High-Dose Chemotherapy in Poor-Risk Germ-Cell Tumors

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Testicular cancer is a highly curable cancer. However, 30% of patients are refractory to standard therapy and will need additional therapy. This article focuses on the use of high-dose chemotherapy in germ-cell tumors.

One noted investigator posed the following questions in lectures: (1) What is the most curable solid tumor? (Answer: testicular cancer); (2) What is the second most curable solid tumor? (Answer: recurrent testicular cancer). In light of the fact that germ-cell tumors are the poster child for medical oncology, there is certainly truth to these observations.

Over the last quarter of a century, our understanding of the biology and treatment of this disease has grown impressively. As Dr. Srinivas notes, 95% of all patients with testicular cancer should be cured with appropriate therapy. For those patients with disseminated disease, however, the prognosis varies with the extent and level of serum markers. The International Germ Cell Consensus Classification underscores the relationship of primary site (mediastinum vs other) serum markers (beta-human chorionic gonadotropin [HCG], alpha-fetoprotein [AFP], lactic dehydrogenase [LDH]), extent of disease, and histology (seminoma vs nonseminomatous germ-cell tumor) with prognosis.

In contrast to acute leukemia, where a similar percentage of patients achieve a complete remission, relapse from complete remission in germ-cell tumors following induction chemotherapy is 10% or less.[1] Fortunately, the number of patients who have an incomplete response or relapse from primary therapy is low, with only a few hundred such patients seen in the United States each year. Nonetheless, patients with a poor prognosis are precisely the ones in whom novel treatment approaches are required.

This article highlights several questions, including whether high-dose chemotherapy is an effective strategy in germ-cell tumors. The concept of dose intensity has permeated the oncology literature for many years. As mentioned by Dr. Srinivas, a dose threshold for cisplatin (Platinol) was demonstrated by the Southwest Oncology Group (SWOG) several years ago.[2] The latter trial, conducted by Indiana University and SWOG, demonstrated that doubling the dose of cisplatin from 20 mg/m² to 40 mg/m², both given on days 1 through 5, not only failed to improve complete remission or overall survival rates, but also substantially increased the incidence of grade 4 neuropathy. Other trials mentioned by Dr. Srinivas—using modest increases in dosages of cisplatin or etoposide—have demonstrated either little or minimal support for higher-dose therapy in this disease.

**Salvage Therapy**

In the salvage setting, high-dose chemotherapy with stem-cell rescue has proven effective for a patient population not felt to be curable with standard therapy.[3] With such an approach, 15% to 21% of heavily pretreated patients may achieve a durable, complete remission. These trials have encouraged the earlier use of this therapy in patients with first relapse or even as part of primary therapy, thereby leading to a seemingly better outcome. In addition, earlier treatment and patients with a better performance status have resulted in decreased morbidity and mortality of therapy in this population.[3]

In patients with recurrent testicular cancer (excluding an extragonadal primary) whose disease is not cisplatin refractory (ie, progressing within 3 to 4 weeks of prior cisplatin), a 50% cure rate has been observed with tandem transplants.[4] This contrasts with an approximate 30% cure rate for those treated with conventional doses of VIP (vinblastine, ifosfamide [Ifex], cisplatin) in a similar patient population as part of second-line therapy.[5]

These data reaffirm the observation that selection bias may alter results. Patients with primary mediastinal tumors, patients who progress within 3 weeks of prior chemotherapy, and patients with non-germ-cell malignancies associated with teratoma do not fare well with standard salvage or high-dose chemotherapy with stem-cell rescue.

Another group with unfavorable results are those patients who develop recurrences beyond 2 years from primary therapy. Although brief objective responses are seen with chemotherapy, only those...
patients who have disease that is surgically extirpated are associated with long-term survival.[6]
Similarly, although some brief remissions are seen in patients who relapse following high-dose chemotherapy and stem-cell rescue, this response rate is less than 20%, which includes about 5% who were long-term survivors requiring surgical extirpation of disease as part of their treatment armamentarium.[7]

**Primary Therapy**

Another question is whether a role exists for high-dose chemotherapy as part of primary chemotherapy in patients with poor-risk disease. This is the objective of an ongoing prospective, randomized trial that is evaluating standard BEP (bleomycin [Blenoxane], etoposide, Platinol) to two cycles of BEP followed by high-dose carboplatin (Paraplatin), etoposide, and cyclophosphamide (Cytoxan, Neosar) with stem-cell rescue. This is an extremely important trial that is still accruing patients.

Outside the confines of a clinical trial, we are often asked whether bone marrow transplantation should be used as part of initial induction therapy for patients whose serum markers seem to be declining at a rate less than predicted. Although this is an interesting concept, many of these patients treated with standard therapy will continue to respond to treatment.

In addition, several factors may also be associated with a slower decline of serum markers, including occult central nervous system metastases, an intact primary in the testis, or false marker elevations secondary to marijuana use (elevated HCG) or hepatitis (elevated AFP). Since virtually all patients respond to initial induction chemotherapy, this will be a difficult concept to test prospectively.

**Conclusions**

In summary, high-dose chemotherapy with peripheral stem-cell rescue has an essential role as part of salvage chemotherapy in patients with recurrent, but cisplatin-sensitive, disease. When performed at established centers, the mortality rate should be considerably less than 5%. The high degree of activity in this setting has prompted an evaluation of this strategy’s role in primary therapy for patients with poor-risk disease. We believe that until this trial is completed, front-line use of high-dose therapy remains investigational.

**References:**


