Multimodality Therapy for Thymic Carcinoma (TCA)

Results of a 30-Year Single-Institution Experience

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Abstract: The aim of this study was to correlate the clinicopathologic features and therapeutic approaches with the outcome of patients with thymic carcinoma (TCA), an aggressive, uncommon malignancy of the anterior mediastinum. TCA is morphologically distinct from thymoma, a cytologically bland, often encapsulated, locally invasive, rarely metastatic tumor. The Roswell Park Cancer Institute tumor registry was used to identify patients with TCA or invasive thymic neoplasm of the epithelial type (TNET). Between 1971 and 2001, 22 patients had a pathologic diagnosis of TCA and/or TNET. The mean age at diagnosis was 53 years (range: 19–77), and the male/female ratio was 3:1 (16/6). Initial symptoms were respiratory in about half the patients (10/22). Complete surgical resection was done in five patients. Postoperative cisplatin-based chemotherapy and radiation was administered to seven patients. Pathologic examination showed low grade (n = 14), intermediate grade (n = 7), and high grade (n = 1) TCA. Capsular invasion was present in 83% of the specimens. As of June 2002, nine patients are alive and eight are disease free. The median survival is 44.7 months. Locally invasive disease precluded complete surgical resection in more than half of our cases. Incomplete surgical resection did not preclude long-term survival if multimodality platinum-based therapy was used.

Key Words: thymic carcinoma, multimodality therapy, anterior mediastinum

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Thymic carcinoma (TCA) is a rare, aggressive neoplasm of the anterior mediastinum that is morphologically and biologically distinct from thymoma.1 TCA is often locally advanced or metastatic at presentation, precluding a curative surgical resection. The current literature on TCA consists of clinical case reports and description of histopathologic features. The majority of these reports include patients with thymomas, which may affect data interpretation in a particular study.2–5

One of the earliest proposed classification of thymic epithelial neoplasms was developed by Bernatz et al.6 In this model, TCA was divided into four groups: lymphocyte predominant, epithelial predominant, mixed lymphoepithelial, and spindle cell. Another classification based on "organotypic differentiation" was proposed by Muller-Hermelink.7 Based on the predominant morphologic components, TCAs were classified as medullary, cortical, or mixed types. However, because of poor correlation with the patient’s clinical outcome and prognosis, these classifications are not in use.

Levine and Rosai proposed a pathologic classification for TCA (reviewed in 8). The tumors were classified as histologic low or high grade. Low grade TCA included squamous cell carcinoma, mucopidermoid carcinoma, and basaloid carcinoma. High grade TCA included lymphoepithelioma-like carcinoma, small cell, undifferentiated, sarcomatoid, and clear cell carcinomas. Patients with low grade TCA have a longer median survival (25.4 months) than those with high grade thymic carcinoma (11.3 months).8 Although other pathologic and clinical features have been studied,9–11 the histologic grade remains the best prognostic indicator of outcome.

For several years, TCA was staged using the Masaoka clinical staging criteria.6 However, this staging system was designed for thymomas and has never been validated in patients with thymic epithelial neoplasms. In a recent study from the Memorial Sloan Kettering Cancer Center (MSKCC), Blumberg et al.7 demonstrated that the proposed Masaoka staging system does not predict prognosis and/or survival for TCA.

The optimal treatment for TCA remains to be defined. The low incidence of the disease has precluded the development of well-designed prospective clinical trials. However, it is accepted that a multidisciplinary approach that includes surgical resection followed by postoperative radiation therapy and/or chemotherapy must be used.12–15 Initial complete
surgical resection (if possible) followed by postoperative radiation therapy has been used in most of the studies with median survival of 9.5 months at best.16,17 The role of adjuvant/neoadjuvant chemotherapy is less clear and the clinical responses are variable.

The radiation dose, the most effective chemotherapy combination(s), dose, and delivery sequence are only a few of the unanswered questions in the treatment of patients with TCA. We report our experience with TCA during the last three decades.

MATERIALS AND METHODS

The Roswell Park Cancer Institute registry database was used to identify patients with the diagnosis of TCA or invasive thymic neoplasm of the epithelial type (TNET) who were treated at our institution between 1971 and 2001. Patients for whom a record was not available (seven patients) or with a diagnosis of a thymic neoplasm other than TCA/TNET were excluded from the analysis.

The study was conducted under the Institutional Review Board–approved protocol EDR 01-11. Demographic and pathologic characteristics, therapeutic interventions, and outcomes were delineated for each patient. Descriptive statistics were performed using the SPSS-10 for Windows 2000.

RESULTS

Clinical and Demographic Characteristics of Patients With TCA/TNET

Twenty-two patients with a pathologic diagnosis of TCA/TNET were identified from the tumor registry. The mean age at diagnosis was 53 years (range: 19–77 years), the male/female ratio was 3:1 (16/6), and all but one of the patients were white (Table 1). Clinically, the most frequent symptom at the time of diagnosis was cough/shortness of breath. Four patients sought treatment for a paraneoplastic syndrome. Two patients presented with myasthenia gravis, one with agammaglobulinemia, and another with autoimmune hemolytic anemia.

Other clinical presentations consisted of chest pain, gastroesophageal reflux, and superior vena cava syndrome. Four patients were found to have an abnormal chest radiograph during a routine examination for other disorders.

Pathologic Characteristics of Patients With TCA/TNET

The pathologic diagnosis of TCA was made by the application of strict criteria. The diagnosis of TCA/TNET was considered only if a particular specimen did not have any of the ancillary features of thymomas, which include the presence of 1) perivascular spaces; 2) foci of medullary differentiation; 3) abortive Hassall's corpuscles; 4) rosettes; 5) glandular-like spaces; and 6) immature T-lymphocytes.

In some specimens, lymphocytes were present and even in numerous quantities, but they exhibited the phenotype of mature T cells or rarely B cells. The morphologic appearance of TCA was indistinguishable from the corresponding carcinoma types in other organs. In the present study, most of the cases (n = 20) were diagnosed by examining conventional hematoxylin–eosin slides. The majority of the tumors were well to moderately differentiated carcinomas. There was one nonkeratinizing carcinoma (Figs. 1 and 2). There was one squamous cell carcinoma with evidence of focal sarcomatoid component ( carcinosarcoma). One tumor had a basaloid infiltrating pattern extending to adjacent lung parenchyma. The remaining (n = 2) were characterized by using ancillary tests.
Three patients had surgical resection alone. Two patients with a limited Eastern Cooperative Oncology Group performance status (PS) received definitive radiation therapy. Supportive care was offered to one patient who sought treatment for disseminated disease and who had a PS of 3 (Table 3).

Of the 22 patients, 18 were considered surgical candidates, of whom only 5 had a complete surgical resection. Postoperative radiation therapy was given to 13 of 18 patients. The radiation doses varied between 40 Gy and 60 Gy.

Systemic chemotherapy was used in 55.5% (10/18) of the patients. In 9 of 10, the chemotherapy was administered after surgery. Several chemotherapy regimens were used. Standard doses of regimens to treat lymphoproliferative disorders such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or mechloretamine, vincristine, procarbazine, and prednisone (MOPP) were used in the early 1970s. Subsequently, cisplatin-containing regimens became available, and most of the patients received cisplatin in combination with ifosfamide, etoposide, or doxorubicin (Table 4).

Therapeutic interventions at the time of relapse or disease progression consisted of palliative cis-platinum-based chemotherapy or second-line therapy with paclitaxel (administered in two patients in the context of a phase I clinical trial).

In June 2002, nine patients are alive (41%), and eight of them do not have evidence of disease recurrence. The median survival time from the initial diagnosis was 44.7 months. Death was related to disease progression/relapse in all patients. No treatment-related deaths were reported. Fifteen patients with TCA were treated using a multidisciplinary approach with either bimodality or trimodality therapy; six of these patients are currently alive (40%).

DISCUSSION

Thymic carcinoma is an epithelial neoplasm for which specific therapeutic guidelines are still unclear. Among the
Thymic carcinoma is an aggressive neoplasm. Locally invasive disease precluded complete surgical resection in more than 70% of our cases. Multidisciplinary approach with postoperative chemotherapy and/or radiation therapy is well tolerated and may be effective in eradication of either residual or microscopic disease. A recent report suggests a higher response rate (75%) with combination chemotherapy involving cis-platinum, doxorubicin, vincristine, and cyclophosphamide in patients with locally advanced or metastatic TCA. In our experience, incomplete surgical resection did not impact negatively on long-term survival if postoperative

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