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.

Introduction

Testicular cancer has become a model for a curable neoplasm. The results of the treatment of disseminated germ-cell tumors have dramatically improved by utilization of platinum-containing combination chemotherapy regimens. Patients with metastatic disease are allocated to either good-risk or poor-risk groups according to prognostic classifications or models.[1-3] The standard treatment for good-risk patients is three cycles of PEB (Platinol [cisplatin], etoposide, bleomycin [Blenoxane]), with poor-risk patients receiving four cycles. The standard treatment achieves 95% and 65% cure rates in good-risk and poor-risk patients, respectively. However, 10% to 25% of patients in complete remission fail to maintain the remission. The standard second-line treatment is VeIP (Velban [vinblastine], ifosfamide [Ifex], Platinol) or VIP (VePesid [etoposide], ifosfamide, Platinol), which induces a complete response in 60% of patients and a long-term remission in 20% to 30% of patients.[4] Thus, a number of patients may fail to attain complete responses. Durable complete responses have been achieved in only one-third of patients with poor-risk germ-cell tumors (GCT) by Memorial Sloan-Kettering Center (MSKCC) criteria (Table 1). Likewise, one-half of those considered poor risk by Indiana criteria achieve a durable complete response to four cycles of PEB chemotherapy.[5] The use of high-dose chemotherapy with autologous bone marrow transplantation (BMT) and/or peripheral stem-cell transplantation (PSCT) as salvage therapy for relapsed or refractory germ-cell tumors has been explored. The object of this article is to review the various trials employing high-dose chemotherapy. High-dose chemotherapy has been used in two settings: in heavily pretreated patients and in first-salvage or first-line therapy.

Risk Assessment and Classification of Patients

Bajorin et al.[6] compared the criteria that were assigned to patients by different groups and found substantial differences in the sensitivity, specificity, and overall predictive values for the various selection criteria. The investigators classified these patients and found that the allocation of patients to good- or poor-risk categories was concordant in only 56% of cases. In particular, the allocation of poor-risk varied from 31% to 72% of patients. The reported outcome of a trial in poor-risk patients with germ-cell tumors is profoundly affected by the eligibility criteria. Use of less restrictive criteria can include a large number of patients who might otherwise be classified as good risk. The nonuniformity of entry criteria may account for the wide variability in response rates reported in the literature. To resolve this controversy, the International Germ Cell Cancer Collaborative Group (IGCCCG) was formed in 1991, and it put forth an International Germ Cell Consensus Classification for germ-cell tumor risk (Table 2).[7] The use of such standard and uniform criteria in future trials would help interpretation of data on the use of high-dose chemotherapy in patients with germ-cell tumors.

Treatment of Poor-Risk Disease

Rationale for Use of High-Dose Chemotherapy

Patients with testicular cancer tend to be younger, and to tolerate dose intensity therapy well. They most likely do not experience metastasis to the bone marrow. Germ-cell tumors are chemosensitive,
and effective agents such as carboplatin (Paraplatin) and etoposide can be dose escalated. All these factors make the use of high-dose chemotherapy very feasible in germ-cell tumors. A dose-response effect has been reported for cisplatin at doses of 75 to 120 mg/m², [8] although a similar study of cisplatin (200 mg/m²) failed to demonstrate a survival benefit.[9]

**High-Dose Chemotherapy in Cisplatin-Refractory Patients**

Collective results from various studies show that high-dose chemotherapy can cure 15% to 20% of patients experiencing multiple relapses. Therapy-related mortality in this heavily pretreated population varies from 0% to 30% (Table 3).[10-21] The increase in mortality may be due to an early learning curve associated with the procedure, or, in part, to the heavily pretreated population. There appears to be a suggestion of a survival advantage to a three-drug combination regimen. A large study on multivariate analysis, however, did not find the chemotherapy regimen to be a significant influence on treatment outcomes.[22] The absolute contribution of the oxazaphosphorines is unknown at this time.

**High-Dose Chemotherapy as Primary Treatment of Poor-Risk Disease**

Clinical trials using high-dose chemotherapy plus rescue with stem cells in relapsing or refractory patients have resulted in long-term survivals of 15% to 20%. In contrast, patients who have been refractory to standard-dose platinum-based chemotherapy as first- or second-line treatment have not achieved long-term survival with the same agents at high doses. It is assumed that high-dose therapy was not able to overcome platinum resistance once it developed, leading to the use of high-dose therapy as early as possible.

A trial from the Institute Gustav Roussy has been reported wherein poor-risk patients were randomized to receive two cycles of conventional cisplatin, vinblastine, etoposide, and bleomycin vs the similar regimen followed by a high-dose cycle of cisplatin (40 mg/m² on days 1 to 5), etoposide (350 mg/m² on days 1 to 5), and cyclophosphamide (Cytoxan, Neosar) (1.6 g/m² on days 1 to 4) with autologous support.[23] The trial enrolled 115 patients; 40 of 57 (70%) on the standard arm and 33 of 57 (58%) on the high-dose arm are progression free. This trial failed to demonstrate any advantage for the high-dose arm. The poor results of this trial have been attributed to the inferior regimen used.[24]

Patients at MSKCC[25] with predicted complete response rates of less than 50% were treated with VAB-6 (cisplatin, vinblastine, bleomycin, cyclophosphamide, dactinomycin), and patients exhibiting marker decline consistent with a prolonged half-life were treated with a regimen utilizing high-dose carboplatin (1,500 mg/m²) and etoposide (1,200 mg/m²) plus autologous BMT. Of 28 patients, 22 proceeded to two cycles of high-dose carboplatin and etoposide plus autologous BMT. Twelve of the 22 patients (55%) receiving the high-dose therapy achieved a disease-free status; 57% were alive and disease free at 31 months follow-up. There was less hematologic and nonhematologic treatment-related morbidity associated with high-dose therapy in this setting, compared with its use in heavily pretreated patients.

Motzer[26] and his colleagues reported an investigation using VIP vs VIP plus high-dose chemotherapy with carboplatin (1,800 mg/m²), etoposide (1,800 mg/m²), and cyclophosphamide (150 mg/kg) plus stem-cell rescue as first-salvage treatment of recurrent germ-cell tumors in 30 poor-risk patients. If the serum tumor markers were rising or the half-life was prolonged, patients were changed to two cycles of high-dose chemotherapy plus autologous BMT. If the serum tumor markers declined by their respective half-lives, patients were considered early responders and received two additional cycles of VIP.

Sixteen patients were treated with VIP alone; 14 had VIP plus high-dose therapy. Two relapses were seen in the VIP-alone arm and one in the VIP plus high-dose therapy arm. The median overall survival for these patients was 40 months, and 50% are alive without any evidence of disease. The toxicities were also fewer when the high-dose regimen was administered earlier. Treatment-related mortality has been less than 3%.

Schmoll[27] and colleagues reported on the use of high-dose chemotherapy plus stem-cell support without preceding conventional chemotherapy. Cisplatin at 150 mg/m², along with ifosfamide and etoposide was administered every 3 weeks with stem-cell support for a total of four cycles. The 2-year survival was 82%, with a predicted survival for that risk group category of 60%.

**Prognostic Variables**

Attempts have been made to identify prognostic variables to help optimize the use of high-dose chemotherapy in germ-cell tumors.[10] Progressive disease before high-dose chemotherapy, primary mediastinal nonseminomatous tumor,
refractory or absolute refractory disease to conventional dose cisplatin, and human chorionic gonadotropin (HCG) levels greater than 1,000 IU/L before high-dose chemotherapy served as independent adverse prognostic variables, based on the analysis of 310 patients by Beyer et al.[10] Scores were assigned to these variables, and patients were classified as good, intermediate, and poor risk, which correlated with 2-year failure-free survival rates of 51%, 27%, and 5%, respectively ($P < .001$). There was no difference in outcome with various drug combinations plus either single or tandem transplants.

A second analysis of 58 patients was performed by Motzer and identified complete response before high-dose therapy, primary gonadal tumor, retroperitoneal metastases, and low level of pretreatment HCG as favorable factors for survival.[28]

### High-Dose Chemotherapy in Extragonadal Germ-Cell Tumors

Primary extragonadal germ-cell tumors are rare and account for 1% to 5% of all germ-cell malignancies.[29] In spite of the similarity of the general histologic and serologic characteristics of these tumors to testicular germ-cell tumors, their clinical behavior is very different. Primary chemotherapy regimens have been successful in treating extragonadal germ-cell tumors, with long-term survival approaching that of patients with advanced testicular cancer.[30] However, the reports of curability with salvage therapy have been dismal.

Saxman et al.[31] reported the Indiana University experience on the use of salvage therapy in patients with extragonadal germ-cell tumors. Of 28 patients who received high-dose chemotherapy, none are disease free. Hainsworth et al.[32] have reported on 10 patients who relapsed after primary therapy, with no long-term survivors. Other investigators have reported similarly poor outcomes.[33-35]

The multivariate analysis also supports the poor outcome from high-dose chemotherapy with relapsed extragonadal germ-cell tumors.

### Future Directions

An ongoing phase III trial of PEB alone vs PEB followed by high-dose carboplatin/etoposide/cyclophosphamide in untreated poor- and intermediate-risk germ-cell tumor should give some insight into the role of high-dose chemotherapy as primary therapy. Similarly, a phase III European study with VIP or VeIP alone, or followed by high-dose carboplatin/etoposide/cyclophosphamide and autologous BMT/PBSC rescue in relapse or first partial remission, addresses the same question in the salvage setting.

The other strategy employed in poor-risk patients is the use of new agents and innovative therapies. Paclitaxel (Taxol) in combination with ifosfamide and cisplatin is being studied, as is pyrazoloacridine, in cisplatin-refractory patients.

### Conclusions

Use of high-dose therapy in testicular cancer results in cure in about 10% to 15% of patients. The best drug combination and the optimum dosages are yet to be determined. Whether one cycle or a series of high-dose cycles in a sequence is better is still undetermined. There is a suggestion of better response when high-dose therapy is employed earlier. Patients who are considered high risk may benefit from early use of high-dose chemotherapy.

While the multivariate analysis demonstrates that patients who are in clinical remission prior to high-dose therapy do better, it is unclear if they may be cured by conventional salvage therapy alone.

Ongoing studies will yield answers as to the optimal timing of transplants. Innovative treatments are clearly indicated for relapsed mediastinal germ-cell tumors, rather than high-dose chemotherapy. Selection of patients, based on known prognostic variables, will be helpful.

### References:


