Salvage Chemotherapy for Refractory Germ Cell Tumors

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Most patients with germ cell tumors will be cured with local therapy and/or standard chemotherapy. When relapse occurs, two salvage treatment paradigms exist: standard-dose chemotherapy (SDC), or high-dose chemotherapy (HDC) with autologous stem cell rescue (ASCR). Limited prospective comparative data exist to guide decision making.

At the University of Southern California (USC), it is our practice to begin by estimating the likelihood of a durable remission based on individual characteristics. Factors including pure seminoma, prior complete response (CR) to cisplatin therapy, low-volume metastases, and a testicular primary predict for cure with standard-dose salvage[1-4] and may help clinicians identify patients for whom SDC is preferred. However, it is important to consider that HDC-ASCR may be more effective in patients at first relapse, even in populations expected to respond to SDC salvage, and it may also be safer when administered earlier. For example, in a series of relapsed seminoma patients treated with HDC, 92% of patients in first relapse achieved CR, compared with 67% of those treated in the third- or fourth-line setting.[5] There have been reports of greater toxicity from ASCR in germ cell tumor patients with greater prior cisplatin exposure.[6]

SDC

Ifosfamide-based regimens

Ifosfamide-based regimens are a standard of care in the second-line setting; such regimens include TIP (paclitaxel at 250 mg/m² by continuous infusion on day 1, ifosfamide at 1.2 g/m² daily, and cisplatin at 20 mg/m² daily on days 2 to 6) or VeIP (vinblastine at .11 mg/kg for 2 days plus ifosfamide and cisplatin). These regimens result in a CR rate of 36% in first-relapse patients[7] but a 70% CR rate in selected good-risk patients.[8] In seminoma patients, VeIP as first salvage yielded a CR in 83% of patients.[1] Toxicity with ifosfamide-based combination regimens is substantial, with the hospitalization rate for neutropenic fever as high as 89%.[7] We routinely use granulocyte colony-stimulating factor (G-CSF) prophylaxis during salvage treatment for patients with germ cell tumors.

Gemcitabine-based therapy

A regimen of gemcitabine at 1,000 mg/m² on day 1 and day 8, and oxaliplatin at 130 mg/m² on day 1 of a 21-day cycle, produced CR rates of 8% to 14% and partial response (PR) rates of 17% to 37% in 2 small prospective series.[9,10] All patients with a PR subsequently had progression, with duration of PR ranging from 2 months to 8 months. Up to 10% of patients experience grade 3 neuropathy, although in one series there was complete resolution after treatment cessation.[10] Adding paclitaxel to gemcitabine and oxaliplatin (GOT) probably improves efficacy. Bokemeyer and colleagues reported on 73 patients treated with GOT, of whom 78% had received prior HDC (half as primary treatment).[11] A total of 4 patients (5.5%) achieved CR, while 6 additional men achieved CR after resection of residual disease (total, 13.7%). Toxicity was similar to that of the doublet regimens. At USC, we designed a dose-dense form of GOT, cycled every 14 days,[12] with paclitaxel at 170 mg/m² on day 1. We escalated the oxaliplatin dose from 100 mg/m² in the first cycle to 125 mg/m² in the second and subsequent cycles if the absolute neutrophil count was greater than 1,500 cells/μL and platelet counts were over 75,000/μL, and neuropathy was less than grade 2 with no infection present. We found a 6.7% CR rate, with 5 additional patients (total, 16.7%) becoming resectable, resulting in durable remission in a population with a median of 2 prior lines of therapy. This has become our standard salvage regimen for patients in whom second line cisplatin-ifosfamide
combinations fail and/or who are not candidates for HDC stem-cell therapy.

**HDC With ASCR**

The efficacy of HDC-ASCR in germ cell tumor patients at first relapse or with primary refractory germ cell tumors is controversial. Our approach to these patients incorporates the risk-stratification system outlined by the International Prognostic Factors Study Group (IPFSG).[13] After studying 1,594 patients with relapsed germ cell tumors who progressed after more than 3 cycles of first-line cisplatin-based therapy, multivariate analysis identified histology, primary tumor location, response, and progression-free interval from first therapy; alpha-fetoprotein and human chorionic gonadotropin levels; and presence of liver, bone, or brain metastasis as independent prognostic factors (see Table).

There are five prognostic groups, beginning with very-low-risk patients (−1 point), who had an overall survival (OS) rate at 5 years of 77%, and ending with a very-high-risk group (3 points), whose 5-year OS was 6.1%. Our practice is to offer HDC-ASCR to patients unlikely to be cured by SDC: those in the (very) high-risk IPFSG groups (with scores of 2 or 3 points), and selected intermediate-risk patients (with a score of 1 point). We offer HDC-ASCR to all patients at second relapse, based on single-arm studies demonstrating long-term survival in this setting.[14,15] Despite the lack of prospective randomized data favoring HDC over SDC in first relapse, retrospective data suggest that HDC with tandem ASCR may be preferable. In a retrospective analysis of the IPFSG database, 821 patients who received HDC as first salvage treatment were compared with 773 patients who received SDC. Although bias may confound the results, 2-year event-free survival was significantly better with HDC than with SDC (55% vs 44.1%, \( P < .001 \)) in all 5 risk groups, and there was an overall survival advantage (60.6% vs 46.3%, \( P < .001 \)) except for patients in the lowest risk groups.[16]

**Key Points in the USC Approach to Salvage Chemotherapy for Germ Cell Tumors**

- IPFSG very-low-risk and low-risk patients, such as those with seminoma and low levels of tumor markers, may be effectively salvaged with standard-dose chemotherapy, typically TIP.
- HDC-ASCR (we use TI-CE) should be offered to very high-risk and high-risk relapsed patients with germ cell tumors, as well as select intermediate-risk patients at first relapse, and all patients beyond first relapse.
- Chemotherapy regimens such as intensified GOT may offer remissions even after failure of transplant.

GOT = gemcitabine, oxaliplatin, paclitaxel; HDC-ASCR = high-dose chemotherapy with autologous stem cell rescue; IPFSG = International Prognostic Factors Study Group; TI-CE = paclitaxel, ifosfamide induction followed by high-dose carboplatin, etoposide; TIP = paclitaxel, ifosfamide, cisplatin; USC = University of Southern California.

We generally exclude patients with (very) low-risk prognosis (0–1 point) from HDC in first relapse based on the lack of OS benefit identified in the IPFSG study, and on the efficacy of TIP in these patients. Of note, patients in the very-low-risk group in the IPFSG study showed a 40% event-free survival when treated with SDC, which is significantly lower than the rate seen with HDC. However, the OS was similar, indicating that salvage therapies were effective in this subset. The intermediate-risk group (1 point) experienced a 31% event-free survival at 2 years and a 45% OS at 5 years with SDC, with a statistical difference favoring HDC. Thus, our practice is to strongly consider intermediate-risk patients for HDC, especially those with high levels of tumor markers or early relapse. Initial HDC salvage therapy for patients with primary mediastinal disease was not believed to be beneficial in the Indiana experience,[17] although some durable remissions were seen in these patients using the TI-CE regimen (paclitaxel, ifosfamide induction followed by high-dose carboplatin, etoposide).[18]

Definitive recommendations cannot be made until additional randomized studies are completed. The single prospective randomized study that compared HDC (VIP [cisplatin, ifosfamide, etoposide]/VeIP × 3 cycles with single HDC-ASCR) to SDC (VIP/VeIP × 4 cycles) in first relapse did not show an event-free survival or OS advantage.[19] However, this study has been criticized because a large number of patients did not receive the intended HDC, and because single HDC-ASCR was utilized, which has been associated with inferior outcomes compared with tandem transplant approaches.[20] We favor tandem high-dose treatment with stem cell rescue following the TI-CE regimen published...
Conclusions

For patients experiencing their first relapse of seminoma, and other patients whose IPFSG scores classify them as low risk, SDC is a reasonable choice for salvage treatment. For those whose IPFSG scores classify them as intermediate to very high risk, our preferred treatment is HDC-ASCR, and we offer HDC-ASCR to all SDC-pretreated patients at second relapse. Resection of residual disease is an important consideration and contributes to cure even in heavily pretreated patients. An intensified GOT regimen can yield a CR even in patients with highly refractory disease, including those who relapse after transplant.

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Table: International Prognostic Factors Study Group (IPFSG) Risk-Strat...


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