TABLE 116-1 INTERNATIONAL GERM CELL CANCER CONSENSUS GROUP RISK CLASSIFICATION FOR ADVANCED GERM CELL TUMORS

Risk	Nonseminoma	Seminoma
Good	Gonadal or retroperitoneal primary site Absent nonpulmonary visceral metastases AFP <1000 ng/mL β-hCG <5000 mIU/mL LDH <1.5 × upper limit or normal (ULN)	Any primary site Absent nonpulmonary visceral metastases Any LDH, hCG
Intermediate	Gonadal or retroperitoneal primary site Absent nonpulmonary visceral metastases AFP 1000–10,000 ng/mL β-hCG 5000–50,000 mIU/mL LDH 1.5–10 × ULN	Any primary site Presence of nonpulmonary visceral metastases Any LDH, hCG
Poor	Mediastinal primary site Presence of nonpulmonary visceral metastases AFP >10,000 ng/mL β-hCG >50,000 mIU/mL LDH >10 × ULN	No patients classified as poor prognosis

Abbreviations: AFP, α fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.

Source: From International Germ Cell Cancer Consensus Group.

maximum efficacy with minimal toxicity. For intermediate- and poor-risk patients, the goal is to identify more effective therapy with tolerable toxicity.

The marker cut offs are included in the TNM (primary tumor, regional nodes, metastasis) staging of GCT. Hence, TNM stage groupings are based on both anatomy (site and extent of disease) and biology (marker status and histology). Seminoma is either good- or intermediate-risk, based on the absence or presence of nonpulmonary visceral metastases. No poor-risk category exists for seminoma. Marker levels and primary site play no role in defining risk for seminoma. Nonseminomas have good-, intermediate-, and poor-risk categories based on the primary site of the tumor, the presence or absence of nonpulmonary visceral metastases, and marker levels.

For ~90% of patients with good-risk GCTs, four cycles of EP or three cycles of BEP produce durable complete responses, with minimal acute and chronic toxicity, and a low relapse rate. Pulmonary toxicity is absent when bleomycin is not used and is rare when therapy is limited to 9 weeks; myelosuppression with neutropenic fever is less frequent; and the treatment mortality rate is negligible. Approximately 75% of intermediate-risk patients and 50% of poor-risk patients achieve durable complete remission with four cycles of BEP, and no regimen has proved superior.

POSTCHEMOTHERAPY SURGERY Resection of residual metastases after the completion of chemotherapy is an integral part of therapy. If the initial histology is nonseminoma and the marker values have normalized, all sites of residual disease should be resected. In general, residual retroperitoneal disease requires a modified bilateral RPLND. Thoracotomy (unilateral or bilateral) and neck dissection are less frequently required to remove residual mediastinal, pulmonary parenchymal, or cervical nodal disease. Viable tumor (seminoma, embryonal carcinoma, yolk sac tumor, or choriocarcinoma) will be present in 15%, mature teratoma in 40%, and necrotic debris and fibrosis in 45% of resected specimens. The frequency of teratoma or viable disease is highest in residual mediastinal tumors. If necrotic debris or mature teratoma is present, no further chemotherapy is necessary. If viable tumor is present but is completely excised, two additional cycles of chemotherapy are given.

If the initial histology is pure seminoma, mature teratoma is rarely present, and the most frequent finding is necrotic debris. For residual retroperitoneal disease, a complete RPLND is technically difficult due to extensive postchemotherapy fibrosis. Observation is recommended when no radiographic abnormality exists on CT scan. Positive findings on a positron emission tomography (PET) scan correlate with viable seminoma in residua and mandate surgical excision or biopsy.

SALVAGE CHEMOTHERAPY

Of patients with advanced GCT, 20–30% fail to achieve a durable complete response to first-line chemotherapy. A combination of vinblastine, ifosfamide, and cisplatin (VeIP) will cure approximately 25% of patients as a second-line therapy. Patients are more likely to achieve a durable complete response if they had a testicular primary tumor and relapsed from a prior complete remission to first-line cisplatin-containing chemotherapy. Substitution of paclitaxel for vinblastine (TIP) in this setting was associated with durable remission in nearly two-thirds of patients. In contrast, for patients with a primary mediastinal nonseminoma or who did not achieve a complete response with first-line chemotherapy, then VeIP standard-dose salvage therapy is rarely beneficial. Such patients are usually managed with high-dose chemotherapy and/or surgical resection.

Chemotherapy consisting of dose-intensive, high-dose carboplatin plus high-dose etoposide, with peripheral blood stem cell support, induces a complete response in 25–40% of patients who have progressed after ifosfamide-containing salvage chemotherapy. Approximately one-half of the complete responses will be durable. High-dose therapy is standard of care for this patient population and has been suggested as the treatment of choice for all patients with relapsed or refractory disease. Paclitaxel is active when incorporated into high-dose combination programs. Cure is still possible in some relapsed patients.

EXTRAGONADAL GCT

The prognosis and management of patients with extragonadal GCT depends on the tumor histology and site of origin. All patients with a diagnosis of extragonadal GCT should have a testicular ultrasound examination. Nearly all patients with retroperitoneal or mediastinal seminoma achieve a durable complete response to BEP or EP. The clinical features of patients with primary retroperitoneal nonseminoma GCT are similar to those of patients with a primary tumor of testis origin, and careful evaluation will find evidence of a primary testicular GCT in about two-thirds of cases. In contrast, a primary mediastinal nonseminomatous GCT is associated with a poor prognosis; one-third of patients are cured with standard therapy (four cycles of BEP). Patients with newly diagnosed mediastinal nonseminoma are considered to have poor-risk disease and should be considered for clinical trials testing regimens of possibly greater efficacy. In addition, mediastinal nonseminoma is associated with hematologic disorders, including acute myelogenous leukemia, myelodysplastic syndrome, and essential thrombocytosis unrelated to previous chemotherapy. These hematologic disorders are very refractory to treatment. Nonseminoma of any primary site may change into other malignant histologies such as embryonal rhabdomyosarcoma or adenocarcinoma. This is called *malignant transformation*. i(12p) has been identified in the transformed cell type, indicating GCT clonal origin.

A group of patients with poorly differentiated tumors of unknown histogenesis, midline in distribution, and not associated with secretion of AFP or hCG has been described; a few (10–20%) are cured by standard cisplatin-containing chemotherapy. An i(12p) is present in ~25% of such tumors (the fraction that are cisplatin-responsive), confirming their origin from primitive germ cells. This finding is also predictive of the response to cisplatin-based chemotherapy and resulting long-term survival. These tumors are heterogeneous; neuroepithelial tumors and lymphoma may also present in this fashion.