization estimates that cancer-associated deaths will account for 70% of overall mortality in developing countries by the year 2030. In the world, there are approximately 12 million of people diagnosed with cancer; and nearly 3% are children.

Pediatric cancer is a problem in developing countries due to its high incidence and health systems’ limited resources, which delays diagnosis and hinders adequate management of these patients. In 2012, a higher incidence of pediatric cancer was estimated in developed than in developing countries, with 147,000 cases/year and a higher mortality rate, which is associated with the fact that two-thirds of children and adolescents with a malignancy do not receive opportunune diagnosis and adequate multidisciplinary treatment. In Mexico, only 20% of this population has social security; the rest has to cover expenses with its income, with most part of this population having to travel from its communities to be able to receive treatment.

Pediatric cancer is the second cause of death in people younger than 20 years. It comprises a group of diseases with particular characteristics that differentiate them from adult diseases such as anatomical localization, histological pattern, and different behavior. The most common pediatric neoplasms are leukemia (30-50%), lymphomas (17.1%), and central nervous system tumors (11.9%).

In spite of advances in treatment and medicine, pediatric cancer remains a public health problem. Fajardo-Gutiérrez et al. reported that in the period between 1996 and 2007, a total of 3,238 new cases were recorded only in 5 states of the Mexican Republic, with the most commonly recorded neoplasms being leukemia (46.1%), central nervous system tumors (12.0%), and lymphomas (10.8%). Health system in Mexico is divided into public and private sectors. The public sector provides care to two populations: With social security and without social security through the people’s health insurance (Seguro popular), with the latter being the most vulnerable population of the country from the socioeconomic point of view.

According to data of the last population census by the National Institute of Statistics, Geography and Informatics (Instituto Nacional de Estadística, Geografía e Informática [INEGI]), in the state of Puebla there were 2,315,923 people younger than 20 years of age in the year 2010. The Ministry of Health in Mexico reports an annual average of 122 cases of pediatric cancer per million population of 0-20 years of age. The 2008-2012 bulletin of cancer information on children and adolescents with cancer reports that, in the state of Puebla, the three main neoplasms in people younger than 18 years are: Leukemia (52%), lymphomas and reticuloendothelial neoplasms (12%), and germ cell neoplasms (9%). The purpose of this study was to identify a geographic pattern of pediatric cancer in the state of Puebla, as well as some sociodemographic and clinical characteristics.

MATERIALS AND METHODS

A retrospective study was conducted with data of 406 children who were beneficiaries of the Una Nueva Esperanza A.B.P. foundation in Puebla. Sociodemographic data were obtained of children attended to during the 2005-2010 period. Since 1999, the foundation provides care to low-income children with cancer who lack social security. Since its opening and until 2010 its population has been increasing every year, with 71 beneficiaries per year being attended to, with this figure increasing from 2010 to 2015 to a total of 110 beneficiaries per year.

For the analysis, the state of Puebla was divided according to the seven socioeconomic regions managed by the National Institute for Federalism and Municipal Development (INAFED-Instituto Nacional para el Federalismo y el Desarrollo Municipal), which together comprise 217 municipalities, as follows: I Huachinango/Sierra Norte, II Teziutlán/Sierra Nororiental, III Ciudad Serdán, IV Angelópolis/San Pedro Cholula, V Valle de Atlixco and Matamoros, VI Izúcar de Matamoros/Mixteca, and VII Tehuacán/Sierra Negra (Fig. 1). Each patient was located according to his/her municipality at any of these regions.

To calculate the incidence, data of the 2010 INEGI population and housing census were used. To obtain the population data by age and gender, the request was made to INEGI through the citizen transparency portal, and only population attended to at the foundation until 2010 could, therefore, be analyzed.

Incidence is defined as the number of new cases of a disease occurring in a specific period of time, which is calculated with the formula: Incidence rate = (Number of cases × 100,000 or 1000,000)/Total population. The formula was applied depending on the number of total inhabitants of the region. This information was used to calculate the number of children expected per economic region.

Data obtained from each patient’s medical record were captured in a Microsoft Excel 2010 spreadsheet.
RESULTS

The geographic distribution of the 406 children with cancer was determined, and each one was assigned a geographic region within the state of Puebla. Among the seven socioeconomic regions, the most populated had larger numbers of children with cancer, except for region III (Ciudad Serdán), which was found to be the second, in percentage of children with cancer while being the fourth in children population (Table 1).

The sample was comprised by 53.69% of boys and 46.31% of girls, and cancer was, therefore, more common in the male gender; however, in regions II (Teziutlán) and VI (Izúcar de Matamoros), the distribution of these percentages is inverted (Table 2).

Mean age of the sample was 7.73 ± 4.89 years, although the population mode was 4 years (10.10%) at diagnosis.

The most common condition found in the children population of the state of Puebla was acute lymphoblastic leukemia (ALL) (48.02%). The percentage of children with ALL in the state of Puebla ranges from 6.4% (region V-Atlixco) to up to 69.1% (Region IV-Angelópolis/San Pedro Cholula) (Table 3). Among other conditions, germ cell tumors, acute myeloblastic leukemia, Hodgkin’s lymphoma, among others, were found in the population (Table 4).

Region VII (Tehuacán and Sierra Negra) showed an abnormal behavior in the incidence of central nervous system tumors (astrocytomas, medulloblastomas, and anaplastic ependymomas) since these were at a second place in incidence (1.3) of neoplasms of that region with a total of 7.4% of children with cancer of this region. On the other hand, no children with central nervous system tumors were detected in region V (Valle de Atlixco and Matamoros).

Histiocytosis is within the five main types of cancer in 3 regions of the state (II Teziutlán/Sierra Nororiental, VI Izúcar de Matamoros/Mixteca, and VII Tehuacán/Sierra Negra), with incidence rates of 0.8%, 0.7%, and 0.6%, respectively.

DISCUSSION

The state of Puebla has a very varied geography and is a state crossed by the main mountain ranges of the country, and when analyzing it by economic regions, municipalities with similar orographic characteristics are, therefore, grouped. In 2007, Fajardo-Gutiérrez et al. published a study with 2,663 children younger than 15 years from 11 states of the Mexican Republic where ALL was the main oncologic condition, with an incidence ranging from 28.2% to 74.2%.

In that study, Puebla had an incidence of 72.9% for leukemia; however, in this study, the results differ with regard to incidence, since an incidence of 8.6% was obtained in all 7 regions of the state. The population assessed in this study has different characteristics because it is a population in poverty that lacks social security. The incidence of ALL in the

### Table 1. Population younger than 20 years, expected incidence of neoplasms, number of minors without social security attended to during 5 years and incidence of population attended to by UNE per year

<table>
<thead>
<tr>
<th>Region</th>
<th>Total population younger than 20 years</th>
<th>Cases expected per year</th>
<th>Minors attended to by UNE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Huauchinango</td>
<td>318,988</td>
<td>39</td>
<td>45 (9.0)</td>
</tr>
<tr>
<td>II. Teziutlán/Sierra Nororiental</td>
<td>247,234</td>
<td>30</td>
<td>41 (8.2)</td>
</tr>
<tr>
<td>III. Ciudad Serdán/Chalchicomula de Sesma</td>
<td>310,531</td>
<td>37</td>
<td>57 (11.4)</td>
</tr>
<tr>
<td>IV. Angelópolis/San Pedro Cholula</td>
<td>1,114,998</td>
<td>136</td>
<td>148 (29.6)</td>
</tr>
<tr>
<td>V. Valle de Atlixco</td>
<td>171,636</td>
<td>21</td>
<td>27 (5.4)</td>
</tr>
<tr>
<td>VI. Izúcar de Matamoros/Mixteca</td>
<td>146,063</td>
<td>18</td>
<td>34 (6.8)</td>
</tr>
<tr>
<td>VII. Tehuacán and Sierra Negra</td>
<td>312,411</td>
<td>38</td>
<td>54 (10.8)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,621,861</strong></td>
<td><strong>122</strong></td>
<td><strong>406 (81.0)</strong></td>
</tr>
</tbody>
</table>

### Table 2. Proportion by gender of children attended to by 2010

<table>
<thead>
<tr>
<th>Puebla socioeconomic region</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Huauchinango</td>
<td>55.56</td>
<td>44.44</td>
</tr>
<tr>
<td>II. Teziutlán/Sierra Nororiental</td>
<td>41.46</td>
<td>58.54</td>
</tr>
<tr>
<td>III. Ciudad Serdán/Chalchicomula de Sesma</td>
<td>52.63</td>
<td>47.37</td>
</tr>
<tr>
<td>IV. Angelópolis/San Pedro Cholula</td>
<td>58.78</td>
<td>41.22</td>
</tr>
<tr>
<td>V. Valle de Atlixco</td>
<td>59.26</td>
<td>40.74</td>
</tr>
<tr>
<td>VI. Izúcar de Matamoros/Mixteca</td>
<td>50.00</td>
<td>50.00</td>
</tr>
<tr>
<td>VII. Tehuacán and Sierra Negra</td>
<td>48.13</td>
<td>51.85</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>53.69</strong></td>
<td><strong>46.31</strong></td>
</tr>
</tbody>
</table>

### Table 3. Percentage of the main tumors occurring in the state of Puebla in the study population from 1999 to 2010

<table>
<thead>
<tr>
<th>Condition</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>195 (48.02)</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>23 (5.66)</td>
</tr>
<tr>
<td>Acute myeloblastic leukemia</td>
<td>18 (4.43)</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>15 (3.69)</td>
</tr>
<tr>
<td>Wilms’ tumor</td>
<td>14 (3.44)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>8 (1.97)</td>
</tr>
<tr>
<td>Central nervous system tumors</td>
<td>8 (1.97)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>5 (1.23)</td>
</tr>
</tbody>
</table>
state of Puebla varied according to the region from 6.9% to 69.1%, with the capital city of the state having the highest incidence5,8.

In contrast with reports in the USA literature, where the highest incidence of ALL is described to occur between 2 and 3 years of age, the present study found that the most common age of diagnosis was 4 years in the study population. The 2011 Ministry of Health epidemiological profile of cancer in children and adolescents in Mexico states that the main age range for cancer diagnosis is 10-14 years, followed by the 5-9 years group. However, among the groups analyzed in this study, the 0-4 years group (n = 133) is at first place, while the 10-14 years group (n = 104) is at third place. It is important mentioning that central nervous system tumors, identified in the study by Fajardo-Gutiérrez et al. as the second cause of children’s neoplasms, was found to be the sixth cause of pediatric cancer in our population5,8.

Histiocytosis was found to be among the first five most common types of neoplasm in 3 regions of Puebla (II: Teziutlán/Sierra Nororiental, III: Ciudad Serdán, and VI: Iztucar de Matamoros/Mixteca)5. This is a finding that should be further studied, as this is not a common neoplasm in the pediatric population5.

### Table 4. Main conditions found by socioeconomic region

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean age (SD)</th>
<th>Main conditions found</th>
<th>Percentage</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Huauchinango</td>
<td>7.2 ± 4.7</td>
<td>1. ALL</td>
<td>52.27%</td>
<td>7.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. AML</td>
<td>9.09%</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Non-Hodgkin lymphoma</td>
<td>6.82%</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Rhabdomyosarcoma Hodgkin’s lymphoma and germ cell tumors</td>
<td>4.55% each</td>
<td>0.63 each</td>
</tr>
<tr>
<td>II. Teziutlán/Sierra Nororiental</td>
<td>8 ± 4.9</td>
<td>1. ALL</td>
<td>41.46%</td>
<td>6.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Wilms’ tumor germ cell tumors</td>
<td>7.32% each</td>
<td>1.2 each</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. AML Hodgkin’s lymphoma, histiocytosis</td>
<td>4.88% each</td>
<td>0.8 each</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Osteosarcoma, retinoblastoma, CNS tumors sarcomas</td>
<td>2.44% each</td>
<td>0.4 each</td>
</tr>
<tr>
<td>III. Ciudad Serdan/Chalchicomula de Sesma</td>
<td>8.2 years ± 5.7</td>
<td>1. ALL, Non-Hodgkin lymphoma</td>
<td>39.66%</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. AML, Wilms’ tumor</td>
<td>6.90% each</td>
<td>1.3 each</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Histiocytosis, germ cell tumors</td>
<td>3.45% each</td>
<td>0.6 each</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Hybrid leukemia, Hodgkin’s lymphoma, Wilms’ tumor, osteosarcoma, and retinoblastoma</td>
<td>1.72% each</td>
<td>0.3 each</td>
</tr>
<tr>
<td>IV. Angelópolis/San Pedro Cholula</td>
<td>8.1 years ± 5.1</td>
<td>1. ALL</td>
<td>52.38%</td>
<td>69.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Germ cell tumors</td>
<td>7.48%</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Wilms’ tumor</td>
<td>4.08%</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. AML</td>
<td>3.4%</td>
<td>4.5</td>
</tr>
<tr>
<td>V. Valle de Atlixco</td>
<td>7.8 years ± 5.8</td>
<td>1. ALL</td>
<td>40.74%</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Hodgkin’s lymphoma, non-Hodgkin lymphoma, Wilms’ tumor and germ cell tumors</td>
<td>7.41% each</td>
<td>1.2 each</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. AML, abdominal sarcomas, Ewing’s sarcoma and chondrosarcomas</td>
<td>3.70% each</td>
<td>0.6 each</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Unidentified neoplasms</td>
<td>11.11%</td>
<td>-</td>
</tr>
<tr>
<td>VI. Iztucar de Matamoros/Mixteca</td>
<td>7.7 years ± 5.4</td>
<td>1. ALL</td>
<td>41.18%</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Hodgkin’s lymphoma</td>
<td>11.76%</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Germ cell tumors</td>
<td>8.82%</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. CNS tumors</td>
<td>5.88%</td>
<td>1.4</td>
</tr>
<tr>
<td>VII. Tehuacán and Sierra Negra</td>
<td>8.3 years ± 5.1</td>
<td>1. ALL</td>
<td>53.70%</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. CNS tumors</td>
<td>7.41%</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. AML, histiocytosis, retinoblastoma</td>
<td>3.7% each</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Hybrid leukemia, Wilms’ tumor, rhabdomyosarcoma, osteosarcoma, hepatoblastoma and Ewing’s sarcoma</td>
<td>1.85% each</td>
<td>0.3 each</td>
</tr>
</tbody>
</table>

ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia; CNS: Central nervous system; SD: Standard deviation.

### Conclusion

Cancer opportunite diagnosis is an essential element for patient survival since the sooner it is detected, the probabilities for cure are higher. In Mexico, epidemiological data on pediatric cancer distribution are still limited. The data obtained in the present study will be useful for health systems and physicians, in general, to detect municipalities with higher incidence of cancer, and this way, alerts will be able to be created for earlier diagnosis of the disease and hence increase children survival, in addition, that they will contribute to national cancer epidemiology databases enrichment.

### Declaration of Interest

The authors declare not having any conflicts of interest.
REFERENCES

Nutritional status and chemotherapy-associated toxicity in patients with cervical cancer

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Received for publication: 5 July 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

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doi:10.24875/j.gamo.M17000067

Gaceta Mexicana de Oncologia. 2017;16(3):167-170

KEY WORDS
Malnutrition; Chemotherapy; Nutritional Status; Cancer

Abstract

Introduction: Cervical cancer (CC) is a public health problem; it is the second most common cause of cancer in Mexico and the third cause of death worldwide. Malnutrition in the cancer patient is present in 80-90% of cases of advanced disease. Objective: To analyze the relationship of the nutritional status of patients with clinical Stage IV and recurrent CC with palliative chemotherapy-associated toxicity. Materials and methods: This was a prospective, descriptive, and observational study. Patients with clinical Stage IV CC recurring on palliative chemotherapy were recruited. Nutritional status was assessed before treatment as well as its relationship with toxicity. Associations between qualitative categorical variables were searched for with Spearman’s correlation, and statistically significant differences (p < 0.05) for dichotomous variables were looked for using Fischer’s exact test. Results: A total of 17 patients were included, out of which 5 (29.4%) had normal nutritional status, 8 patients (47%) had moderate malnutrition, and 4 patients (23.5%) had severe malnutrition. A positive correlation was found between the degree of malnutrition and the presence of diarrhea (rho = 0.626), nausea (rho = 0.556), and hypoalbuminemia (rho = 0.559). Conclusions: Nutritional status before chemotherapy was shown to be highly important, since a malnutrition status implies higher toxicity by the treatment, which entails an increase in malnutrition for the next chemotherapy session as well as hospital readmissions. (creativecommons.org/licenses/by-nc-nd/4.0/).
INTRODUCTION

Cervical cancer (CC) is a public health problem. It is the second most common cause of cancer in Mexico and the third cause of death worldwide. It accounts for 9% (529,800) of total new cancer cases and 8% (275,100) of total cancer-related deaths in women in 2008. Unfortunately, it affects women with economic, social, and cultural disadvantages, and therefore, it is more common in developing countries, where 85% of cases are recorded. Risk factors associated with this type of cancer include age, human papillomavirus infection, multiple sexual partners, vaginal parity, and low socioeconomic status, among others.

CC is currently staged according to the International Federation of Gynecology and Obstetrics guidelines, where the advanced or metastatic disease is regarded as recurrent or persistent clinical Stage IV B, with survival probability for these patients ranging from 15% to 30%. Most commonly used chemotherapeutic agents for the treatment of CC are hydroxyurea, cisplatin, 5-fluorouracil, carboplatin, oxaliplatin, mitomycin C, epirubicin, topotecan, and irinotecan, among others. In metastatic disease (clinical Stage IVb), the indicated treatment is based on different chemotherapy regimens using cisplatin, carboplatin, and paclitaxel.

Malnutrition is a common problem in cancer patients that is present in 15-20% at tumor diagnosis and in up to 80-90% in cases of advanced disease. An undernourishment status is associated with poorer response to chemotherapy and worse tolerance (increased toxicity), since on such clinical conditions there is a decrease of circulating proteins, which can even cause treatment discontinuation. Every nutritional intervention must start with an appropriate nutritional assessment to be able to prevent and/or treat malnutrition and to reduce adverse effects of antitumor therapy and to improve the quality of life.

For this reason, it is important for nutritional status assessment to be carried out since the start or during treatment. Nutritional status patient-generated subjective global assessment (PG-SGA) is a quick and reliable tool that allows for patients with malnutrition or at risk of malnutrition to be identified. This nutritional assessment method has been approved by different international oncology and nutrition societies such as the American Dietetic Association, the Clinical Guide to Oncology Nutrition, and in Spain, with modifications by the Spanish Society of Basic and Applied Nutrition (Sociedad Española de Nutrición Básica y Aplicada). The purpose of the present study is to analyze the relationship of the nutritional status of patients with clinical Stage IV CC with the toxicity associated with the treatment with palliative chemotherapy.

MATERIALS AND METHODS

This was a prospective, descriptive, and observational study where patients older than 18 years diagnosed with clinical Stage IV and recurrent CC treated with palliative chemotherapy were selected. Nutritional status was assessed by means of the PG-SGA. Data were collected, and toxicity symptoms such as nausea, vomiting, diarrhea, leukopenia, lymphopenia, and hypoalbuminemia were assessed using the CTCAE v 4.03 criteria at the next chemotherapy cycle. Associations between categorical quantitative variables were searched for with Spearman’s correlation as well as statistically significant differences (p < 0.05) by means of Fischer’s exact test.

RESULTS AND DISCUSSION

A total of 17 patients were included, out of which 4 (23.5%) are ISSEMyM beneficiaries and 13 (76.47%) are covered by the Seguro Popular (People’s Insurance). The mean age was 56.1 years ± 12.75 (standard deviation). In the entire sample, 5 patients (29.4%) had normal nutritional status, 8 patients (47%) had moderate malnutrition, and 4 patients (23.5%) had severe malnutrition.

Associations were sought between nutritional status (independent variable) and the nausea, vomiting, diarrhea, leukopenia, lymphopenia, neutropenia, and hypoalbuminemia variables (dependent variables) by calculating Spearman’s correlation coefficient (r_s) for categorical variables, which required for nutritional status to be categorized as normal, moderate malnutrition, and severe malnutrition. Similarly, the nausea, vomiting, diarrhea, constipation, leukopenia, lymphopenia neutropenia, and hypoalbuminemia variables were categorized as grade 1, 2, and 3.

After variables were categorized, the Rho coefficient was obtained to determine correlations between the dependent and independent variables. The magnitude of association was categorized according to the Rho coefficient value as no correlation (r_s = 0-0.19), low correlation (r_s = 0.20-0.39), moderate correlation (r_s = 0.4-0.59), good correlation (r_s = 0.60-0.79), and very good correlation (r_s = 0.80-1.0), with correlation being positive (direct) when the coefficient value is negative, and negative (inverse) with r-coefficient negative values.

Positive and moderate correlation was found between the degree of malnutrition and the presence of diarrhea (r_s = 0.626), nausea (r_s = 0.556), and hypoalbuminemia (r_s = 0.559), and low, but positive correlation between the degree of malnutrition and the presence of vomiting (r_s = 0.242), leukopenia (r_s = 0.267), and lymphopenia (r_s = 0.262), respectively (Table 1).

Once these factors whose presence appeared to be associated with the degree of malnutrition of the studied patients were identified, converting our dependent variables into dichotomous variables (present/absent) was required to find out if these associations were statistically significant (p < 0.05) by means of Fischer’s exact test, since the small size of our sample would make the analysis of associations between each variable’s different degrees impossible.
Among the obtained results, only the fact that malnutrition was significantly associated with hypoalbuminemia stands out (relative risk [RR] = 2.4; 95% confidence interval [CI]: 1.22-4.68; p = 0.04), since there were no cases of hypoalbuminemia in those patients with normal nutritional status, and 58% of patients with some degree of malnutrition had hypoalbuminemia. The remaining possible associations were not statistically significant (Table 2). According to the obtained results, the presence of nausea and diarrhea is directly associated with malnutrition, and these symptoms worsen as malnutrition status deteriorates, since, in both cases, the rs coefficients found were within the 0.5-0.6 range; however, these associations were not statistically significant when said variables were dichotomized.

Finally, of all studied dependent variables, only hypoalbuminemia showed significantly higher incidence in patients with malnutrition (RR = 2.4; 95% CI: 1.22-4.68; p = 0.04), and the degree of hypoalbuminemia had a direct and positive relationship with the degree of malnutrition (rs = 0.559).

Malnutrition status has been described to decrease the response to chemotherapy and increase toxicity7,10,13; however, specifically in the studied population, there is no evidence by means of which nutritional status outcomes and treatment response might be contrasted.

CONCLUSIONS

Malnutrition is highly prevalent in this group of patients (70.1%). CC is mostly diagnosed in patients referred by the Seguro Popular who, given their socioeconomic conditions, are at high risk to suffer some degree of malnutrition. Malnutrition status was shown to be associated with the presence of diarrhea, nausea, and hypoalbuminemia, which translates into most patients with malnutrition requiring post-chemotherapy hospitalization, which in turn entails additional hospital costs.

The presence of malnutrition, regardless of the degree of severity before treatment, increases the risk for protein malnutrition on the next chemotherapy cycle which, as previously mentioned, reduces treatment efficacy, with response and toxicity, therefore, being more affected in the next chemotherapy cycle.

Table 1. “rs” correlation coefficient for nutritional status (normal, malnutrition, serious malnutrition) vs. nausea, vomiting, diarrhea, leukopenia, lymphocytopenia, neutropenia, and hypoalbuminemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>“rs” coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0.556</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.242</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.626</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.267</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0.262</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.107</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>0.559</td>
</tr>
</tbody>
</table>

Table 2. Contingency table for nutritional status and presence of nausea, vomiting, diarrhea, constipation, leukopenia, lymphopenia, neutropenia, and hypoalbuminemia

<table>
<thead>
<tr>
<th>Nutritional status</th>
<th>Present n (%)</th>
<th>Absent n (%)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1 (5.9)</td>
<td>4 (23.5)</td>
<td>0.101</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (52.9)</td>
<td>3 (17.6)</td>
<td>0.515</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0)</td>
<td>5 (29.4)</td>
<td>0.261</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4 (23.5)</td>
<td>8 (47.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0 (0)</td>
<td>5 (29.4)</td>
<td>0.515</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (5.9)</td>
<td>4 (23.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>0 (0)</td>
<td>5 (29.4)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Significance was considered at p < 0.05 for Fischer’s exact test.

ACKNOWLEDGMENTS

To the ISSEMyM State Oncology Center authorities for authorizing the present study.

DECLARATION OF INTEREST

The authors declare not having any conflicts of interests.

REFERENCES


16. Grupo de Trabajo de la Sociedad Española de Nutrición Básica y Apli-

REVIEW ARTICLE

Angiogenesis and hemostasis in colorectal cancer

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Received for publication: 20 April 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

Abstract Worldwide, colorectal cancer is the third cause of death in men and the second cause of death in women, with nearly 1.2 million newly-diagnosed cases and 600,000 estimated deaths. A significant proportion of patients have metastatic disease at diagnosis. Neoangiogenesis is the formation of new blood vessels from those already existing, which play an important role in tumor growth and progression. Factors related to endothelial growth have been identified including vascular endothelial growth factor. Different studies have demonstrated coagulation and fibrinolysis systems activation participation in tumor angiogenic development. Some of these factors are Von Willebrand factor, fibrinogen, type I plasminogen activator inhibitor and receptor, in addition to D-dimer and platelets. Serum concentrations of these proteins are considered to be predictors of treatment response, disease progression and survival. Interaction between tumor cells, angiogenesis and coagulation activation is a positive feedback, and strategies interfering in this relationship, such as the use of chemotherapy in combination with new specifically targeted agents, can prevent or treat cancer. In addition, the role of anticoagulant or antiplatelet agents in the treatment of cancer has not yet been determined.

KEY WORDS
Angiogenesis; Colorectal cancer; Prothrombotic state; Prognosis; Thrombosis; Vascular endothelial growth factor

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doi:10.24875/j.gamo.M17000068
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INTRODUCTION

Colorectal cancer (CRC) is a public health problem. At the moment of diagnosis, 15% of patients already have metastasis, and 50% with initially localized disease will develop metastasis regardless of the treatment used. It is important to have minimally invasive techniques that allow for CRC patients survival prognosis to be known, as well as their response to treatment. CRC is the fourth most common malignancy and the second cause of death in the United States. In 2013, there were 96,830 new cases of colon cancer and 40,000 cases of rectum cancer recorded, as well as 50,310 related deaths. Incidence and mortality have decreased as a result of prevention and early diagnosis. Some factors have been associated with a decreased incidence of CRC, including low body mass index and exercise, with increased incidence being associated with (neoplastic) polyps, the diet (high fat content, low consumption of fiber, and high caloric intake), inflammatory bowel disease (chronic ulcerative colitis and Crohn’s disease), genetic factors (Lynch syndrome and familial adenomatous polyposis), smoking, personal or family history of cancer in other anatomical locations (breast, endometrium, and ovary).

CRC left colon localization accounts for 60% of cases and right colon for 30%, with the rest being located in the rectum. Clinical manifestations are associated with tumor size and location. Lesions in the right colon are usually asymptomatic, with subsequent pain, hemorrhage and anemia. Left colon lesions usually produce changes in bowel habits, hemorrhage, pain, decreased caliber stools, and obstruction. In 40-70% of cases, there is regional lymph node involvement, and most common metastases are to the liver, peritoneum, and lung.

CRC is staged with the tumor-node-metastasis system. Stage is the most important prognostic factor, and some characteristics influence on survival, such as histological grade, anatomical localization, obstruction, and perforation at diagnosis. The American Society of Clinical Oncology recommends systematic carcinoembryonic antigen detection as a means to identify early relapse.

Surgical treatment is potentially curative in CRC. By means of colectomy and locoregional lymph node en bloc resection, a complete surgery can be curative in patients without metastasis.

Patients with clinical Stage I disease do not require adjuvant therapy.

Adjuvant chemotherapy is recommended in CRC in the following circumstances:

Patients with clinical Stage II low-risk disease can be maintained on observation or receive treatment with capecitabine or 5-fluorouracil/leucovorin.

Patients with clinical Stage II high-risk disease, those with poor prognosis: T4 tumors (clinical stage IIB/IIC); poor histological differentiation, lymphovascular invasion, perineural invasion, and bowel obstruction; lesions with perforation, positive margins or inadequate lymph node specimen (<12 lymph nodes) can receive 5-fluorouracil/leucovorin, oxaliplatin (FOLFOX), capecitabine/oxalipatin (Cape/Ox), or 5-fluorouracil/leucovorin/oxalipatin (FLOX).

For patients with clinical Stage III disease, 6-month chemotherapy is recommended, and they can receive FOLFOX or CapeOx; FLOX, or capecitabine monotherapy or 5-fluorouracil/leucovorin in those in whom oxaliplatin is contraindicated.

Out of 60% of CRC patients that will develop metastasis, 80% will develop unresectable liver disease, with liver disease being the most common cause of death in these patients. Their treatment includes systemic chemotherapy. Pre-operative chemotherapy provides early treatment of micrometastatic disease and allows for sensitivity to chemotherapy to be determined. Treatment includes 5-fluorouracil/leucovorin, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, and regorafenib.

THE IMPORTANCE OF ANGIogenesis IN CANCER

Maintaining tumor growth requires sufficient nutrient supply, which is accomplished by angiogenesis. Angiogenesis is the formation of new vessels from those already existing. Blood vessel cells are maintained at rest, but they are able to divide in response to stimuli and generate neoangiogenesis. Angiogenesis positive-regulation molecules are vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor, epidermal growth factor, transforming growth factor, matrix metalloproteinases (MMPs), tumor necrosis factor, and angiopoietins. Some endogenous angiogenesis inhibitors are interferon, interleukins, tissue inhibitors of matrix metalloproteinases, and angiostatin and endostatin. Angiogenesis biological process is initiated when there is hypoxic stress in the tumor cell, and it activates hypoxia-inducible factor-1 bis transcription, which promotes VEGF expression. The secreted VEGF binds to its receptor on the surface of endothelial cells and, in addition, increases MMP expression in tumor cells. This generates the angiogenesis process and triggers endothelial cells growth, proliferation, and migration.

Four stages subsequent to endothelial cells activation can be distinguished: (1) Basement membrane and extracellular matrix degradation is produced by proteolytic enzymes, (2) endothelial cell proliferation, (3) pericytes retraction and endothelial cell migration, which form solid cellular cords, and (4) formation of new vessels, anastomosing with preexisting vessels. With the formation of cords, the endothelial cell that is found at the advancement site navigates across the stromal surroundings, while the group of proliferating endothelial cells pushes from the rear, with this advancement across the stroma connecting with other newly formed vessels. The dynamical aspect of this tip-cell has been documented with confocal microscopy. There is intercommunication between angiogenesis and the extracellular matrix, with endothelial cells producing soluble and insoluble paracrine signals that modulate and direct growth, and with the matrix providing a biomechanical environment of stability that favors new vessels growth and morphology. In tumor angiogenesis, endothelial cell activation is induced by tumor originating angiogenic factors (autocrine), and by cells of the tumor stroma, mast-cells, fibroblasts, and macrophages, which are recruited (tumor chemotaxis), in addition to angiogenic factors that are sequenced in the extracellular matrix (paracrine). The angiogenic process is regulated by activating and inhibiting factors, between which there is a state of balance that can be altered in physiological or pathological conditions. Tumor cells alter this
angiogenic balance, the pro- and anti-angiogenic balance, which allows for the “angiogenic switch” to be turned on, triggered by tumor hypoxia and oncogene activation, which would facilitate angiogenesis by an increase in activators or loss of suppressor genes, which would in turn decrease inhibitors.

In experimental models, some oncogenes (v-ha ras, v-raf, k-ras) stimulate angiogenesis by inducing VEGF formation and reducing thrombospondin 1, which is a potent angiogenesis inhibitor; the loss of p53 causes a decrease in thrombospondin 1 and an increase in VEGF. The presence of oncogenes and the loss of p53 would result in tumor cells shifting toward an angiogenic phenotype. Acquisition of this angiogenic phenotype takes place at early stages of tumor development. Cancer biological process starts with the loss of cell proliferation control, which gives origin to carcinoma in situ. Folkman et al. demonstrated that solid tumors cannot continue to grow beyond 2-3 mm in diameter without inducing their own vasculature. Carcinoma in situ can acquire an angiogenic phenotype that induces new capillary formation and starts to invade surrounding tissues. This angiogenic phenotype can be acquired by high production of growth factors or low expression of negative modulators. The last stage of tumor growth is the formation of metastasis. Angiogenesis, which is an initial process in growth, facilitates tumor cells entering the circulation and spread. Extracellular matrix components are regulated by the angiogenic cascade. Factors related to endothelial growth have been identified, including VEGF. VEGF intervenes in three basic functional processes of tumor angiogenesis: Coagulation system activation, adhesion interactions between endothelial surface integrins and extracellular matrix, and extracellular proteolysis control. The VEGF family is comprised by six members: VEGF-A (also known as VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, and PIGF or placental growth factor. Its structure is composed of homodimers, which contain polypeptide chains that, in their general structure and in the cysteine residues spacing, are relayed to PDGF.

VEGF biological effects are mediated by its binding to three structurally-related cell-surface specific receptors: VEGF-R1 or Flt-1, VEGF-R2, KDR or Flk-1, and VEGF-R3 or Flt-4. R1 and R2 are essential for vascular development and are mainly expressed in the vascular endothelium, while R3 is found in the lymphatic endothelium. In the past few years, an intense search for new biologic markers, such as VEGF, has been carried out, to allow for CRC patients’ evolution follow-up. However, only a few studies have so far been conducted trying to elucidate the progression predictive and survival prognostic role of VEGF levels prior and after chemotherapy in patients diagnosed with CRC. Patients with VEGF elevated levels have worse prognosis in terms of response to chemotherapy. VEGF determination is made both in serum and plasma. Patients whose concentrations of these factors, such as VEGF, before antineoplastic treatment is elevated, might benefit from chemotherapy in combination with new specific targeted agents.

HEMOSTASIS IN CRC AND PROGNOSIS

Hemostasis is defined as hemorrhage arrest. The term originates from hema = blood and stasis = to stop; its concept is: Thrombohemorrhagic balance maintained by interactions between coagulation, the fibrinolytic system, platelets and vascular wall. Coagulation activation requires the participation of platelets, endothelium, monocytes, and coagulation factors and it can occur by the extrinsic and intrinsic pathways, both comprised in the cell-based model of coagulation.

The elements that constitute hemostasis can be divided into thrombogenic elements, which include the exposed endothelium, tissue factor, prothrombin, fibrinogen, collagen, platelets, platelet-activating factor and von Willebrand factor (vWF), and anti-thrombogenic factors, which include heparin, thrombomodulin, plasminogen, tissue plasminogen activator, antithrombin III, C-protein, and S-protein. Cancer induces a prothrombotic state, which occurs as venous thrombosis or often as a subclinical state that manifests itself by alterations in thrombogenic biomarkers that show coagulation and fibrinolysis activation, with these changes paralleling tumor growth and dissemination. Tumor cells express tissue factor, other procoagulant proteins and MMP, which activate coagulation and also activate host cells (endothelium, platelets, and leukocytes); these, in turn, release soluble and contact factors and express their procoagulant phenotype by forming a structure that favors platelet adhesion and thrombin generation and activation. Some thrombotic factors are related to cancer patients, such as demographic factors, treatment-related factors and central venous catheter. The use of predictive risk assessment models (RAM) is recommended to identify patients at high risk for thrombosis, such as the deep venous thrombosis RAM in patients who will receive chemotherapy.

Thrombocytosis, hyperfibrinogenemia, D-dimer, fibrin degradation products, or vWF is associated with clinical progression and prognosis in patients with cancer. Some biomarkers are correlated with progression and poor prognosis: Thrombocytosis, hyperfibrinogenemia, D-dimer, fibrin degradation products, or vWF. Gil-Bazo et al. report vWF elevated plasma concentrations in patients with breast, prostate, bladder, head and neck, ovary, cervix, larynx, and colon cancer. Elevated vWF is associated with worse prognosis in patients with metastatic CRC, as well as D-dimer and fibrinogen. Beer et al. point out the predictive and prognostic value of D-dimer plasma concentrations in cancer patients. Kawai et al. report that pre-operative thrombosis is associated with tumor size and invasiveness in
CONCLUSIONS

In spite of the continuous increase in the number of potential biomarkers in CRC, standardization of their determination is necessary. The interaction between cancer and coagulation activation is a positive feedback, and strategies interfering with this relationship may modify the outcomes. Anticoagulant or antiplatelet agents’ efficacy in the treatment of cancer has not yet been clearly determined, and study on this relationship is required to be continued.

DECLARATION INTEREST

The authors declare not having any conflicts of interest.

REFERENCES


Review Article

Real-world evidence: A review of clinical experience in metastatic gastric cancer second-line treatment with ramucirumab

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Received for publication: 6 August 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

Abstract

An improvement in overall survival of patients with gastrointestinal tumors has been observed in recent years, with main factors for this being an in-depth understanding of molecular biology, determination of prognostic factors, and of course, the development of new drugs, all of which has allowed gradual but significant advances in the treatment of gastric cancer. First-line treatment has shown benefits; however, many of these patients show disease progression, which raises the challenge of optimizing the ensuing treatment lines and developing better treatment strategies. The role of second-line treatment has recently been introduced and discussed, although there is evidence regarding the benefit of some drugs such as docetaxel, paclitaxel and irinotecan in second-line treatment, with this benefit having shown a reduction of approximately 18% in the risk of death, there is still a need to discuss and analyze efficacy in overall survival, progression-free survival and toxicity profile, with a special emphasis on the appropriate choice of drugs according to efficacy, toxicity, prognostic factors, and patient characteristics. The objective of this cross-sectional study is

Key Words

Gastric cancer; Stomach cancer; Metastatic gastric cancer; Advanced gastric cancer; Ramucirumab; Second-line; Antiangiogenic; Real-world evidence

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INTRODUCTION

Gastric cancer (GC) is the third cause of cancer-related death worldwide. Around 1 million new cases are diagnosed every year. GLOBOCAN 2012 statistics record GC diagnosis in 930,000 individuals annually. Incidence shows the strong influence of ethnic and geographic factors: It is higher in Asia, East Europe, and South America, while incidence rates reported in Africa and North America are lower. GC in México is a public health problem and the third cause of cancer-related deaths from the third decade of life on, with a trend that does not decline over time. A GC mortality rate of 6.4 cases per 100,000 population has been reported in men, as compared with 4.7 cases per 100,000 in women.

In spite of advances regarding the knowledge of molecular biology and surgical techniques, improvements in diagnosis and development of new chemotherapy protocols, clinical outcome for patients with GC is generally limited, with about 90% of patients experiencing disease progression; this poses the challenge of optimizing subsequent therapeutic lines and developing improved therapies.

The role of second-line therapy has recently been introduced and reviewed. Despite the fact that some evidence points to the benefits of some drugs, such as docetaxel, paclitaxel, and irinotecan in second-line treatment, a benefit that has shown a decrease of almost 18% in the risk of death, efficacy has yet to be examined in terms of overall survival, progression-free survival and toxicity profile, with special emphasis on adequate drug selection based on efficacy, toxicity, prognostic factors, and patient characteristics. At present, this need has led to the development of new therapeutic measures to achieve better results and incorporate new molecular targets.

The purpose of this cross-sectional study is to examine medical experience in real-life clinical practice, in the setting of second-line treatment of metastatic gastric cancer in patients treated with ramucirumab, and to describe prognostic factors and their impact on real-life clinical practice.

Metastatic gastric cancer second-line treatment with ramucirumab

...
The knowledge of GC molecular profile has enabled the examination of more promising signaling pathways, which opens new opportunities for the treatment of GC. However, as previously mentioned, therapeutic progress has been limited, with the exception of two targeted therapies. One of these is trastuzumab as first-line treatment of GC, supported by the ToGA trial, which enrolled patients with GC or non-resectable or metastatic gastro-esophageal junction cancer with HER2 overexpression (22%), and the results of which regarding survival found benefit favoring this drug. An overall survival of 13.8 months was reported with trastuzumab in comparison with 11.1 months for chemotherapy alone, and progression-free survival (PFS) of 6.7 in comparison with 5.5 months.

The other therapeutic approach that has shown an effect on survival in patients with GC is the inhibition of angiogenesis signaling pathways, where multiple preclinical trials have shown an improvement in tumor growth control and metastases progression in GC through the inhibition of the VEGF pathway.

Several clinical trials were carried out with drugs aiming to inhibit angiogenesis, with the purpose to explore this signaling pathway. However, compounds such as bevacizumab, afibercept, axitinib, sorafenib, pazopanib, regorafenib, telatinib, and vandetanib have not shown positive results. So far, the only angiogenesis-inhibiting drug with proven efficacy and positive effects on survival has been ramucirumab. This drug is a fully humanized monoclonal antibody that targets the VEGF receptor.

Two large clinical trials have evaluated the efficacy of ramucirumab in terms of overall survival in patients progressing to a first-line of treatment: REGARD and RAINBOW. These trials show the most robust data, with more adequate available evidence for second lines, since they included large numbers of patients and are appropriately designed. They are adequately conducted, double-blind, placebo-controlled trials that achieved the primary endpoint of overall survival improvement and also showed a consistent improvement in PFS, while maintaining the quality of life.

The REGARD trial assessed ramucirumab as second-line treatment in patients with advanced GC or cancer of the gastro-esophageal junction; mean survival was 5.2 months for the antibody treatment and 3.8 months in the control group (P = 0.0047). Greater PFS was also reported for ramucirumab (2.1 months, compared with 1.3 months with placebo). These results revealed that ramucirumab is the first biologic treatment with a proven benefit on survival after progression with a first-line of therapy.

A second trial (RAINBOW) investigated the same antibody in combination with weekly paclitaxel, compared to a taxane and best supportive medical care as second-line therapy in patients with gastric and gastro-esophageal cancers that had progressed on a first-line of treatment with chemotherapy. Survival was significantly longer in the ramucirumab plus paclitaxel group in comparison with the control group (9.6 vs. 7.4 months).

Ramucirumab plus paclitaxel delayed disease progression (PFS of 4.4 vs. 2.9 months) and showed a higher response rate (28 vs. 16%). Based on these results, regulatory authorities approved the drug as monotherapy or in combination with paclitaxel in patients with advanced or metastatic gastro-esophageal junction or GC after progression, over fluoropyrimidine or platinum-based schemes.

Ramucirumab is the first compound approved for the treatment of advanced or metastatic GC after first-line therapeutic failure. If the abovementioned information is considered, it is important to have local experience available regarding population characteristics, as well as treatment results, and prognostic factor identification, which allows for the therapeutic approach and its results in GC to be improved.

Therefore, as part of SMeO initiatives, an epidemiological, observational, cross-sectional study was conducted by means of a self-administered questionnaire, designed for the purpose of this study, and administered as a survey during the period of January 12 to 27, 2017. Primary interest events included population epidemiological characteristics, number of received treatment cycles, total treatment duration (months), and PFS (months). Frequency of Grade 3 and 4 toxicity and overall treatment response (partial response, stable disease, or complete response) were also evaluated.

RESULTS

A total of 66 patients were included, out of which a total of 58 were analyzed, since eight patients were excluded because they had initiated therapy not even completing two cycles of the scheme.

When demographic data were analyzed, mean age for the 58 patients was found to be 56 years; in this respect, age showed the following distribution: 32.8% were 28-48 years old and 34.4% were 49-63 years old.

Regarding distribution by age, median age at disease onset was found to be lower than that reported in the medical literature, with a mean of 64 years. Conversely, 32.8% of patients were 48 years old (Fig. 1). Gender distribution was as follows: females, 37.9%; males, 62.1%.

With regard to the ECOG score reported at the beginning of second-line therapy, the following distribution was identified: ECOG 0, 14%; ECOG 1, 65%; ECOG 2, 21%; ECOG 3 patients were not included.

Undoubtedly, one of the most relevant prognostic factors is the ECOG performance status (PS) scores, a parameter that is widely used as a predictor related to treatment. An ECOG of 0 to 1 has been previously shown to be considered the best predictor when compared with patients with an ECOG of 2-3 (poor performance status). One of the trials showing the effect of the ECOG score on mean survival is that of Lee and colleagues, which examined 1,455 patients showing the effect of the ECOG score on mean survival is that of Lee and colleagues, which examined 1,455 patients with GC on first-line therapy; this study concluded that in patients with an ECOG > 2 the survival rate was 17.1%, in comparison with 39.2% in patients with an ECOG of 0 to 1.

In this study, the authors found that performance status (ECOG) was correlated with PFS and that patients with an ECOG of 0 exhibited a PFS period of 5 months, in contrast with those with an ECOG of 2, where PFS was 3 months. This revealed, once again and without a doubt that ECOG remains a highly relevant prognostic factor.

In the report by Catalano et al., which specifically examined the influence of pathological clinical factors on survival in patients on second-line chemotherapy for GC, a 1-year
survival of 25% was reported in patients with an ECOG of 0 to 1, in comparison with 8% in subjects with an ECOG of 2, who had two- to three-fold more probabilities of dying within one year (HR, 1.79 [1.16-2.77]; \( P = 0.008 \))\cite{24}.

As for histological types, the intestinal type prevailed in 31 patients (54%), followed by diffuse and mixed types in 18 and 9 patients (30% and 16%), respectively. The proportions of patients with poorly and moderately differentiated tumors were similar: 48% of cases were Grade 1 and 2 adenocarcinomas; only 3 patients (4%) had highly differentiated tumors. No link was identified between histological type and degree of differentiation and PFS.

Previous trials have identified metastatic sites as prognostic factors. For example, the study by Wang and colleagues showed that the presence of liver and bone metastases was an independent prognostic factor, even in patients with adequate performance status. Both these metastatic sites are poor prognostic factors. The authors of this retrospective series of 310 patients assigned to first-line treatment with chemotherapy found that patients with metastases in more than two organs experienced a worse effect on survival in comparison with those with metastasis to a single organ (HR, 1.47; 95% CI, 1.11-1.96; \( P = 0.007 \))\cite{25}.

In the study by the above-mentioned authors, metastatic disease (Stage IV) was observed in all patients receiving first-line treatment with chemotherapy, and 30 of them (49%) had multiple metastatic sites: 0 to 1 site was found in 27.6% of cases; 1 to 2 sites in 17.2%; and 2 to 3 metastatic sites in 55.2%.

The most common metastatic site was the liver (46%), followed by the peritoneum, retroperitoneal lymph nodes and the lung. A trend toward a longer PFS period was identified in patients with 0 to 1 metastasis, although this finding was not conclusive owing to the sample size.

Regarding the presence of carcinomatosis in 60.3%, although no relationship as a prognostic factor was found. With regard to ascites, it was observed in 36.2% of patients.

Weight loss prior or during chemotherapy has been noted in several cancers, including GC, and it is generally associated with an attenuated tolerance to treatment, which affects the strength of the chemotherapeutic dosage. In the study by Ock et al. that examined 719 patients, mean survival in subjects receiving palliative chemotherapy as first-line treatment with a weight loss of 3% during the 1st month of therapy was significantly shorter in comparison with patients with no weight loss (9.7 vs. 16.3 months; \( P = 0.001 \))\cite{26}.

Notwithstanding, weight loss is not mentioned as a factor in prognostic scales. In the above-mentioned study, the authors observed that a weight loss > 10% in 50% of the sample showed a correlation between PFS and absence of weight loss, with an improvement in PFS to 6.9 months in comparison with the subgroup with > 10% weight loss, which reported 3.8 months. However, these results are not statistically significant owing to the patient population size.

**Number of treatment cycles**

With regard to treatment duration, overall median treatment cycles with ramucirumab per patient were 4.0 (95% CI, 3.1-5.0).

**TREATMENT RESPONSE AND QUALITY OF LIFE**

**PFS**

PFS (Fig. 1) in the entire study sample was 4.0 months (95% CI, 2.5-5.5). In the stratified analysis by age, the largest median was observed among participants aged from 70 to 89 years (6.0 months; 95% CI, 1.0-12.0). However, differences between age groups were not statistically significant.

Regarding of toxicities none Grade 3 or 4 was reported, the most common toxicity reported was hypertension.

**DISCUSSION**

GC is a highly common neoplasm in underdeveloped countries, with practically comparable incidence and lethality. In Mexico, it constitutes an important cause of death and occupies the first place in gastrointestinal tumors. This lethal prognosis is due to late diagnosis and advanced sta-
ges at diagnosis in more than 80% of cases; consequently, therapeutic options are merely palliative in patients suitable for systemic oncologic management. At progression after receiving a first-line of chemotherapy, a portion of these patients (nearly one third) is eligible for second-line treatment. However, this is a difficult challenge in clinical practice because patients are generally fragile, almost all of them compromised in terms of nutritional status. In addition, evidence of a benefit with second-line treatment is relatively recent and, furthermore, this is a heterogeneous disease and knowledge on its biological and molecular behavior has emerged only recently in investigations to identify different GC groups. These treatment approaches have the purpose to improve prognosis and, in the mid-term, to have targeted therapeutic schemes available. These differences may explain treatment response variable effects.

In spite of advances in the knowledge about the biology of GC and the availability of new therapeutic regimens that have led to increases in the parameters of PFS and mean survival in the setting of first-line therapy, the prognosis for patients with GC is still very poor. Second-line treatment is systematically being introduced in many patients, and there are several variants in current clinical practice. This study attempted to evaluate patients exposed to a second-line of treatment with ramucirumab and chemotherapy.

The benefits exhibited by the RFG-2 inhibitor, ramucirumab, and the VEGFR-2 tyrosine kinase inhibitor, apatinib, represent an advance in the development of antiangiogenic drugs for metastatic GC27,28. Future trials should investigate ramucirumab given as first-line therapy in combination with other chemotherapeutic agents, or with a specific molecular determination. Therefore, its use as maintenance therapy and the sequence with other active therapies are pending resolution. The choice of chemotherapy, in particular, seems important and demands further investigation to assess combinations with drugs other than taxanes29. Thus, performing this type of studies is desirable. Dose strength constitutes an additional problem that should be examined, as should the relationship with exposure, pharmacokinetic concentrations and effectiveness of ramucirumab30. On the other hand, it should be pointed out that, in this analysis, most patients had normal weight, which may have related to adequate effectiveness and better tolerance as well as therapeutic compliance.

If increasing costs in oncologic care are considered, a cost-effectiveness analysis is mandatory. In addition, apart from having biomarkers to target these molecular therapies, better clinical tools should be used to select those patients most suitable for these treatments, since we should take into account that the performance status level is a crucial parameter when choosing a therapy. A large proportion of patients herein examined had an ECOG PS of 1 to 2, as in other previously published works. As in the RAINBOW trial, the intestinal type prevailed in this population, although a limiting factor should be mentioned: The number of patients previously exposed to anti-HER therapy was not determined, and the documented proportion of carcinomatosis was lower.

By the same token, tumor burden with regard to metastatic sites has been determined to be a response parameter to second-line therapy.

CONCLUSION

The treatment of GC continues to pose a challenge due to the heterogeneity of the disease; hence, it is of utmost importance to have reports on real-world clinical experience. Such reports will allow for a more orderly and systematized identification of population characteristics and prognostic factors in patients treated in regular clinical practice. Therefore, this information makes it possible to have access to more elements contributing to identify the group of patients who will benefit most from a determined therapeutic approach, which will undoubtedly contribute to therapeutic behaviors optimization.

This review concludes that ramucirumab constitutes an adequate second-line treatment in patients with GC to improve time to progression and quality of life. Although there is no available biomarker for selecting those patients who are eligible for ramucirumab, there are indeed certain clinical parameters such as an ECOG PS of 0-1 and PFS > 6 months, which may constitute appropriate parameters for selecting patients who will be adequate responders and will obtain clinical benefits.

ACKNOWLEDGMENT

We especially acknowledge the collaboration and information provided for this article by the oncologists who contributed with information from their patients.

REFERENCES


Relationship between aspirin, radiation therapy, and hormone deprivation in prostate cancer

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Received for publication: 24 June 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

Abstract Systematic review of studies published in PubMed about the relationship between prostate cancer and anticoagulants, especially aspirin. We analyze the role that their association with radiation and hormone deprivation and his possible synergistic effect in treatment. We describe bibliographic evidence of possible association between aspirin use and the onset, development and mortality by prostate cancer. Continue delving into the pathophysiological mechanisms involved. Finally, we describe and discuss the works related to the association between anticoagulants, radiation and hormone deprivation. Randomized trials are guaranteed, taking into account disease-related, patients and therapies factors, in order to obtain unbiased evidence of their likely relationship. Once confirmed the hypothesis of its synergistic effect, in prevention and/or in adjuvant treatment setting of prostate cancer, it opens up a whole range of future possibilities of great impact in the management of this prevalent disease. (creativecommons.org/licenses/by-nc-nd/4.0/).
OBJECTIVE, MATERIALS AND METHODS

The purpose of this work is double: On the one hand, to review existing evidence on the possible epidemiologic relationship of anticoagulants (AC), especially aspirin with prostate cancer (PC), and on the other, the role they might play, together with radiation therapy and hormone deprivation (HD), in the treatment of PC. A selective search was conducted in PubMed using the terms “cancer of prostate” or “prostatic cancer” together with the terms “aspirin,” “AC,” “nonsteroidal anti-inflammatory drugs (NSAIDs),” “anticoagulants,” “radiotherapy,” “brachytherapy,” “irradiation,” “hormonal deprivation,” and “androgen deprivation.” After their review, those articles of the highest relevance due to their methodology or outcomes were selected without any retrospective limitation and up to March 2016. Through them, other articles of interest for the present work were accessed. After briefly reviewing epidemiological evidence on the use of aspirin or ACs to prevent cancer, the pathophysiological mechanisms involved in the possible beneficial effect of ACs on PC will be described. Then, those studies associating ACs, radiation therapy, and HD to each other will be shown. Finally, those aspects that beforehand may be of higher interest such as the hypothesis of a possible synergistic interaction, where the addition of these factors may play an important role with regard to cancer treatment, will be discussed.

DEVELOPMENT

There is evidence that drugs that alter hemostasis, such as aspirin and other AC, may play an important role with regard to PC. This evidence suggests that ACs might prevent its onset, development, and dissemination. Nevertheless, clinical data examining such an association shows results that are not entirely conclusive. There is also evidence of a positive association between neoplastic conditions and the coagulation system. Increased risk for thromboembolism in cancer patients is a known fact as well as the higher risk for the development of cancer in patients with a history of blood dyscrasia3-4. Studies carried out with aspirin in primary prevention of cardiovascular disease (CVD) have also demonstrated a reduction in long-term cancer-related mortality5.

There is evidence available on the possible effect of aspirin on a number of particular cancers. We know that it can prevent their onset and decrease their mortality6. Different studies, including a meta-analysis, confirm the efficacy of aspirin in the reduction of adenocarcinoma-related mortality risk, especially in colorectal adenocarcinoma7-9, hence, the interest to verify a possible relationship with prostate carcinoma. There are multiple epidemiological studies that refer an association between the use of ACs and a reduced risk of PC onset, PC-related mortality, and PC diagnoses with less aggressive initial clinical factors7,10-14. Even when there are also studies against this relationship15-18, some of them show important biases19. Recently, some meta-analyses that appear to confirm this positive relationship have become available20. Prolonged intake of the drug appears to be necessary for its positive effects with regard to cancer prevention to be obtained21. That means that after 5-10 years of use, one can expect to obtain a positive effect on cancer prevention.

On the other hand, the pathophysiological processes involved in cancer prevention and mortality are mediated by several cyclooxygenases (COXs)-dependent and independent mechanisms of action. COX-dependent mechanisms are those mediated by the COX enzyme. COX is an enzyme that converts arachidonic acid into eicosanoids including leukotrienes, thromboxanes, and prostaglandins. The latter are potent mediators of inflammation and other physiological processes. Aspirin inhibits in a nonselective form both COX isozymes: COX-1 and COX-2. COX-1 pathway inhibition is irreversible, even at aspirin low daily doses22. This is the main pathway involved in the control of platelet aggregation, although it is also responsible for gastrointestinal (GI) mucosa integrity preservation. Higher aspirin doses are required to inhibit the COX-2 pathway23. COX-2 is inducible by the action of mitogens, growth factors, oncogenes, cytokines, and carcinogens24. After induced activation of this pathway, a whole range of mechanisms such as angiogenesis promotion, apoptosis inhibition, cell proliferation stimulation, and immunity suppression reduction all of them factors clearly associated with carcinogenesis are set in motion25. All these observations prompted an interest on looking into the role of COX-2 selective inhibitors, both in the prevention and treatment of cancer. Such interest decreased when their toxic profile was demonstrated. COX-2 is responsible for the synthesis of prostaglandin I2 (PGI2), which is a vasodilator and platelet aggregation inhibitor agent. Therefore, by selectively inhibiting COX-2, the balance between the antithrombotic effect and the prothrombotic effect mediated by COX-1-generated thromboxane A2 (TXA2) is broken, which generates the possibility of cardiovascular thrombosis. This is the mechanism that would explain its toxicity. Increased expression of COX-2 has been substantiated in certain cancers, such as prostate, bladder, and colon cancer, as well as a possible relationship between this overexpression inhibition by aspirin and lower risk of PC development and aggressiveness26. The role of COX-2 in the genesis of cancer is reaffirmed when a higher possibility for developing PC in certain polymorphisms such as rs2745557, rs20415, and rs20417 is verified27,28.

To conclude this section, apoptosis and angiogenesis can be activated by COX-independent mechanisms that are also affected by ACs29. These mechanisms are multiple, and daily there are new ones described, but an exhaustive description of them is beyond the scope of the present work (Table 1). In addition, aspirin might act on chronic inflammatory processes involved in the development of PC. Specifically, it might act by inhibiting prostaglandin E2 (PGE2) formation, which is involved in carcinogenesis through the activation of mediators26. Recently, PGE2 has been described to silence tumor-suppressor and DNA-repair genes through DNA methylation, a mechanism that helps to clarify its mechanism of action29.

Association of ACs with radiation therapy and HD

The use of aspirin or ACs is correlated with the use of radiation and/or HD in different works. Thus, in the study by Chloe et al., the effect of ACs on survival was tried to be assessed in a prospective cohort of 662 patients with PC who received radiation therapy with curative intent. About 37% of them (243 patients) were on medical treatment with warfarin, clopidogrel, and/or aspirin. All of them received external beam radiation therapy (EBRT), permanent seed implants, or both procedures. Prostate-specific antigen
(PSA) was monitored for biochemical control of the disease. With a median follow-up of 49 months, 4-year biochemical control was significantly higher in those patients using ACs, specifically, 91% versus 78% (p = 0.0002). Furthermore, 4-year metastatic disease-free survival (MDFS) was higher (99% vs. 95%; p = 0.0248). In the subgroup analysis, significant improvement of biochemical control was recorded only in high-risk patients. Together with the Gleason score, the stage and baseline PSA, the use of AC was independently associated with biochemical control improvement in the multivariate analysis.

In another work of the same group, the benefit of the use of ACs is observed in a cohort of 5295 patients with PC treated with radical prostatectomy (RP) (n = 3523) and radiotherapy (n = 1772). In this group, 37% (1982 patients) were receiving ACs at study enrollment, with the intake being maintained over the course of it. ACs used were warfarin (n = 428), clopidogrel (n = 287), enoxaparin (n = 26), aspirin (n=1649), or combinations (n = 408). The mean PSA was 6 ng/mL. According to a risk group, the patients were divided as low risk (41%), intermediate risk (37%), and high risk (21%). HD was also received by 28%. The primary endpoint of the study was disease-specific mortality (DSM) risk assessment. Of note, patients without ACs were younger (median of 64 vs. 66 years, p < 0.01), and more often treated with surgery (69% vs. 62%; p < 0.01). Both the Gleason score and stage were similar in both groups. After a 59 months median follow-up, DSM was significantly lower in patients who used ACs versus those who did not (1% vs. 4% at 7 years and 4% vs. 10% at 10 years; p < 0.01). By risk groups, mortality reduction was greater for high-risk patients (8% vs. 2% at 7 years and 22% vs. 4% at 10 years; p < 0.01). In addition, lower risk for developing bone metastases was observed. The analysis according to the AC suggested that the positive effect was basically due to the use of aspirin. In the multivariate analysis, the use of AC was independently associated with lower risk of PC-related death (hazard ratio HR: 0.53; p < 0.01). Other independent factors were the Gleason score, use of radiotherapy combined with HD, and the use of statins.

Cohen et al. assessed a prospective cohort of 189 patients who received tridimensional EBRT or modulated intensity radiotherapy as rescue therapy. The mean dose used was 68 Gy, and pre-EBRT mean PSA was 0.5 ng/mL. All patients with HD were excluded. Of the entire cohort, 31% were on AC treatment. On the other hand, this was a high-grade cohort, since 35% of patients had T2, 63% T3, and 2% T4, in addition to, 57% of them having positive margins. After 50-month median follow-up, the univariate analysis showed a relationship with 5-year biochemical relapse-free survival (BRFS), with overall survival (OS), and with MDFS, whereas the multivariate analysis only showed BRFS improvement (HR: 0.35; 95% confidence interval [CI]: 0.155-0.786).

Caon et al. studied the association of ACs/statins and comorbidity with survival in a prospective cohort of 3898 patients treated with EBRT. The mean age was 70.3 years, with 23% of patients using statins and 29% ACs. Charlson comorbidity index was 0 in 65%, 1 in 25%, and ≥2 in 10%, with 39% at intermediate risk and 44% at high risk. HD was received by 67%, and EBRT median dose used was 70 Gy; mean follow-up was 5.3 years. In the multivariate analysis, statins intake was associated with better cancer-specific survival (p = 0.049). Better OS was associated with statins and HD treatment (both p < 0.01), with a deleterious trend for the use of ACs (p = 0.04).

Finally, Katz et al. reviewed the relationship of ACs and statins with the risk for PC and survival improvement in a retrospective cohort of 7042 patients, 4611 of them treated with RP, and 2431 with EBRT. After a median follow-up of 4 years, the multivariate study showed an association between lower all-cause mortality after RP (HR: 0.47; 95% CI: 0.30-0.75) or EBRT (HR: 0.39; 95% CI: 0.25-0.59) and the use of ACs. This association was also demonstrated for the use of statins (HR after RP: 0.35; 95% CI: 0.21-0.58; and HR after EBRT: 0.59; 95% CI: 0.37-0.94). This study evidence the need for data collection to be as extensive as possible to obtain the most information with regard to existing interrelations.

**DISCUSSION**

From the observations exposed in the review, it can be inferred that AC may contribute to prevent tumor development, growth, and dissemination in patients with prostate carcinoma. Specifically, patients at higher risk of dissemination can derive the most benefit. Nevertheless, there is still no clear information based on adequate clinical trials. In addition, there are data endorsing lower aggressiveness in PC presentation with the use of ACs, which can
also be highly important to decrease PC-associated mortality, which is a condition of high incidence and prevalence in developed countries. However, there is also information against this correlation with PC presentation profile.

At present, radiotherapy with HD addition is the standard of care in high-risk PC. A clear benefit has been corroborated in cancer-specific survival, OS, and in clinical relapse-free survival, BRFS, and MDFS. HD can be neoadjuvantly, concomitantly, or adjuvantly administered. In high-risk patients, it is common to start it in the neoadjuvant setting to continue concomitantly and adjuvantly for a prolonged period (for a total of 1.5-3 years). The rationale to combine HD with radiation therapy in the neoadjuvant setting lies in several factors: Prostatic volume debulking, which allows for doses to be increased without much toxicity, tumor hypoxia reduction, which increases radiosensitivity, cell cycle slowing, which would result in decreased cell repopulation during radiation therapy, and finally, an apoptosis direct effect on tumor cells through an immunomodulation phenomenon. Based on this, it has been speculated that HD neoadjuvant administration and radiation might have an additive (confirmed in animal models) and even supra-additive effect. Finally, HD would act by sterilizing occult metastases, whereas radiation would kill tumor cells regardless of hormone sensitivity in a spatial cooperation phenomenon similar to that of chemoradiation.

As a result of all this, ACs addition to radiation might be thought of as possibly playing a similar role than that of HD, in this case by preventing metastatic dissemination throughout the development of cancer. This hypothesis seems to be reaffirmed by the work of Rothwell et al., where aspirin prolonged intake, fewer cancers had metastasis at diagnosis, the risk for the development of metastasis was decreased, and finally, cancer-related mortality risk was reduced, particularly in those patients with no metastasis at diagnosis. This suggests that aspirin would generate both tumor growth delay and decreased metastatic dissemination, hence, the importance to exclude patients with metastasis at diagnosis from all clinical trials assessing cancer-specific mortality with the use of ACs. On the other hand, Woodward et al. proposed that HD increases tumor oxygenation by radiosensitizing them. The implicated mechanism would be through vascular endothelial growth factor inhibition, which would prevent neo-proliferation of a fragile and inefficient vascular network around the tumor that would limit oxygen supply. This same anti-angiogenesis mechanism could be generated by addition of ACs in an additive mechanism together with radiation and even a synergistic one together with HD.

With regard to other interrelations between ACs and radiation, in the study by Anai et al., COX-2 overexpression was observed to increase PC cells chemoresistance. With escalating doses of celecoxib added to radiotherapy, an increase in radiation cytolytic effect is observed. Other studies show COX-2-overexpressing PC cells increased resistance to radiation as well. As in the study by Anai et al., other works with COX-2 selective inhibitors have shown their radiosensitizing effect, even in situations of hormone refractoriness, although there is also some work available with opposing information.

As for the relationship between ACs and HD, a recent work demonstrated both in vitro and in vivo that after complete blockade using flutamide as an androgen antagonist, the COX-2 expression is increased, with this mechanism likely being involved in the development of HD resistance. This information opens the door to the study of PC adjuvant treatment with HD combined with COX-2 inhibitors in a cooperative mechanism. The role of adjuvant with HD and ACs is prospectively and comparatively studied as well with the use of intermittent HD (IHD) at biochemical relapse after RP, using bicalutamide 150 mg/day at “on” periods in both comparative groups and etoricoxib at “off” periods in the intervention group. A higher percentage of responses to IHD and longer “off” periods are observed with the use of the COX-2 inhibitor. Moreover, finally, a synergistic effect can also be obtained from ACs and HD, since some ACs have been found to exert a potent inhibitory effect of the androgen receptor function. In any case, caution should be exercised with the concurrent use of ACs and HD due to the potential risk for liver toxicity, which might limit the alleged benefit owing to the need for HD early discontinuation.

The influence of COX-2 overexpression and its relationship with survival in patients treated with radiation and HD was also substantiated in a sub-study of the RTOG 92-02 trial. After assessing the 586 patients with sufficient immunohistochemical information on the individual, the multivariate analysis demonstrated that COX-2 overexpression status as a continuous variable is an independent predictive factor of distant metastasis, biochemical failure (according to ASTRO and Phoenix criteria) and of any failure. As a dichotomous covariable, COX-2 overexpression appears to better discriminate survival of patients receiving HD short sequence versus those receiving the extended sequence. This study supports the possible association between COX-2 expression and the response to HD. This reaffirms the need to stratify our PC patients according to COX-2 expression as an independent prognostic factor of both hormone and radioresistance and worse survival. Depending on this information, we can assess reinforcing the treatment by prolonging HD time or by adding COX inhibitors, with the latter point yet to be studied.

When assessing the possible cooperation in the PC adjuvant setting, it can be claimed that the effect of COX-2 inhibitors has shown to be independent of the response to HD in PC cell lines in vitro, even with regard to apoptosis generation. Its radiation-independent effect has also been demonstrated since no differences with regard to its efficacy in biochemical relapse rates decrease were observed when its use was initiated prior or after radiation therapy.

Another role to be played by ACs would be in delaying the need for treatment after biochemical relapse. In a Phase II trial in recurrent disease after RP or EBRT, Pruthi et al. showed celecoxib efficacy in the decrease of PSA concentration, thus delaying the need for treatment.

With regard to higher relative efficacy between different ACs, there is evidence that aspirin, versus other ACs, is the main responsible in PC prevention as well as in its decreased mortality. Although there are also studies that do not find a clear relationship with aspirin or its dose or length of administration, there are also data on PC prevention and lower aggressiveness with acetaminophen (paracetamol). In experimental in vitro studies on androgen-dependent and androgen-independent PC cells, ibu-
profen was considerably superior versus other ACs with regard to apoptosis induction and survival reduction. These diverging data between different NSAIDs may be related to the degree of inhibition of the COX pathway as well as to its reversible or irreversible nature. We know that studies in vivo showed that 95% suppression of COX-1 activity is required to block TxA2-induced platelet aggregation. This degree of suppression, being also of an irreversible nature, is only achieved by aspirin. The remaining NSAIDs exert a reversible and less intense inhibition (between 50% and 95%)\textsuperscript{65}. Therefore, it can be deducted that high doses of NSAIDs are required to obtain a beneficial effect, which was confirmed by one study of colorectal adenocarcinoma\textsuperscript{11}. Somehow, this could be extrapolated to the effect of different ACs on cancer.

Some of the negative results in the presented epidemiological studies, or even the conclusions, should be assessed with caution due to the possibility of biases. In many of them, confounding factors may be involved including the use of statins, the type of diet, body mass index (BMI), smoking, physical activity, administered treatments, comorbidities, sample size, doses, and intervals of ACs used, or even the use of different PC screening and follow-up protocols\textsuperscript{16,17,64}. It should be pointed out that most studies contemplating ACs positive effect do not report statins intake and vice versa. Another interesting observation arises from the work by Salinas et al., where a positive effect is demonstrated in cancer prevention in one of the COX expression phenotypes, specifically r12042763, which opens the door to research in those cases with COX overexpression caused by single-nucleotide polymorphisms\textsuperscript{10}.

In retrospective studies, the use of statins has also been observed to be associated with lower risk for PC, with less aggressive presentations, lower rates of biochemical relapse, and longer survival\textsuperscript{14,41,67-69}. Similar effects have been observed in breast\textsuperscript{20} but not in colon cancer\textsuperscript{71}. The use of statins could also be related to clinical factors of disease presentation such as PSA level, stage, or Gleason score\textsuperscript{67,68}. Their possible action might be related to the type of statin, the dose used and length of use, since a decrease in the risk of biochemical relapse has been observed in relation to dose increase\textsuperscript{63}. Based on preclinical studies, statins anti-cancer potential would be based on their antiproliferative, proapoptotic, radiosensitizing, and lipid profile regulating capacity\textsuperscript{63,68}.

Going back to the ACs role, long duration therapy (between 5 and 7.5 years) is required to obtain chemoprevention benefits in PC and other cancers such as colorectal cancer. In addition, there is a latency period to obtain benefits in terms of cancer onset and mortality, which in the case of PC will be longer than 5 years, probably between 8 and 15 years\textsuperscript{6,9,12,21}. Such latency period has also been proven necessary with acetaminophen (paracetamol)\textsuperscript{69}. On the other hand, intake interruptions would make for all obtained prevention benefit to be lost.\textsuperscript{6} These data suggest the possibility of starting aspirin intake at low doses at 40-50 years of age to prevent PC onset, aggressiveness, and mortality\textsuperscript{10,72}. The dose and duration to obtain the maximum benefit would remain to be elucidated. All this should be counterbalanced with possible related toxicity. There is certain evidence in favor and against a dose-response relationship with the use of aspirin and its beneficial effect, although a recent consensus statement considers benefits to be superior\textsuperscript{7,21}. The use of low doses (75-300 mg/day) versus high doses (>500 mg), continues to prevent cancer incidence and mortality, with a more adequate toxicity profile\textsuperscript{1,7,12,72}. In spite of the use of low-dose aspirin, the incidence of peptic ulcer disease is still 11%\textsuperscript{73}. The risk factors associated with the development of GI bleeding would be the existence of an ulcer or previous GI bleeding, aspirin higher doses, age older than 70 years, NSAIDs and corticosteroids concomitant use and Helicobacter pylori infection\textsuperscript{74}. Therefore, it is necessary bearing in mind GI toxicity prevention by adding proton-pump inhibitors, which have shown efficacy at this point\textsuperscript{74}. On the other hand, a decrease in the risk for intracranial bleeding has been shown with aspirin prolonged use, which contributes with data on long-term safety\textsuperscript{75}.

Its toxic profile, in particular, the risk of severe hemorrhage has limited the use of aspirin in cancer prevention\textsuperscript{76}. This could be counterbalanced by those epidemiological studies that demonstrate that aspirin regular use has protective effects against CVD\textsuperscript{77}.

To conclude, recent findings associate androgen deprivation with an increased risk for the development of colorectal cancer\textsuperscript{78}. To the benefit obtained by continued aspirin intake in terms of PC-related mortality prevention, the fact of counterbalancing the higher risk to develop colorectal cancer would be added in HD-treated patients\textsuperscript{72}. Furthermore, according to some preclinical and clinical studies, it might prevent radio-induced rectitis\textsuperscript{77}, although there are also works that refer an increase in seriousness with its use\textsuperscript{79}.

CONCLUSION

Positive effects of AC, especially of aspirin, have been demonstrated in PC, in terms of incidence, presentation profile, progression velocity, and metastasis development. All this can considerably impact on PC survival, especially considering its high incidence and prevalence as well as aspirin greater effect on high-risk patients. All the above exposed suggests that aspirin might play an important role in PC chemoprevention and treatment, provided the risk/benefit balance of its use would suggest so. Its effect would be added to the therapies established today for high-risk prostate cancer, such as radiaLon and hormonal deprivation. It would consist of a exercise of temporos paLaL cooperaLon, has not yet evaluated, and which if confirmed, has great potential.\textsuperscript{7} mejor que lo que pone ” Its effect would this way add to that of high-risk PC currently established therapies such as radiotherapy and HD. It would constitute a time-spatial cooperation exercise hitherto not assessed that holds if so confirmed great potential. Therefore, randomized trials are warranted to give an answer to these questions. This would require for future investigations to include patients on treatment with radio- tion and HD and to record a series of items related to PC onset, evolution, and mortality such as ACs and/or statins intake, usage time, type, and doses as well other factors that may confound the results such as the diet, daily activity, weight, BMI, smoking, and frequency and type of PC screening.
Aspirin, radiation, and hormone deprivation in prostate cancer

DECLARATION OF INTEREST

The authors declare not having any conflicts of interests.

REFERENCES


REVIEW ARTICLE

Multidisciplinary approach in head and neck cancer

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Received for publication: 14 August 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

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doi:10.24875/j.gamo.M17000071

Abstract This is a review article intended to let the medical community know the procedures regarded as the gold standard in the multidisciplinary approach to patients with head and neck cancer. A review was carried out in PubMed looking for works published between January 2010 and December 2015. The search used the terms “interdisciplinary”, “multidisciplinary”, “management groups”, “clinical rounds”, “tumor boards”, and “head and neck cancer” (n = 57). Subsequently, information related to specific experiences on head and neck was selected and analyzed (n = 29). Relevant information will be presented. In addition, the approach to these neoplasms in Mexico will be described based on the treatment guidelines used by Health Institutions with the largest numbers of patients with this pathology. (creativecommons.org/licenses/by-nc-nd/4.0/).
INTRODUCTION

The purpose of head and neck cancer treatment, as in other neoplasms, is to obtain locoregional control and thereby improve survival. Owing to the anatomical regions involved in this pathology, its treatment has an important impact on patient quality of life in aspects such as ventilation, swallowing, and phonation and the quality of life is therefore of key importance in the therapeutic algorithm. Therapeutic goals in head and neck cancer are as follows: (a) To prevent lesions resulting from procedures intended to aid the patient, (b) to offer efficacious services based on scientific knowledge and avoid therapeutic options without proven benefit, (c) to offer individualized treatment that respects and answers to the patient’s preferences, needs, and values, (d) to offer opportune care, reducing waiting time and harmful delays, (e) to increase services’ efficacy by optimizing the teams, supplies, ideas, and energy, and (f) to offer equitable care without personal, gender, ethnicity, geography, or socioeconomic characteristics having any influence.

With regard to therapeutics, it is important to specify that, at early clinical stages, single treatment either with surgery or radiotherapy (RT) is the cornerstone, and that surgeons, medical oncologists, and radiotherapists are therefore the professionals responsible for tumor control. In patients undergoing surgery, chemotherapy (CT) associated with RT in the adjuvant setting is indicated when there are adverse prognostic factors in the surgical specimen such as resection margins or adjacent involvement, multiple lymph node metastases or when there is lymph node extracapsular dissemination. Concomitant chemoradiotherapy (CTRT), preceded or not by induction CT (ICT), is indicated at locoregionally advanced stages or organ preservation intent, mainly the larynx. In patients with recurrent and/or metastatic carcinoma, CT and best supportive approach are the main options, although local treatments, such as reirradiation and rescue surgery, are also considered depending on the case. The treatment of locally advanced and recurrent and/or metastatic carcinomas has evolved, and important efforts have been made to further improve the outcomes, especially with the addition of new biologics such as those targeting the epithelial growth factor receptor for the management of locally advanced, recurrent, or metastatic disease in concomitance with RT or CT.

The concept of multidisciplinary management (MDM)

MDM is the backbone of high-quality management in the treatment of cancer in general and head and neck cancer in particular. MDM groups are working teams comprised by different health specialists who gather relatively frequently and regularly to prospectively and individually (one by one) analyze together clinical cases to formulate recommendations on the best clinical management. The objective of MDM is to ensure that all patients benefit from a team of specialists able to share their experience, knowledge, and personal insight. Other recently agreed MDM definition is about alliances of medical and health professionals related to a specific tumor disease, whose treatment approach is guided by the willingness to make clinical decisions based on scientific evidence and to coordinate the delivery of care at all stages of the process, encouraging the patients to assume an active role in their own care. MDM team’s objective is to promote better decision-making ensuring that all diagnostic tests, options, and treatment recommendations are the most adequate for each patient. Secondary functions include continuing education, patient quality of care improvement, development of standard guidelines for patient management, and participation in clinical research. MDM-based health-care final goals are to improve local survival with adequate quality of life. MDM can occur through multidisciplinary clinical sessions or tumor boards. In these meetings, several specialists examine patients in a sequential and ordered manner, coordinately carrying out diagnostic procedures and considering treatment options. There are two versions of joint clinical rounds: One where all cases are briefly presented and analyzed and another where only specific complex cases are analyzed in depth. Positive results depend on the presence of qualified professionals, on the preparation and selection of cases, structure of the meeting, experience, efficient leadership, and interactions between the physicians present. MDM strengths are based on its benefits (Table 1). Limitations in the implementation of this approach are related to the requirements of time, space, and material resources. However, there are opportunities to adopt this approach, since there is a need to optimize human and physical resources to decrease health services’ costs. MDM groups are generally composed by a central group, a medical support group, and an administrative support group. In the first case, members include surgical oncologists, medical oncologists, radiation oncologists, pathologists, plastic and reconstructive surgeons, maxillofacial surgeons, palliative care specialists, oncology nurses, and psycho-oncologists. Medical support group members include odontologists, speech therapists, palliative care specialists, nutritionists, social workers, and physiotherapists. The administrative support group includes the MDM team coordinator, a data manager, and ideally, a secretary. Wiederholt et al.4 discussed the role of the oncology nursing unit coordinator with the purpose to reduce differences by means of care continuity, promotion of an interdisciplinary approach, and patient-centered quality of life improvement. Similarly, Leib et al.5 showed that specialist physicians focus their attention mainly on body structures (88%), their functions (76%), and environmental factors (21%); however, several functioning aspects related to daily life activities and socioemotional aspects are not addressed by medical oncologists and must be opportunely treated by other health professionals, members of the MDM team.

International experiences of MDM in the treatment of head and neck cancer

The influence of MDM teams on decision-making has been poorly studied. In general, there are few high-level trials assessing the beneficial effects of MDM teams on quality of care. Wheeles et al.6 determined the efficacy of the MDM team on diagnosis, staging, and treatment plan in a group of patients with head and neck cancer. The study consisted in a prospective analysis of 120 consecutive patients. Prior and after the presentation of each patient to the tumor board,
joint discussions were held on diagnosis, clinical stage, and treatment plan. Approximately 27% of patients had changes in diagnosis, stage, or treatment plan. Change of treatment was significantly more common in cases of malignancy (24% vs. 6%; p = 0.0199). Treatment changes occurred mainly due to MDM addition (p = 0.0084). The study concluded that a multidisciplinary tumor board significantly influences on diagnosis and treatment.

Nguyen et al. conducted a retrospective analysis of 213 patients with locally advanced tumors in a single institution. All treatments were adjusted to MDM team recommendations; 115 patients underwent CT and RT and 98 received post-operative RT. There were no differences in survival, locoregional recurrence, and metastasis between both groups; survival was comparable with the survival rates reported for randomized trials. The study identified the disease site as a determinant factor for treatment selection. The study demonstrated that the MDM approach generated optimal treatment outcomes, with comparable overall survival rates to those reported in randomized clinical trials.

Stalfors et al. assessed MDM quality based on two questions: How many times can diagnosis, classification, and treatment plan be successfully established on a patient's first contact with the MDM team? And what are the reasons for failure? The study concludes that the validity of MDM team-adopted decisions is satisfactory and that telemedicine does not affect the quality of decisions.

Kelly et al. carried out a study intended to determine the impact of MDM care on clinical quality measurable indicators including: Dental and nutritional assessment, access to positron emission tomography (PET) as indicated, CT at III/IV Stages, access to CT in cases of capsular rupture or positive margins, and times between surgery and RT. The study made indicator-adherence comparisons in patients treated prior (pre-MDM) and after MDM (post-MDM). Post-MDM treatment was associated with higher adherence to indicators. Patients with MDM had higher rates of dental assessment (59% vs. 22%; p < 0.0001), nutritional assessment (57% vs. 39%; p = 0.015), PET (41% vs. 2%; p < 0.0001), CTRT in locally advanced disease (66% vs. 16%; p < 0.0001), and adjuvant CTRT in high-risk disease (49% vs. 16%; p < 0.0001). The interval between surgery and RT was shorter in the post-MDM group (p = 0.009), as was hospitalization mean duration (p = 0.002). This study underscores MDM teams' measurable advantages.

Another study assessed the effect of MDM by comparing a group of patients that had had access to MDM (395 patients) with a group without MDM (331 patients). In the group with MDM, patients at Stage IV had significantly higher 5-year survival rates with regard to those who had no access to MDM (hazard ratio [HR] = 0.69; p = 0.004).

Many patients referred to tertiary care centers often arrive with imaging studies that require reinterpretation. Loenner et al. assessed the clinical value of imaging studies reinterpretation in an MDM team. CT scans and MRIs of 136 patients were reinterpreted by a radiologist within the frame of an MDM team. Diagnostic change verification was confirmed by pathology analysis (75%), radiologic findings (18%), or clinical and imaging follow-up (7%). Interpretation changes occurred in 56 patients (41%); in 46 (34%), changes were made in the tumor-node-metastasis classification. Three patients with initial diagnosis of cancer turned out to be misdiagnosed, and six patients were diagnosed with a second primary lesion that was absent in the original diagnosis. Changes in image interpretation modified the treatment in 55 out of 56 patients (98%) and affected the prognosis in 53 (95%; p < 0.001). The study concluded that image reinterpretation by the MDM team has a significant effect on classification, management, and prognosis.

Birchall et al., when comparing the standard care process and 2-year survival between two patient cohorts found higher survival rates in patients treated by an MDM team (HR = 0.7; p = 0.02). On the other hand, Mullan et al. explored the relationship between the time required to dis-
cuss each case, the number of specialists and the type of case. A total of 105 cases were discussed in 10 MDM meetings. Each discussion was timed, and the number of specialists, the diagnosis, and characteristics of each patient were recorded. Times had a 2-min mean (1.8 min), and the discussion was directly related to the number of specialists \( p < 0.001 \). The longest discussions occurred with patients at advanced T-stage \( p = 0.006 \), advanced N-stage \( p = 0.009 \), older age \( p = 0.02 \), and of the male gender \( p = 0.05 \). Histological findings and tumor site were not significant factors in the duration discussions. Most discussions about patients with early clinical stage tumors were short (T1: 58% and ≤60 years, 90-s mean); these patients required little discussion, and their treatment could be reasonably planned according to protocols, leaving more time for those who required further multidisciplinary debate, which implies that the more advanced the stage, the more complex the case will be, and therefore, it will require longer time of discussion.

To date, quality of life assessment has only been a research tool and has not been incorporated to clinical practice. Oates et al.\(^{14}\) coordinated a prospective study to assess the quality of life that included 288 patients, out of which 134 completed the EORTC C30 (QLQ-30) quality of life survey QLQ-H&N head and neck module before treatment and 3, 6, and 12 months after therapy conclusion. The study demonstrated the need to assess the quality of life within an MDM team as part of the care of patients with head and neck cancer.

Rehabilitation planning simultaneously with anti-tumor treatment within an MDM team reduces post-treatment morbidity by shortening rehabilitation and recovery time\(^{15}\). A study assessed the effect of a post-treatment rehabilitation program within the MDM approach \( n = 27 \). The program included 8 weeks of nutritional control, 6-min walks, body weight control, anxiety control, and quality of life assessments at the beginning and the end of the program. Patients improved the walking distance (effect size = 0.8), 78% of patients maintained or increased their body weight, had a significant reduction on insomnia seriousness, pain, anorexia, shortness of breath, depression, and distress, and in general, had their quality of life improved (effect size = 0.6-0.9). To sum up, the interdisciplinary rehabilitation program is beneficial for patients with head and neck cancer\(^{16,17}\).

Head and neck cancer treatment can imply partial or total communication impairment, and a multidisciplinary approach with speech and language therapy (SLT) can help the patient to maximize functionality and establishing when additional supportive methods are required when assessing the MDM effect on SLT compliance. Machin and Shaw\(^{18}\) and Starmer et al.\(^{19}\) found that patients who were initially assessed by multidisciplinary clinical rounds complied better with SLT than those who were not \( p < 0.0001 \).

### National experiences on MDM in the treatment of head and neck cancer

Mexico has different health systems, and each system has reference hospitals, such as the CMN SXXI Oncology Hospital of the Mexican Institute of Social Security (Instituto Mexicano del Seguro Social), the 20 de Noviembre National Medical Center of the Institute of Security and Social Services of State Workers (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado), the State Oncologic Center of the Institute of Social Security of the State of Mexico and Municipalities (Instituto de Seguridad Social del Estado de México y Municipios [ISSEMyM]), and the National Cancer Institute (Instituto Nacional de Cancerología [INCAN]).

Each hospital receives different users; however, medical care provided to cancer patients is in general terms very similar in the different health institutions. Usually, when referred, a patient has to carry out a series of administrative procedures to be admitted into any specialty department to corroborate the diagnosis and start treatment. These procedures include meeting the requirements warranting admission to the institution, suffering from a specific type of tumor pathology and being accepted for admission and treatment, which involves a series of administrative procedures to attend a first-time appointment, undergo a socioeconomic study, have a medical record opened, etc. Some stages of the cancer patient route are as follows: Pre-consultation, performance of studies, results consultation, first-time appointment, socioeconomic study, and medical record number assignment, history taking, the performance of studies, treatment establishment, treatment administration, and follow-up appointments. In the middle of paperwork, the patient can wait from weeks to months to be referred to the specialist of the specific pathology. In addition, the patient will receive treatment according to the experience of the doctor he or she was assigned to leaving out the MDM concept\(^{20}\). Several institutions have made special efforts to foster the practice of MDM and have different MDM approaches in head and neck cancer, which are described in Table 2.

### Management of patients with head and neck cancer at ISSEMyM State Oncologic Center

The patient is referred with a diagnosis of malignancy or suspicion thereof from units of the Institution and/or Seguro Popular (people’s health insurance). He/she is seen in pre-consultation (resident), and general studies, tissue slides review or pathology study are ordered, and history is taken. In the next appointment, approximately 2 weeks later, the patient is received at the functional unit, the case is discussed, and management is decided based on already established guidelines. Some special cases such as vascular tumors are consulted with the hemodynamics area with the ensuing treatment. For patient care, there is support of the anesthesiology, endocrinology, internal medicine, neurology, endoscopy, plastic surgery, maxillofacial prosthetics, and psychology departments. The assessment is carried out by the departments of head and neck oncologic surgery, medical oncology, RT, pain clinic, and palliative care; for supportive studies, there are the departments of imaging, nuclear medicine, laboratory, and pathology. Management is multimodal, and post-treatment follow-up is the area of head and neck oncology; in case the neoplasm is benign, the patient is counter referred. There is participation in study protocols of the institution itself and the pharmaceutical industry in communication with the otorhinolaryngology departments of the institution and occasionally with other oncologic units of the country.
Management of patients with head and neck cancer at INCAN

Initial assessment is made by a physician who is a head and neck tumors specialist. On the same day, history is taken, and the patient’s disease and his/her sociofamilial environment are assessed. On the second appointment, 2-3 weeks later, the diagnosis is corroborated, the extent of disease is evaluated, consultations are reviewed, and treatment is proposed. If the patient is a surgical candidate, programming is
carried out. The patient undergoes surgery, usually 3 weeks later. During this time, nutritional treatment is administered, dental repairs are made, prostheses are prepared, and analgesic treatment is administered. The first post-operative appointment carried out by the treating physician and consulted departments 1 week after hospital discharge. In case multimodal management is required as induction, definitive or post-operative treatment, it is usually started in 2 weeks. According to protocols, if the patient requires post-operative multimodal treatment, the supporting departments normally assess the patient in <2 weeks, which are used for surgical recovery and RT or CTRT planning. Radiotherapists and medical oncologists know treatment and evaluation most appropriate times and observe them. They explain treatment details with regard to times, costs, toxicity, benefits, etc., but the treating physician has already explained the general plan of treatment. During definitive, pre-operative or post-operative treatment, it is usually started in 2 weeks. Patients who are candidates to surgery are programmed, and if necessary, consultations are requested to move the RT appointments forward and obtain the benefit of adjuvant. Patients that by consensus are to receive ICT are scheduled to attend the RT outpatient clinic on the 2nd cycle to program the simulation and initiation 3 weeks after the 3rd cycle. During CT, the patient attends the office every 3 weeks with laboratory tests to assess for toxicity. The RT department initially assesses the patient to inform him/her and his/her family on the treatment and acute and late side effects. During RT, the patient is weekly assessed for the management of acute toxicity. Patient follow-up is carried out by the department of surgical oncology with imaging studies, which, in case of radical management with CT and/or RT, are requested 12 weeks after treatment conclusion, every 3 months on the first 2 years, and every 6 months thereafter.

Management of patients with head and neck cancer at CMN SXXI

At initial assessment patients are divided into two groups, these whose therapeutic decision does not depend on a consensus and those in whom treatment is controversial. In the first group, treatment decision is made on the second appointment. Most patients belong to the second group, where the decision is by consensus. Guidelines that usually are followed include: In locoregionally advanced oral cavity cancer, concomitant CT and RT or ICT followed by a clinical assessment to decide if surgery enabling downstaging was achieved. In oropharyngeal cancer, CT associated with RT, upfront cervical surgery and adjuvant CTRT, or RT based on stage and HPV status, or concomitant CTRT. In very advanced disease without HPV expression, the possibility of ICT is discussed. Laryngeal cancer: In patients with localized tumors, factors that even at initial stage may imply a poor prognosis such as total cord tumor extension, anterior commissure infiltration and epilaryngeal localization are assessed by the multidisciplinary board for surgical conservative treatment or nonsurgical, conservative treatment. In patients with locally advanced tumors but with functional organ, the board assesses both conservative treatments, and in patients in whom there is no laryngeal function, total laryngectomy is performed, with the voice being rehabilitated by means of speech therapy or prosthesis; for this purpose, patients are previously evaluated by speech therapy personnel. Patients with tumors at the base of the skull are assessed in a joint and multidisciplinary form. Patients with the persistent or metastatic disease, those who have failed to previous therapies, deserve to be mentioned apart. They are jointly assessed by surgeons, plastic surgeons, radiotherapists, and medical oncologists to decide the best way to offer rescue therapy. Pain and nutritional status assessment are offered.

Management of patients with head and neck cancer at CMN 20 de Noviembre

The patient attends the MDM session with the purpose to be examined and to define the best management option based on his/her condition and clinical guidelines. A clinical summary of the case is presented along with imaging studies, the clinical consensus is reached, and the patient and family companion are informed on management decision, side effects, and treatment sequence. In some cases, patients are referred to the maxillofacial prosthesis department for devices to be made or for prophylaxis or dental extractions; in others, imaging studies or complementary biopsies have to be obtained and an appointment for a new assessment is set in 2 weeks. Patients who are candidates to surgery are programmed, and if necessary, consultations are requested to move the RT appointments forward and obtain the benefit of adjuvant. Patients that by consensus are to receive ICT are scheduled to attend the RT outpatient clinic on the 2nd cycle to program the simulation and initiation 3 weeks after the 3rd cycle. During CT, the patient attends the office every 3 weeks with laboratory tests to assess for toxicity. The RT department initially assesses the patient to inform him/her and his/her family on the treatment and acute and late side effects. During RT, the patient is weekly assessed for the management of acute toxicity. Patient follow-up is carried out by the department of surgical oncology with imaging studies, which, in case of radical management with CT and/or RT, are requested 12 weeks after treatment conclusion, every 3 months on the first 2 years, and every 6 months thereafter.

Head and neck functional units

The oncology functional units (OFUs) are cross-sectional management and service provision models based on multidisciplinary teams, where experts in a particular neoplastic disease, in this case those originating in the head and neck area, share time and space to design the best diagnostic and therapeutic strategy as well as to facilitate the relationship of the patient with the hospital setting since the first visit. The OFU vision is to continuously improve quality of care by facilitating faster diagnosis with correct staging of the disease, to provide the best oncologic treatment and to reduce concomitant morbidity to the minimum. Among the OFUs benefits, the following deserve to be mentioned: Decrease of the diagnosis - treatment interval, facilitating specialists’ interaction, standardization of criteria, simplification of medical and administrative attention, standardization of information to the patient, cost reduction, and improvement of working environment.

In the management of the OFUs organizational model, the participation of all oncology specialists as well as medical supporting specialists, paramedical areas, administrative area, residents on training, nursing personnel and social work is essential. Assessment must be performed in physical space designed for this purpose, with the generation of research protocols being also assessed. In practical terms, having a coordinator, making the diagnostic evaluation, identifying necessities, multidisciplinary work, and finally, the therapeutic decision should be contemplated. The general plan includes making an initial appointment at the pre-consultation area where the patient will be seen by the area’s doctor, residents, and nurses, with initial staging being made and related laboratory, imaging, and pathology tests being ordered. Subsequently, an appointment is scheduled at the functional unit, where its team members will
analyze and review the case and provide the diagnosis and treatment proposal as well as the sequence of the patient across the different oncology areas. In case any kind of specialist consultation is required, it will be done through the functional unit itself after clinical summary. As an example of head and neck tumors functional unit, there is the University Hospital of Girona and the Catalan Institute of Oncology, with the latter having completed its first 2 years functioning with more than 1500 patient consultations, out of which 217 were first-time appointments and the rest control visits.

Recently, the European Partnership for Action Against Cancer published a consensus on MDM policy, which focused on five organizational components: (a) Definition of clear objectives of diagnostic and therapeutic care agreed by the MDM team and the patients; (b) establishment of leadership and operative coordination together with inclusion of points of contact with patients and reservation of health professionals time and resources to participate in MDM meetings; (c) implementation of databases about decisions, results, and MDM performance indicators that facilitate assessment of the process and identification of areas for improvement; (d) patient-centered approach, with available and understandable information on clinical and psychosocial aspects of the process of care, unification of communication channels between the health-care team and the patient and participation promotion; and finally, (e) consolidation of supportive policies by national and regional health authorities, scientific societies and patient associations, with special attention to the inclusion of mechanisms to establish and maintain MDM schools. Owing to the increase in cervical-facial cancer prevalence, and to the complexity that has developed over the past 10 years for its treatment, clinics or units highly specialized on this neoplasm are with no doubt the best alternative to reduce the number of therapeutic decision mistakes and to increase treatment success, thus improving survival and quality of life.

CONCLUSIONS

The care of patients with head and neck cancer in the different health institutions in Mexico is similar with minimal differences. The trend in our country is to integrate attention boards for initial assessment of these patients. The multidisciplinary team grouped in a functional unit ensures that professional efforts are opportune and correctly coordinated in an environment of continuous discussion between peers. This approach implies care centralization, which benefits diagnostic-therapeutic outcome for patients, and hence, their quality of life. Based on the complexity the diagnosis and treatment of patients with cancer originating in the head and neck area implies, the gold standard for assessment and therapeutic decision should be based on peer discussion in a joint clinical round or multidisciplinary board. Finally, and in addition, a spirit of communication, cooperation, and mutual respect are the basis to obtain the best possible care to the benefit of patients and members of the health system.

DECLARATION OF INTEREST

The authors declare not having any conflicts of interests.

REFERENCES

CASE REPORT

Alveolar rhabdomyosarcoma of nasal presentation: Case report

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Received for publication: 30 January 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

Abstract Sarcoma is a malignant tumor originating in mesenchymal primitive cells that in normal circumstances develops in supportive tissues such as muscle and bone. There are three rhabdomyosarcoma variants according to its histological presentation: Embryonal, alveolar, and pleomorphic with alveolar rhabdomyosarcoma being the most aggressive. The case is presented of an 8-year-old male patient who started with a progressively growing left nasal wing 3-4 mm mass with no color change diagnosed as an alveolar rhabdomyosarcoma with pathology documenting a small round blue cell tumor with positive immunohistochemistry to desmin and myogenin. Skull and face magnetic resonance, chest computed tomography, and bone marrow aspirate were negative for disease extension. The lesion was macroscopically resected at 100%, with pathology reporting isolated tumor foci, with microscopic residual tumor on lateral margins, and it is therefore finally classified as E II. This is a very rare neoplasm with an unusual presentation, with only 4 cases reported in the literature, hence, the importance of taking into account this diagnostic possibility as well as the knowledge on how to approach it.

Key words
Alveolar rhabdomyosarcoma; Nasal; Multidisciplinary; Sarcoma; Pediatric age

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INTRODUCTION

Sarcoma is a malignant tumor originating in primitive mesenchymal cells that under normal circumstances develops in supportive tissues such as muscle and bone. Since skeletal muscle cells are present in most part of the body, this malignancy can occur on almost any anatomic location.

There are three variables of rhabdomyosarcoma according to its histological presentation such as the embryonal type with its variants botryoid and spindle-shaped cells, alveolar (including the solid alveolar variant), and pleomorphic. Alveolar rhabdomyosarcoma is the most aggressive, it occurs more commonly in adolescents and young adults, and accounts for 20% of all rhabdomyosarcoma cases, generally with onset on the torso and limbs.

Annual incidence of rhabdomyosarcoma in 20-year-old or younger individuals is 4.3 cases per millions of children, with approximately 350 new cases diagnosed in the US every year. Of the tumors occurring in head and neck structures, almost 40% correspond to rhabdomyosarcomas.

Anatomically, they are classified as parameningeal, orbital, nonparameningeal, and nonorbital; parameningeal sites include the nose, paranasal sinuses, nasopharynx, middle ear, mastoid process, infratemporal fossa, and pterygopalatine fossa. In nearly 90% of cases, chromosomal translocations are appreciated in genes PAX3 (2q33) FKHR/ALV (13q14), and less commonly in PAX7 (1p36) KHR/ALV (13q14).

The purpose of the present article is to describe the case of a patient with Stage II nasal alveolar rhabdomyosarcoma, which is a rare neoplasm in our country and worldwide and worthy of a comprehensive literature review with regard to multidisciplinary treatment, to begin with, the participation of radiologists, well-trained pathologists familiarized with pediatric tumors and surgeons as well as oncologists specialized in the treatment of this neoplasm.

CASE REPORT

This is the case of an 8-year-old boy without a family history of cancer. His ailment started on December 2014 with a progressively growing 3-4 mm swelling without color change on the left nose wing. When the mass reached 2.5 cm × 2.5 cm in size, the boy was brought to the dermatologist, who classified it as a hemangioma and started management with topical hydrocortisone for 10 days.

The boy was seen on March 28, 2015, with the same red wine color lesion, which reached the upper third of the nose and covered the entire left nasal wing and was fixed, hard, painless, and indurated, with collateral circulation, without regional lymph node involvement, or visceral growth (Fig. 1). In view of the diagnostic uncertainty, a biopsy was taken on April 7, 2015, with pathology reporting a small round blue cell tumor with positive immunohistochemistry to desmin and myogenin (Figs. 2 and 3), which was finally characterized as primary alveolar rhabdomyosarcoma of the skin.

Skull and face magnetic resonance imaging, chest computed tomography, and bone marrow aspirate were negative to tumor extension (Fig. 4). Since the lesion was unresectable, debulking chemotherapy was started on May 3, 2015, with VCR, IF + Mesna and VP-16, weekly the former, every 3 weeks both the latter (VIE) with VCR for 9 weeks and 3 IF, and VP-16 cycles and with very good response, since the boy’s tumor was reduced in size and remained at
2.5 cm × 2 cm with even color to the boy’s skin and with 60% reduction in volume (Fig. 5). On July 21, 2015, the lesion was 100% macroscopically resected (Fig. 6), but the pathology report indicated isolated tumor foci with lateral margins microscopic residual tumor, and the lesion was finally classified at Stage II. Owing to the permanence of residual disease, and to the fact that it was an aggressive histological variety, the patient was referred for radiotherapy to the primary site.

He received CT with weekly VIE alternating with VAC every 3 days for 3 weeks and VAC + IF and EF every 3 weeks twice with the treatment concluding on July 21, 2016.

**DISCUSSION**

Rhabdomyosarcoma is an extremely rare malignant tumor that accounts for 0.4-1.0% of all soft tissue sarcomas. These tumors usually occur in adolescents or young adults’ lower limbs with rhabdomyosarcoma of the nasal or paranasal region even being more unusual. Rhabdomyosarcomas are generally divided in meningeal and parameningeal sites with parameningeal sites including the middle ear, nose cavity, paranasal sinuses, nasopharynx, and the infratemporal fossa. There are only 4 cases reported in the literature, with this malignancy being more common in females than in males at a 2:1 ratio.

In general, it is a slowly growing, well-vascularized mass, with no clinical characteristics suggesting malignant disease. When it occurs in the nasal cavity, the nasal obstruction can be the only symptom.

Different histological types of rhabdomyosarcoma of head and neck region have been identified, including embryonal, alveolar, and pleomorphic rhabdomyosarcoma. Embryonal and alveolar patterns are the most common. Histologically, embryonal rhabdomyosarcoma is comprised by primitive round spindle-shaped cells with rhabdomyoblasts, whereas alveolar rhabdomyosarcoma consists of malignant cells grouped in fibrovascular septae that form alveoli-like spacings.

Poorly differentiated rhabdomyosarcomas can be difficult to distinguish from poorly differentiated Ewing sarcoma or neuroblastoma. Tumors with a high predominance of fusiform cells can be confused with leiomyosarcomas, fibrosarcomas or malignant fibrous histiocytomas. Immunohistochemically, intermediate filaments specific to muscle cells such as myoglobin, myosin, desmin, and creatine kina-
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se MM isoenzyme are regarded as rhabdomyosarcoma-specific markers.

Microscopically, tumor cells tend to be smaller and rounded, offering a densely cellular appearance, and they are named after the similarity they show with the tiny air sacs within the lungs, and therefore, they are often included in the round, blue cells classification, where malignant lymphoma, neuroblastoma, and synovial sarcoma (biphasic) often stand out as differential diagnoses.

In spite of tumor slow growth, the prognosis is generally poor and depends on a combination of patient age, histological nature, clinical stage, and tumor location, with a high tendency toward early metastatic spread. Prognostic variables identification depends on different groups of patients with excellent, very good, fair, and poor prognosis; on the site (favorable vs. unfavorable, with the orbit being the most favorable site); surgical respectability (Groups I and II vs. Group III); histology (embryonary vs. alveolar); and age, with intermediate grade alveolar rhabdomyosarcoma showing 40-50% prognosis.

CONCLUSIONS

The article represents a case report of an alveolar rhabdomyosarcoma nasal presentation. We might conclude that the approach should be multidisciplinary and individualized.

DECLARATION INTEREST

The authors declare not having any conflicts of interest.

REFERENCES

CASE REPORT

Cutaneous melanoma single metastasis to the pancreas: Results of combined treatment with surgical resection and immunotherapy

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Received for publication: 31 August 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

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doi:10.24875/j.gamo.M17000073

Abstract Metastatic melanoma to the pancreas was first described in 1931. Pancreatic metastasis occurs commonly in patients with diffuse disease with solitary metastasis being quite rare. The role of pancreatic metastasectomy in patients with malignant melanoma is currently not defined because there are very few available reports. The case is reviewed of a 54-year-old male patient with a history of left thigh Stage IIIC malignant nodular melanoma. After 11-month follow-up, a single metastasis to the head of the pancreas was detected. To improve our understanding on these lesions, a case treated with pancreatic resection in our hospital is described. Here, clinical features of presentation, treatment and follow-up are discussed, along with a literature review. Most authors recommend surgery as the treatment of choice for pancreatic metastases that are amenable to resection since it appears to be the only treatment able to prolong survival, although there are no large studies fully demonstrating this assumption. This review suggests that, in a patient with favorable tumor characteristics, surgery should be considered a viable treatment option, but studies have to be conducted with larger numbers of patients. (creativecommons.org/licenses/by-nc-nd/4.0/).
CLINICAL CASE

The case is reviewed of a 54-year-old male Caucasian patient who was native of Germany and resident of Mexico since 14 years prior. He was vegetarian and had no history of chronic diseases. He had a 2-year history of a left thigh ulcerated malignant nodular skin melanoma with 6.5 mm Breslow’s depth, Clark level 5 and 3 mitoses per mm, treated with wide resection of the lesion plus inguinal lymphadenectomy, with seven positive lymph nodes. It was classified as Stage IIIIC due to pN3. Subsequently, the patient received adjuvant radiotherapy (RT) to the inguinal region at 50 Gy in 20 fractions with a 6 MV photon beam linear accelerator using the volumetric modulated arc therapy technique. A follow-up positron emission tomography-computed tomography (PET-CT) 2 months after the surgical event reported a SUVmax increase of 5.8 in soft tissue heterogeneous zone, in addition to, the right inguinal canal prominence with SUVmax of 4 associated with inflammation (Fig. 1). The patient was considered to be a candidate to adjuvant treatment with interferon alpha 2b at 10 million units (MUs) doses Monday through Friday for 4 weeks, and subsequently, at 10 MU 3 times a week for 12 months. After 11-month asymptomatic follow-up, a control abdominal CT scan documented main pancreatic duct dilatation caused by a small tumor mass; lipase and amylase were higher than 2000 IU, and there was no hyperbilirubinemia (Fig. 2). A new PET-CT documented a solid tumor on the head of the pancreas with SUV of 8. An endoscopic ultrasound demonstrated a 10 mm × 7 mm lesion on the head of the pancreas close to the neck. A fine-needle aspiration biopsy establishes the diagnosis of malignant neuroendocrine tumor (Fig. 3); tumor markers were negative (carcinoembryonic antigen and carbohydrate antigen 19.9), there was no carcinoid syndrome, and chromogranin A and 5-hydroxyindoleacetic acid were negative. Studies for disease extent were negative. A pancreatic scintigram with octreotide reported tumor activity only in the pancreatic head, and the lesion was classified as a second primary tumor. The patient underwent pancreaticoduodenectomy without pyloric preservation with no complications. Transoperatively, a tumor was found in the neck of the pancreas, solid on palpation and of approximately 1.5 cm in size, which caused important dilatation of the duct of Wirsung (Fig. 4); lymph nodes were macroscopically negative. The patient was dis-

Figure 1. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography 2 months after initial treatment with report of SUVmax increase of 5.8 in soft tissue heterogeneous zone in addition to the right inguinal canal prominence with SUVmax of 4 in association with inflammation, with no additional distant lesions being appreciated.

Figure 2. Double-contrast helical tomography of the abdomen 11 months after initial treatment, where main pancreatic duct dilatation is observed, caused by a small tumor mass; a second primary lesion is suspected.
charged 9 days after the surgical event due to improvement. The pathology report determined metastatic melanoma of 1.2 cm × 0.9 cm × 0.9 cm in size, located at the pancreatic neck, with negative margins, tumor necrosis, and presence of lymphatic, vascular and perineural invasion (Fig. 5); all lymph nodes were negative for metastatic disease. The diagnosis was corroborated by immunochemistry studies: S-100 protein, HMB-45, MART-1, and tyrosinase were positive.

The patient evolved satisfactorily with 2-month follow-up free of symptoms and no evidence of relapse in other sites. Since BRAF V600 tested negative, starting management with ipilimumab was decided. 12 months after treatment completion, the patient is on surveillance, asymptomatic and with no evidence of disease progression.

**DISCUSSION**

Isolated metastasis to the pancreas from another primary tumor is quite rare (<2%)

![Figure 1](image1.png)  
*Figure 1. Endoscopic ultrasound and fine-needle aspiration biopsy. In image a, the tumor is appreciated; image b shows the moment the fine-needle biopsy is taken; image c shows the relationship with the portal vein and the common bile duct; and image d shows the tumor with the main pancreatic duct obstruction, which appears dilated.*

![Figure 2](image2.png)  
*Figure 4. Macroscopic image of the specimen, where (A) a 1.2 cm × 0.9 cm × 0.9 cm lesion, with malignant neoplastic aspect, ovoid-shaped, with lobulated, pushing borders, hard in consistency, and black color is identified (red circle) at the neck of the pancreas. It is located at 1.5 cm of the pancreatic surgical margin. On the right (B), a tumor extension is appreciated; the main pancreatic duct, which appears dilated, is also appreciated (red arrow).*
with 5-year survival lower than 10% and median survival of 6-9 months. Nevertheless, several retrospective studies have suggested a survival increase after pancreatic metastasis complete resection, which generates great interest on this approach. However, there is very little literature on pancreatic resection for metastatic melanoma. Pancreatic metastases occur only in 2% of resectable metastatic disease cases. Primary tumors that most commonly metastasize to the pancreas are breast, lung, kidney, and colon tumors and less frequently, melanoma and sarcoma. Metastatic melanoma to the pancreas was first described in 1931. Pancreatic metastases commonly occur in patients with diffuse disease. Single metastasis is quite rare, and it has been described mostly in primary ocular melanoma. On the other hand, metastatic melanoma has an unfavorable prognosis: 5-year survival for patients with a single metastasis is 12% (median survival of 11 months), whereas 5-year survival with multiple metastases is 0% (median survival of 4 months). After single metastasis complete resection, 5-year survival shows a significant increase to 18%, with a median survival of 15 months. Survival is dependent on the site of distant metastasis; patients with visceral involvement have less favorable results than those with soft tissue involvement or distant lymph node relapse. In a retrospective study of 49 cases at the Johns Hopkins Hospital in patients with metastasis to the pancreas, the three patients with metastatic melanoma had worse prognosis. The role of pancreatic metastasectomy in patients with malignant melanoma is currently not defined because there are very few available studies. Traditionally, metastasectomy was deemed useless owing to a bad prognosis associated with highly extended disease. However, some patients with limited metastatic disease are able to survive for a reasonable period after surgery, and there are even reports of cure. This, together with an improvement in operative risk associated with the procedure demonstrated by many groups, has led to a renewed interest in surgical treatment of metastatic melanoma. Most authors recommend surgery as the treatment of choice for pancreatic metastases that are amenable to resection since it appears to be the only treatment able to prolong survival. In addition, pancreatic metastases seem to have a higher resectability index in comparison with pancreatic adenocarcinoma, owing to the fact that metastatic lesions borders tend to be better defined. For patients with unresectable lesions, surgery still offers good palliation with the quality of life improvement and very low associated morbidity. However, the role of surgery for melanoma metastases to the pancreas is less clear, since there is very scarce literature available demonstrating a survival advantage. In one series, 5-year survival of patients with multiple metastases was improved from 23% to 37.5% with surgical treatment in selected patients. Median disease-free interval (DFI) in these patients was 24 months. In another series involving four patients, two had died at 25-month follow-up, and two were still alive at 30 and 76 months. The patients who survived were observed to have a DFI of 4 and 14 years, respectively. However, other studies fail to show a significant survival improvement after surgery. Patient survival appears to depend on two main factors: The capability to completely resect the metastases, which makes for the patient to remain disease-free and a prolonged DFI. A DFI increase is thought to be the result of more favorable tumor biology, where tumor cells are less aggressive, slower to divide, and less likely to metastasize. Unfortunately, currently, there is no effective non-surgical treatment, and the role of adjuvant chemotherapy and immunotherapy is under study.

CONCLUSION

Studies suggest that, in a patient with favorable tumor characteristics, discernible by DFI length and complete resection of a solitary metastatic lesion, surgery should be considered as a viable treatment option, but these results have to be corroborated with larger studies.

DECLARATION OF INTEREST

The authors declare not having any conflicts of interests.

REFERENCES