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Chemotherapy for locally advanced and metastatic pulmonary carcinoid tumors

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ABSTRACT

Objectives: The optimal management of locally advanced and metastatic pulmonary carcinoid tumors remains to be determined.
Materials and methods: A retrospective review was conducted on patients with typical and atypical pulmonary carcinoid tumors treated at our institutions between 1990 and 2012.
Results: 300 patients were identified with pulmonary carcinoid, (80 patients with atypical carcinoid), of whom 29 presented with metastatic disease (16 atypical). Of evaluable patients, 26 (41%) with stages I–III atypical carcinoid tumors recurred at a median time of 3.7 years (range, 0.4–32), compared to 3 (1%) patients with typical carcinoid (range, 8–12.3). 39 patients were treated with chemotherapy, including 30 patients with metastatic disease (27 atypical), and 7 patients were treated with adjuvant platinum–etoposide chemoradiation (6 atypical, 1 typical, 6 stage IIIA, 1 stage IIB). At a median follow-up of 2 years there were 2 recurrences in the 7 patients receiving adjuvant treatment. Median survival after diagnosis of metastatic disease for patients with atypical pulmonary carcinoid was 3.3 years with a 5-year survival of 24%. Treatment regimens showing efficacy in pulmonary carcinoid include 15 patients treated with octreotide-based therapies (10% response rate (RR), 70% disease control rate (DCR), 15 month median progression-free survival (PFS)), 13 patients treated with etoposide + platinum (23% RR, 69% DCR, 7 month median PFS), and 14 patients treated with temozolomide-based therapies (14% RR, 57% DCR, 10 month median PFS). 8 of 10 patients with octreotide-avid disease treated with an octreotide-based regimen experienced disease control (1 partial response, 7 stable disease) for a median of 18 months (range 6–72 months).
Conclusions: These results support our previous finding that a subset of pulmonary carcinoid tumors are responsive to chemotherapy.

1. Introduction

Patients with pulmonary carcinoid tumors comprise approximately 2% of all primary lung cancers [1], and the relative rarity of these tumors complicates efforts to effectively plan the therapy of patients with locally advanced or metastatic cancer. Pulmonary carcinoid tumors are defined by their typically bland cytomorphology and neuroendocrine features on histologic examination, and immunohistochemical staining for chromogranin, neural cell adhesion molecule (CD56), or synaptophysin [2]. A spectrum of pulmonary neuroendocrine tumors is thought to exist, with carcinoid tumorlets and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) representing less aggressive forms of the neuroendocrine spectrum, and small cell lung cancer the most malignant [2]. Typical carcinoid tumors behave in a more

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indolent fashion compared to atypical carcinoid tumors, which have a greater propensity for dissemination at the time of presentation and the subsequent development of metastasis. The pathologic criteria that distinguishes typical from atypical carcinoid tumors were proposed by Travis et al., in 1998, and has been widely adopted [3]. Typical carcinoids are distinguished from carcinoid tumorlets by a size larger than 0.5 cm, and have a mitotic rate of <2 mitoses/10 high power field (HPF) with no necrosis [2]. Atypical carcinoids, in contrast, have a mitotic rate of 2–10 mitoses/10 HPF or the presence of necrosis.

Patients with typical carcinoids have an excellent prognosis, with 5- and 10-year survival rates of 85% reported [4]. Atypical carcinoids have a more aggressive course, with 5- and 10-year survival rates in the range of 35–44%, due to a greater frequency of patients presenting with advanced stage and more frequent recurrence [4]. While metastatic disease is rarely reported for typical carcinoid tumors, atypical carcinoid tumors do metastasize in approximately 30–40% of reported cases, with the liver, bone, and brain being the most common sites [4]. Treatment of patients with typical carcinoids has centered on resection, and the vast majority of patients in case-series remain recurrence free for years, and even decades, with little information on systemic treatment [5–7].

The more aggressive nature of atypical carcinoid tumors compared to typical carcinoid tumors prompted investigators to administer adjuvant chemotherapy for high-risk disease (i.e. stage IIB/IIIA) based on data showing a response rate of 20% to any chemotherapy [8], although this approach has been questioned by others who feel the role of systemic treatment is limited [9]. Regimens showing antitumor activity against pulmonary carcinoid tumors include octreotide [10], doxorubicin/capecitabine [11], everolimus + cisplatin [12], everolimus + octreotide [13], and etoposide + cisplatin [8]. The efficacy of adjuvant treatment for stages II and III resected typical and atypical carcinoid tumors is extrapolated from these response rates in metastatic disease, and the efficacy of adjuvant chemotherapy in resected stage II and III non-small cell lung cancer trials [14–16]. While patients with pulmonary carcinoid tumors have been included in large-scale studies of neuroendocrine tumors [17], very little data exist on the role of chemotherapy in locally advanced typical or atypical metastatic pulmonary carcinoid tumors.

To further define the role of chemotherapy and adjuvant treatment of pulmonary carcinoid tumors, this retrospective study of patients with atypical and typical carcinoid tumors treated at our institutions between 1990 and 2012 was undertaken. This study updates our 2004 effort which demonstrated that pulmonary carcinoid tumors can respond to chemotherapy [8].

2. Materials and methods

This study was approved by the Dana-Farber/Harvard Cancer Center institutional review board. Patients with pulmonary carcinoid tumors were identified in the Brigham and Women's Hospital pathology database, and the Tumor Registry and radiation oncology databases of the Dana-Farber Cancer Institute using the search terms: pulmonary carcinoid, bronchial carcinoid, and lung carcinoid. Approximately 800 records from 1990 to 2012 were reviewed, and those that included (1) a diagnosis of typical or atypical pulmonary carcinoid, and (2) treatment with chemotherapy or surgery, are presented. Records were crosslinked to patients reported in our previous study [8], under which tumor samples that predated the 1999 update in the WHO criteria were re-examined. Patients with pathology reports that failed to mention the number of mitoses and/or the presence/absence of necrosis underwent further pathologic review by a pulmonary pathologist (LS) to classify the tumor as typical or atypical carcinoid. Using these criteria, 300 patients are included in our study.

Data from the medical records was reviewed and entered into a computer database by a single investigator (CRC), including gender, age, smoking status, presenting symptoms, date of diagnosis, stage, site of presentation, date of documented metastatic disease, treatment, response to treatment, time to progression, last time of follow-up, and date and cause of death. The duration of survival for early stage disease was determined from time of first diagnosis to the date of last follow-up or death as ascertained from the medical record or the Social Security Death Index. The duration of survival for patients with metastatic disease was determined from date of documentation of metastatic disease to date of last follow-up or death as ascertained from the medical record or the Social Security Death Index. The results of imaging studies (i.e. PET CT and/or octreotide scans) and specialized lab studies (i.e. serum chromogranin and urinary 5-HIAA) were included if studied and reported in the medical record. Disease control is defined as patients who achieve a complete/partial response or stable disease (minimum of 2 months) with treatment. The imaging studies were reviewed by a board-certified thoracic radiologist (MN) to determine response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria if pretreatment and post-treatment scans were available. Progression for patients in whom pre/post-treatment scans were unavailable was determined based on notes in the medical record. Sites of metastatic disease were noted on scans after disease progression as documented in radiology reports.

3. Results

3.1. Patient characteristics

The characteristics of patients represented in this study are presented in Table 1. Patients with pulmonary carcinoid presented at a median age of ~60 years and were predominantly women. Of patients with atypical or typical carcinoid, 48% and 41% had a smoking history, respectively. The most common reason for diagnosis was an unusual finding on chest radiograph or CT performed for other reasons in a patient who did not have any pulmonary symptoms directly related to the tumor. The next most common symptomatic presentation for both typical and atypical carcinoids were cough and recurrent pneumonia. Many of the presenting symptoms were non-specific, and included chest/back/shoulder pain or dyspnea. Symptoms of carcinoid syndrome, which are commonly seen with GI carcinoids, such as flushing were observed in 4 patients with atypical pulmonary carcinoid (5%) and in no patients with typical pulmonary carcinoid. Pulmonary carcinoid has been associated with Cushing syndrome and multiple endocrine neoplasia [18,19]. Typical carcinoid was diagnosed during workup of these diseases in 7 patients.

3.2. Diagnostic evaluation

Carcinoid tumors can produce neuroendocrine secretory proteins such as chromogranin and metabolites such as 5-hydroxyindoleacetic acid (5-HIAA) that can enter the circulation and produce symptoms such as flushing, palpitations, and diarrhea. When tested, the chromogranin level was elevated in 20 of 33 patients (61%) with atypical carcinoid, compared to 11 of 32 patients (34%) with typical carcinoid. The urinary 5-HIAA level was elevated above the limit of normal (>8 mg/24 h) in 15 of 33 patients with atypical carcinoid (46%), and in none of the patients with typical carcinoid. Of patients with metastatic atypical carcinoid, the chromogranin level was elevated in 14 of 19 (74%) and the urinary 5-HIAA level was elevated in 12 of 19 (63%). Significantly, of the 4