Surgical and Medical Management of Germ Cell Tumors of the Chest*

Philip Kantoff, M.D.

Germ cell tumors are highly curable when treated appropriately. The majority of germ cell tumors arise in the testes, with a proportion having pulmonary parenchymal or mediastinal metastases. For patients who have such tumors, prompt diagnosis and treatment with chemotherapy are essential. A subset of these patients will have persistent radiographic abnormalities after chemotherapy and will benefit from postchemotherapy resection of residual masses. These patients need to be distinguished from those who should be observed and those who require further chemotherapy. A small proportion of patients with germ cell tumors will present with tumors arising in the mediastinum. Prompt diagnosis, with adequate tissue for histopathologic and immunohistochemical staining, is essential. Primary therapy for such patients should be chemotherapy, except for some patients with mediastinal seminomas in whom radiotherapy is preferable. Mediastinal nonseminomatous germ cell tumors have a poor prognosis due, in part, to their bulk and relative chemosensitivity, but also due in part to their association with non-germ cell elements and acute leukemia. Proper coordination of the different modalities is essential in optimizing the cure rate of patients with these tumors.

(Chest 1993; 103:331S-335)

Germ cell tumors represent an important model for curable adult solid tumors. Although these tumors are relatively uncommon—only 6,200 new cases of germ cell tumor are expected to be diagnosed in 1992—they are the most common malignancy in men between the ages of 15 and 35 years.

Germ cell tumors have several unique features. First, they are highly curable: more than 90% are cured, including approximately 80% of those in patients with metastatic disease. Second, the serum markers α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) are extremely reliable barometers; thus, they are useful in both diagnosing and managing this disease. Lastly, multimodality therapy has facilitated cures in a proportion of patients who fail to respond or respond only partially to initial chemotherapy. For example, surgery to resect residual tumor is an effective therapeutic adjunct in a patient who has had only a partial response to induction chemotherapy.

The survival of patients with germ cell tumors has increased over the past 30 years. The cures achieved before the advent of combination chemotherapy could largely be attributed to the fact that some patients had localized disease and were therefore cured with orchietomy alone, while a small proportion of patients with metastatic disease were cured with radiotherapy or surgery. With the introduction of cisplatin-based combination chemotherapy, cures became achievable in the majority of patients. Figure 1 demonstrates the survival of the first 150 patients treated at the Dana-Farber Cancer Institute with the initial cisplatin-based combination chemotherapy regimen PVB (cisplatin, vinblastine, and bleomycin). More than 80% of patients in this cohort remain disease-free with long-term follow-up.

A number of risk stratification schemes have been devised to differentiate a good from a poor prognosis in patients with metastatic disease. This has already led to the development of less toxic chemotherapy regimens that diminish treatment-related morbidity while maintaining high cure rates in patients with a good prognosis. In contrast, by delivering more intensive regimens to those with a poor prognosis, it may be possible to achieve a higher cure rate in the future.

The Indiana University staging system, which has been validated with the Dana-Farber Cancer Institute patient database, separates patients according to their prognostic status largely on the basis of tumor bulk. Patients with visceral metastases (liver, bone, central nervous system), those with extensive abdominal disease plus pulmonary disease, those with advanced pulmonary disease, and those with primary mediastinal germ cell tumors comprise the poor-prognosis group. Patients with advanced pulmonary disease and patients with primary mediastinal germ cell tumors are those in whom the interaction between the medical oncologist and the chest surgeon is critical. Despite the best efforts of clinicians, fewer than 50% of patients in these categories will be cured.

Management Strategies

Several important randomized studies in patients with good-risk tumors have been conducted over the past 10 years. These studies have led to the conclusion that, at the present time, standard initial chemotherapy for such patients consists of 3 cycles of the BEP regimen (cisplatin, etoposide, and bleomycin) or 4 cycles of the EP regimen (cisplatin and etoposide). Investigations are currently under way to determine whether the less toxic cisplatin analogue carboplatin can replace cisplatin in these regimens.

In patients with poor-risk features, standard therapy consists of 4 cycles of BEP. A randomized study is currently being conducted that compares BEP with 4 cycles of VIP (cisplatin, etoposide, and ifosfamide).

Germ cell tumors are unique among adult solid tumors since patients who fail primary chemotherapy (either by failing to achieve or to maintain a complete response) may be cured with an alternative chemotherapy regimen. Approximately 20% of patients who fail primary BEP chemotherapy will be cured when given either the VIP combination or cisplatin, ifosfamide, and vinblastine. Furthermore, recent studies have demonstrated that a proportion of patients

*From the Harvard Medical School, and Department of Medicine, Dana-Farber Cancer Institute, Boston.
who fail a second chemotherapy regimen may still be cured with high-dose chemotherapy and autologous bone marrow transplantation (ABMT). These promising results have generated interest in instituting ABMT in poor-risk patients initially as well as in those who have failed initial chemotherapy. With the availability of hematopoietic growth factors and peripheral blood stem cells, the morbidity of ABMT has diminished substantially.

### Pulmonary Parenchymal and Mediastinal Metastases From Testicular Primaries

A significant proportion of patients with metastatic germ cell tumors will manifest pulmonary or mediastinal metastases. Frequently these metastases will disappear radiographically in response to chemotherapy. Some patients, however, will still manifest residual radiographic abnormalities. Several factors should guide the approach to these patients.

First is the status of serum levels of the tumor markers following chemotherapy. One or both of the tumor markers AFP or β-HCG are elevated at presentation in 80% of patients with germ cell tumors. With curative chemotherapy, these markers should decrease to normal in accordance with their expected clearance from the serum. Their respective half-lives are approximately 1 day for β = HCG and 3 to 7 days for AFP. Following initial chemotherapy, persistent radiographic abnormalities accompanied by elevated marker levels in the serum that continue to rise subsequently denote persistent carcinoma. These patients should be treated with an alternative chemotherapy regimen. In contrast, patients whose marker levels have normalized after chemotherapy but who still manifest residual radiographic abnormalities in the chest may require resection of the abnormalities.

The critical factor is whether surgery can achieve disease-free status in the patient. Resection should be considered in any patient whose levels of serum markers have normalized so long as the residual abnormalities are at least 1.5 cm. In such patients, the pathologic findings from the resected specimen will determine the need for further chemotherapy. Approximately 10% of patients will have residual carcinoma, and the remainder will have either necrosis and fibrosis or mature teratoma, with each present at equal frequency. Some studies have reported that certain subgroups of patients may be at higher risk of having carcinoma or teratoma in the resected specimen: those who had a greater tumor bulk at initial presentation, those who had mature teratoma in the orchietomy specimen, and those who achieve less than 90% volumetric regression of tumor masses radiographically with chemotherapy.

When the resected surgical specimen yields mature teratoma or necrosis and/or fibrosis, patients require no further therapy and should simply be observed. These patients have a greater than 90% chance of cure. When carcinoma is found, however, at least 2 cycles of the preoperative chemotherapy regimen should be administered. If the residual abnormality has been resected completely, patients who receive at least 2 further cycles of chemotherapy have a 60% to 70% chance of cure.

Some patients whose serum markers normalize after chemotherapy demonstrate progression of the radiographic abnormalities. This is essentially pathognomonic of teratoma, and these patients should undergo surgery. Patients who have been treated with bleomycin may develop radiographic abnormalities in the chest that mimic new tumor nodules. These bleomycin-induced nodular abnormalities may occur in the lower lobes, but they do not typically affect areas that have had tumor involvement.

In contrast to patients with nonseminomatous germ cell tumors, most patients with metastatic seminoma do not require surgical resection of radiographic abnormalities since teratoma is never found, and carcinoma is found only rarely. Most patients treated for seminoma who have small residual abnormalities can be followed clinically. The management of large (>3 cm) residual abnormalities is contro-
versal. Some institutions favor close observation, while others favor either adjunctive radiotherapy or surgical extirpation.

**Management of Primary Mediastinal Germ Cell Tumors**

Germ cell tumors arise not only in the testes but in other locations including the presacral area, the retroperitoneum, the mediastinum, and the pineal gland. Germ cell tumors are only one of several abnormalities that can arise in the anterior mediastinum, but they should be considered nonetheless, particularly in young men. The presence of an anterior mediastinal mass should prompt an evaluation of levels of β-HCG and AFP. Elevated levels of either or both of these markers strongly suggest a diagnosis of germ cell tumor. A biopsy specimen should be obtained, however, for histopathologic and immunohistochecistry confirmation.2

At times, the only evidence that a highly anaplastic lesion is a germ cell tumor is positive immunoperoxidase staining for either AFP, β-HCG, or placental alkaline phosphatase. Once the diagnosis of germ cell tumor is established, it is essential that a primary testicular cancer be ruled out by physical examination and ultrasound. Similarly, an abdominal pelvic computed tomographic scan should be performed to rule out the presence of retroperitoneal disease.

Although the majority of mediastinal germ cell tumors are mixed germ cell tumors or seminomas, the numbers of pure endodermal sinus tumors and choriocarcinomas are disproportionately high. Nonseminomatous mediastinal germ cell tumors are associated with a poor overall prognosis.10,11 Although due in part to the significant bulk of these tumors in most patients, the poor prognosis is also thought to arise from the differing biologic characteristics of these tumors compared with other germ cell tumors. Specifically, they tend to be less sensitive to chemotherapy and may have a propensity to degenerate into non-germ cell elements, including sarcomas or carcinomas. Very rarely, they can be associated with concomitant non-treatment-related acute myelogenous leukemia.14 For these reasons, although standard chemotherapy is the routine initial approach to these patients, innovative approaches including initial ABMT are being tested.

For patients with persistent radiographic abnormalities following chemotherapy, the considerations regarding further chemotherapy or adjunctive surgery are similar to those in patients with testicular primaries.

In contrast to patients with nonseminomas, patients with primary mediastinal seminomas have a good prognosis as patients with testicular seminomas. Treatment with primary chemotherapy or, if the mass is small, primary radiotherapy is usually curative. The management considerations for residual mediastinal masses in patients treated with chemotherapy for pure seminomas are similar to those for patients with testicular seminomas.

**Conclusions**

Germ cell tumors, although uncommon, are important to recognize and treat appropriately because of their high curability. Appropriate multidisciplinary management is essential to achieve this goal.

**References**