

Systemic Therapy, Clinical Outcomes, and Overall Survival in Locally Advanced or Metastatic Pulmonary Carcinoid

A Brief Report

Patrick M. Forde, MD,* Craig M. Hooker, MPH,† Sosipatros A. Boikos, MD,* Iacope Petrini, MD,§ Giuseppe Giaccone, MD,§ Charles M. Rudin, MD, PhD,* Stephen C. Yang, MD,† Peter B. Illei, MD,‡ Christine L. Hann, MD, PhD,* David S. Ettinger, MD,* Julie R. Brahmer, MD,* and Ronan J. Kelly, MD, MBA*

Background: Data to guide the management of advanced pulmonary carcinoid (APC) come from retrospective reports and subgroup analyses of trials that included mainly extrapulmonary carcinoid tumors. We report the largest series to date of 49 patients with locally advanced or metastatic pulmonary carcinoid.

Methods: The Johns Hopkins Pathology Database was reviewed for APC patients treated between January 1992 and December 2012. Data on time to recurrence, progression-free survival, and overall survival were estimated by using the Kaplan–Meier method.

Results: Forty-nine patients were treated for APC in the specified time period. Median time to recurrence after surgical resection was 2.5 years (atypical carcinoid [AC] versus typical carcinoid [TC], 2.5 versus 6.3 years; $p = 0.063$). Median survival with advanced disease was 7.1 years and significantly longer for TC compared with AC (10.2 versus 4 years; $p = 0.009$). Among the diverse systemic therapies used, responses occurred in four of 17 patients (23.5%) who received platinum/etoposide with a median progression-free survival of 7 months.

Conclusion: Although systemic chemotherapy has moderate activity for APC, novel approaches are required. TC and AC, although both classified as pulmonary carcinoid, are clearly different clinical and molecular entities and require separate treatment paradigms in the advanced/metastatic setting.

Key Words: Pulmonary carcinoid, Metastatic carcinoid, Chemotherapy pulmonary carcinoid, Chemotherapy bronchial carcinoid, Therapy carcinoid, Atypical carcinoid, Typical carcinoid.

(*J Thorac Oncol.* 2014;9: 414–418)

Departments of *Medical Oncology, †Surgery, and ‡Pathology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland; and §Medical Oncology Branch, National Cancer Institute, Bethesda, Maryland.

Disclosure: David S. Ettinger, MD, has served in a consultant or advisory role for Boehringer-Ingelheim GmbH, Eli-Lilly & Co, and Roche/Genentech. The other authors have no relevant disclosures.

This study was presented, in part, at the American Society of Clinical Oncology Annual Meeting, Chicago, IL, May 31 to June 4, 2013.

Address for correspondence: Ronan J. Kelly, MD, MBA, Johns Hopkins University, Cancer Research Building 1, 1650 Orleans Street, Room G93, Baltimore, MD 21287. E-mail: rkelly25@jhmi.edu

Copyright © 2013 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/14/0903-0414

The incidence of pulmonary carcinoid (PC) tumors has increased during the last 30 years in part because of a combination of asymptomatic tumors being incidentally noted on chest imaging and the use of more rigorous histological diagnostic criteria.^{1–3} PC tumors represent 1% to 2% of all lung malignancies and approximately 25% of all carcinoid tumors originate in the lung.^{3,4}

PC tumors are divided into typical carcinoid (TC) and atypical carcinoid (AC) and are classified as foregut neuroendocrine tumors (Table 1).^{1,2} Although the majority of TCs are cured by surgical resection, AC represents a more aggressive phenotype with frequent recurrences being reported.

METHODS

This retrospective cohort study included all patients referred to Johns Hopkins for the management of advanced (unresectable, locally advanced, or metastatic) PC between January 1, 1992 and December 31, 2012. All patients' tumor specimens were reviewed by the Johns Hopkins pathology department and confirmed as PC. Data on time to recurrence, progression-free survival (PFS), and overall survival were estimated by using the Kaplan–Meier method and log-rank test comparing TC and AC.

RESULTS

Patient and Disease Characteristics

Patient characteristics are listed by histologic subtype in Table 2. Forty-nine patients were included in this series; of these, 32 had AC and 17 had TC. The median age at diagnosis of advanced PC (APC) was 56 years (range, 28–79), and 61% of patients were women. At a minimum, all patients were initially staged and followed with regular computed tomography scans of chest and abdomen. The majority of patients (53%) were never smokers. Median follow-up was 54 months (range, 10–183+). Most patients had metastatic disease (83.7% versus 16.3% with locally advanced disease only), and the commonest sites of metastases throughout the course of the disease were liver (59.2% of patients), mediastinum or contralateral lung (36.7%), bone (36.7%), and central

TABLE 1. WHO/IASLC Classification of Pulmonary Neuroendocrine Tumors

Grade	Nomenclature	Histopathologic Characteristics
Low	Typical carcinoid	Carcinoid morphology, less than two mitoses/10 HPFs, no necrosis, >0.5 cm diameter
Intermediate	Atypical carcinoid	Carcinoid morphology, two to 10 mitoses/10 HPFs or foci of necrosis
High	Large-cell neuroendocrine carcinoma	Neuroendocrine structure, >10 mitoses/10 HPFs, necrosis (may be extensive), cytology resembling NSCLC, IHC positive for NE markers
	Small-cell carcinoma	Small cell size, scant cytoplasm, nuclei with finely granular chromatin and faint nucleoli, >11 mitoses/10 HPFs, extensive necrosis

WHO, World Health Organization; IASLC, International Association for the Study of Lung Cancer; NSCLC, non-small-cell lung cancer; IHC, immunohistochemistry; NE, neuroendocrine; HPF, high powered fields.

nervous system (12.2%). All central nervous system metastases occurred in patients with AC. Only eight patients (16.3%; 6 TC and 2 AC), all with liver metastases, had symptoms consistent with the carcinoid syndrome. Median survival from diagnosis of locally advanced unresectable or metastatic PC was 7.1 years and was significantly longer for TC-histology patients compared with AC-histology patients (10.2 versus 4 years; $p = 0.009$) (Fig. 1B).

Therapy Administered

More than half of the patients (25 of 49 patients) had previously undergone lung resections for primary PC. Median time to recurrence for patients who underwent curative resection was 2.5 years, and a trend toward prolonged time to recurrence was noted for TC compared with AC (6.3 versus 2.5 years; $p = 0.063$) (Fig. 1A).

Six patients (3 AC and 3 TC patients) with locally advanced PC received definitive radiation \pm concurrent chemotherapy as primary therapy. This group included three patients who received definitive radiation alone (2 TC and 1 AC patients; radiation dose range, 45 to 67 Gy) and three who received concurrent chemotherapy with cisplatin/etoposide or carboplatin/paclitaxel (2 AC and 1 TC patients). Overall, from this group, five patients had stable disease as best response and one patient had progressive disease. Median PFS after definitive radiation or chemoradiation was 10 months (range, 2–117). All six patients who received radiation \pm chemotherapy for locally advanced disease eventually experienced progressive disease; however, four patients (2 AC and 2 TC patients) had prolonged stable disease lasting between 2 and almost 10 years.

In total, 39 of 49 patients received systemic anti-cancer therapy. Etoposide with either cisplatin or carboplatin was administered to 17 patients (any line of therapy), of whom, four patients (2 AC and 2 TC patients) (23.5%) had a radiologic response. Median PFS for all patients who received platinum/etoposide was 7 months. Long-acting somatostatin analogue therapy was administered to 17 patients with only one tumor response being noted; however, prolonged stable disease was seen in 13 patients (range, 6–25 months). In two patients who received everolimus with sandostatin LAR, one pretreated patient has had an ongoing partial response for more than 8 months. Other therapies used comprised a variety of chemotherapies and targeted therapies administered mainly on phase I clinical trials; however, no tumor responses were seen.

Almost 60% of patients ($n = 29$) developed liver metastases during the course of their disease and of these, nine patients (6 AC and 3 TC patients) underwent hepatic transarterial chemoembolization (TACE) with cisplatin/doxorubicin/mitomycin (7 patients) or doxorubicin-eluting beads (2 patients). TACE had promising efficacy in this cohort with only one patient having progressive disease and eight patients (3 partial responses) experiencing prolonged stable disease in the liver lasting between 5 and 19+ months. In addition, one patient who received therasphere radio-embolization experienced a prolonged partial response lasting 24 months. TACE was overall well tolerated; however, one patient died from Gram-negative bacteremia related to a third TACE procedure.

LITERATURE REVIEW

The only well-described curative option for PC is surgical resection, and large series have described 10-year overall survival rates for resected TC of 82% to 93% and for resected AC of 56% to 64%.^{5,6}

The Role of Adjuvant Therapy

There are currently no clear data available on the use of adjuvant systemic therapy in PC tumors. On the basis of the relatively high rate of recurrence of resected AC and reported responses to platinum/etoposide in advanced disease such as those reported in our series, the National Comprehensive Cancer Network recommends adjuvant cisplatin/etoposide for fully resected stage II AC and consideration of adjuvant chemoradiation for completely resected stage III disease (category 2B evidence).^{7,8} Observation is recommended at the present time for resected stage I AC and stage I to III TC.

Locally Advanced Unresectable PC

There are very limited data to support the use of definitive chemoradiation for PC; however, in the absence of surgical options, it is recommended for stage IIIB AC.⁸ For locally advanced unresectable TC, definitive radiation without concurrent chemotherapy should be considered.⁸

Systemic Therapy for Advanced Disease

Evidence to support systemic therapy for APC comes from small retrospective series and subgroup analyses of clinical trials that enrolled predominantly gastrointestinal

Download English Version:

<https://daneshyari.com/en/article/6193475>

Download Persian Version:

<https://daneshyari.com/article/6193475>

[Daneshyari.com](https://daneshyari.com)