Management of Recurrent Testicular Germ Cell Tumors

GURU SONPAVDE, THOMAS E. HUTSON, BRUCE J. ROTH

U.S. Oncology Research, Houston, Texas, USA; Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, USA

Key Words. Germ cell tumors • Salvage

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the different salvage conventional and high-dose chemotherapy regimens for germ cell tumors.
2. List the prognostic factors for recurrent germ cell tumors.
3. Explain the role of surgical salvage therapy for recurrent germ cell tumors.

ABSTRACT

Although front-line chemotherapy cures most men with testicular germ cell tumors, salvage therapy is still important in a small but significant minority. Second-line conventional-dose or high-dose chemotherapy with stem cell rescue may cure 25%–50% of patients. New chemotherapeutic agents, including the taxanes gemcitabine and oxaliplatin, have added to the therapeutic armamentarium. Salvage surgical resection has an important role in selected patients. Cisplatin-refractory patients have a poor prognosis with current therapy, and novel chemotherapeutic and biologic agents need to be discovered for such patients. The Oncologist 2007;12:51–61

INTRODUCTION

Approximately 8,000 new cases and 400 deaths from testicular cancer are expected in the United States in 2006 [1]. In men 15–35 years old, testicular germ cell tumors (GCTs) are the most common solid tumors. Fortunately, almost all patients with early GCTs and 70%–80% of men with advanced malignancy are cured by front-line chemotherapy. This review article will describe the role of salvage therapy for men who relapse following front-line chemotherapy. Unless specifically indicated, almost all subjects in salvage therapy protocols had nonseminomas.

Efficacy of Front-line Chemotherapy

Approximately 90% of men with good-risk metastatic GCTs by the International Germ Cell Cancer Collaborative Group criteria achieve 2-year freedom from progression with four cycles of etoposide plus cisplatin (EP) or three cycles of bleomycin plus EP (BEP) [2–4]. Poor-risk GCTs require four cycles of BEP that attains an approximately 45% long-term disease-free survival [5]. Most cases of intermediate-risk GCTs are considered to require four cycles of BEP with a durable disease-free survival of approximately 75%. Men with nonseminomatous GCTs require postchemotherapy surgical resection of residual masses, if technically feasible, to attain complete remission (CR). These
residual masses contain teratoma and/or nonteratoma GCT in approximately 50% of patients [6]. If nonteratoma GCT is found, two additional cycles of adjuvant EP have traditionally been offered, although its definitive value is unproven [7]. Men with seminomas who display a residual mass following chemotherapy may be observed if <3 cm or positron emission tomography (PET) scan negative and may need surgical resection if PET scan demonstrates hypermetabolism [8, 9].

**CONVENTIONAL SALVAGE CHEMOTHERAPY**

**VeIP/VIP**

At Indiana University (IU; Indianapolis, IN), 135 patients with progressive GCTs after cisplatin-etoposide-based combination chemotherapy (excluding cisplatin-refractory patients progressing during or within 3 weeks of therapy) were treated with second-line vinblastine, ifosfamide, and cisplatin (VeIP) [10]. Sixty-seven patients (49.6%) achieved disease-free (NED) status after chemotherapy with or without surgical resection of residual tumor. Overall, 42 patients (32%) were alive and 32 (23.7%) were continuously NED after a minimal follow-up of 6 years (Table 1). None of the 32 patients with nonseminomatous extragonadal tumors were NED compared with 30 of 100 patients with testicular primaries. In contrast to patients who relapse within 2 years of chemotherapy, patients with late-relapse GCT beyond 2 years are highly chemoresistant. In a separate report of 65 patients treated for late relapse with cisplatin-based combination chemotherapy, 17 (26.2%) had a CR, and only two patients who had not received prior chemotherapy have been continuously NED with chemotherapy alone [11].

At the Memorial Sloan-Kettering Cancer Center (MSKCC; New York), 56 patients with advanced GCT resistant to one prior cisplatin-containing regimen were treated with a salvage chemotherapy regimen of ifosfamide, cisplatin, and either vinblastine or etoposide (VeIP/VIP) [12]. Twenty (36%) of 56 men achieved a CR. Thirteen (23%) were alive and NED at a median follow-up of 52 months, and the median survival was 18 months (Table 1). Among 17 patients with a testis primary site and a prior CR to first-line therapy, 65% were alive and 41% were NED, and the median survival time had not been reached. In contrast, among 39 patients with an extragonadal primary tumor or with a testis primary and an incomplete response to first-line therapy, 31% were alive and 15% continuously NED, with a median survival of 12 months.

The European Group for Bone and Marrow Transplantation recently reported IT-94, a prospective, randomized trial of second-line therapy of 280 patients assigned to receive either four cycles of VIP/VeIP or three such cycles followed by high-dose chemotherapy (HDCT) with carboplatin, etoposide, and cyclophosphamide with hematopoietic stem cell support [13]. Similar complete plus partial response (PR) rates were observed in both treatment arms (56%). There were 3% and 7% toxic deaths with conventional- and high-dose chemotherapy, respectively. No significant improvements with high-dose therapy were observed in either 3-year event-free survival (35% vs. 42%; \( p = .16 \)) or overall survival (53%). This trial represents more recent and multi-institutional data for the VIP/VeIP regimen and seems to indicate a better outcome with this regimen compared with the single-institution, nonrandomized studies mentioned herein.

**Paclitaxel**

Single-agent paclitaxel has been evaluated in several small phase II trials. In a trial conducted by the MSKCC including patients who had received one previous cisplatin-containing regimen, 250 mg/m² paclitaxel was administered by continuous infusion over 24 hours every 3 weeks [14]. Of 31 patients, eight (26%) achieved a partial or complete response (Table 1). Responses were achieved in those who had failed to respond to VIP and in men with poor prognostic features, including mediastinal primary site, and with an incomplete response to prior cisplatin therapy.

In another phase II German trial, 24 patients with relapsed, mostly cisplatin-refractory, metastatic GCTs were treated with 3-hour paclitaxel infusions of 225 mg/m² every 3 weeks [15]. The patients had received a median of seven platinum-containing treatment cycles prior to paclitaxel, and 12 patients had previously received high-dose carboplatin/etoposide-based salvage therapy with autologous stem cell support. Six patients (25%) achieved partial or complete responses (Table 2). In addition, five patients (21%) displayed stabilization. The median duration of responses to paclitaxel was 8 months.

**TIP**

Forty-six patients with recurrent metastatic GCTs were treated with paclitaxel and ifosfamide plus cisplatin (TIP) as second-line therapy at MSKCC [16]. Eligibility criteria required that patients have both a testis primary site and a prior CR to front-line chemotherapy (i.e., a relatively favorable prognosis). The paclitaxel dose given as a 24-hour infusion was increased until the maximum tolerated dose of 250 mg/m² was reached and all patients received prophylactic granulocyte colony-stimulating factor (G-CSF). Thirty-two (70%) of 46 patients achieved a CR to treatment. Twenty-nine patients were NED at a median follow-up of 69 months, resulting in a 63% durable CR rate.
and a 2-year progression-free survival rate of 65% (Table 1). Seven (50%) of 14 patients with late-relapse disease achieved a CR to treatment with chemotherapy followed by surgical resection, and they remained continuously NED at a median follow-up of 51 months.

A British Medical Research Council (MRC) multicenter phase II trial reported the use of second-line TIP (with 175 mg/m² paclitaxel over 3 hours) without G-CSF support after initial BEP chemotherapy [17]. Of 43 evaluable patients, 26 (60%) achieved a CR with negative markers. Survival at 1 year was 70%, and failure-free survival was 36%. In the group of 26 patients meeting the “good-risk” criteria described by the MSKCC, the CR rate was 73% compared with 41% for the 17 “poor-risk” patients. These results seem inferior to the MSKCC data, where TIP therapy was administered more intensively, at a higher dose, and with

### Table 1. Outcomes with second-line salvage therapy for recurrent germ cell tumors

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Institution</th>
<th>No. of patients</th>
<th>Durable remission rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VeIP [10]</td>
<td>IU</td>
<td>135</td>
<td>23.7</td>
</tr>
<tr>
<td>VeIP/VIP [12]</td>
<td>MSKCC</td>
<td>56</td>
<td>23</td>
</tr>
<tr>
<td>VeIP/VIP [13]</td>
<td>EBMT</td>
<td>128</td>
<td>35</td>
</tr>
<tr>
<td>Paclitaxel [14]</td>
<td>MSKCC</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td>TIP [16]</td>
<td>MSKCC</td>
<td>46</td>
<td>63a</td>
</tr>
<tr>
<td>TIP [17]</td>
<td>MRC</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>TIP [18]</td>
<td>Slovakian</td>
<td>17</td>
<td>47</td>
</tr>
<tr>
<td>VIP/VeIP → HDCT [13]</td>
<td>EBMT</td>
<td>135</td>
<td>42</td>
</tr>
<tr>
<td>VIP/VeIP → HDCT [43]</td>
<td>IU</td>
<td>136</td>
<td>68</td>
</tr>
<tr>
<td>TIP → HDCT [47]</td>
<td>German</td>
<td>62</td>
<td>25</td>
</tr>
</tbody>
</table>

* Favorable prognostic group with prior complete remission and testis primary.

Abbreviations: EBMT, European Group for Bone and Marrow Transplantation randomized trial; HDCT, high-dose chemotherapy; IU, Indiana University; MRC, Medical Research Council; MSKCC, Memorial Sloan-Kettering Cancer Center; VeIP, vinblastine, ifosfamide, and cisplatin; VIP, etoposide, ifosfamide, and cisplatin; TIP, paclitaxel, ifosfamide, and cisplatin.

### Table 2. Outcomes with third-line salvage therapy and beyond for germ cell tumors

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Institution</th>
<th>No. of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine [19]</td>
<td>IU</td>
<td>20</td>
<td>RR: 15%</td>
</tr>
<tr>
<td>Gemcitabine [20]</td>
<td>German</td>
<td>31</td>
<td>Marker normalization: 2 pts</td>
</tr>
<tr>
<td>Gemcitabine + paclitaxel [21]</td>
<td>ECOG</td>
<td>28</td>
<td>RR: 21%</td>
</tr>
<tr>
<td>Oxaliplatin [22]</td>
<td>German</td>
<td>32</td>
<td>RR: 13%</td>
</tr>
<tr>
<td>Oxaliplatin + gemcitabine [23]</td>
<td>German</td>
<td>35</td>
<td>CR: 3 pts</td>
</tr>
<tr>
<td>Oxaliplatin + irinotecan [28]</td>
<td>Greek</td>
<td>18</td>
<td>Durable CR: 3 pts</td>
</tr>
<tr>
<td>HDCT [42]</td>
<td>ECOG</td>
<td>38</td>
<td>Durable CR: 5 pts</td>
</tr>
<tr>
<td>HDCT [43]</td>
<td>IU</td>
<td>48</td>
<td>Durable CR: 48%</td>
</tr>
<tr>
<td>HDCT [45]</td>
<td>German</td>
<td>74</td>
<td>2-year EFS: 35%</td>
</tr>
<tr>
<td>HDCT [49]</td>
<td>MSKCC</td>
<td>58</td>
<td>2-year DFS: 21%</td>
</tr>
<tr>
<td>IT → HDCT [50, 51]</td>
<td>MSKCC</td>
<td>47</td>
<td>3-year DFS: 43%</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HDCT, high-dose chemotherapy; IT → HDCT, ifosfamide plus paclitaxel followed by HDCT; IU, Indiana University; MRC, Medical Research Council; MSKCC, Memorial Sloan-Kettering Cancer Center; pts, points; RR, response rate.

www.TheOncologist.com
growth factor support. In another small, 17-patient Slovakian study of second-line TIP, 11 patients (65%) achieved favorable response, with seven complete responses (41%) [18]. The estimated 2-year disease-free survival was 47%.

**Gemcitabine**

In a phase II IU trial, 13 of 20 evaluable patients had received three prior regimens, and 13 patients were platinum-resistant (defined as progression during or within 4 weeks of platinum treatment) [19]. There were five extragonadal cases and two patients with late relapse beyond 2 years. 15% (5 out of 20) patients achieved an objective response, including one CR (Table 2). Three additional patients had a minor radiographic or serologic response.

In a phase II German trial of 31 patients who had received two or more cisplatin-containing regimens, eight had extragonadal primary tumors [20]. The median number of prior cisplatin-based chemotherapy cycles was seven; 22 patients (71%) had received HDCT with autologous stem cell transplantation, and 19 (61%) had received paclitaxel. Overall, six patients (19%) responded favorably to treatment, including two who experienced marker normalization and four who had a >75% decline of tumor markers (Table 2).

**Gemcitabine Plus Paclitaxel**

A phase II trial was conducted by the Eastern Cooperative Oncology Group (ECOG) to evaluate the efficacy of combination therapy with gemcitabine plus paclitaxel [21]. The patients had received up to three prior regimens, with 10 patients who had undergone HDCT; 6 (21.4%) of 28 patients responded, including three complete responses (Table 2). Two of the complete responders were continuously NED at 15+ and 25+ months. Toxicity was primarily myelosuppression but was manageable, with only a single case of neutropenic fever.

**Oxaliplatin-Based Regimens**

The German Testicular Cancer Study Group has reported the activity of single-agent oxaliplatin and combination oxaliplatin plus gemcitabine. Thirty-two patients with nonseminomatous, cisplatin-refractory GCTs or relapsed disease after HDCT plus autologous stem cell support were treated with single-agent oxaliplatin [22]. Overall, four patients (13%) achieved a partial remission, and two additional patients achieved disease stabilization (Table 2). Another phase II study of 35 men with heavily pretreated GCTs employed oxaliplatin plus gemcitabine [23]. Three patients attained a CR, and all three patients with CR remained NED at 16+, 12+, and 4+ months (Table 2). A Greek phase II study reported the activity of oxaliplatin plus gemcitabine in extensively pretreated men [24]. Of 28 patients assessable for response, four attained a CR (Table 2). One of the complete responders relapsed after 7 months and went into NED status lasting for 11+ months after resection of lung metastases, whereas the rest of the complete responders were continuously NED at 14+, 19+, and 28+ months with the regimen plus or minus surgery.

**Irinotecan-Based Regimens**

Both topoisomerase I inhibitors irinotecan and topotecan demonstrated no activity in phase II trials of patients with recurrent GCT [25, 26]. Because of preclinical evidence for synergy for irinotecan with cisplatin, a phase II trial evaluated cisplatin or nedaplatin plus irinotecan for recurrent GCTs resistant to first- or second-line cisplatin-based chemotherapy [27]. In 18 evaluable patients, the response rate was 50% (two CRs and seven PRs), and the 5-year survival rate was 53% (Table 2). Pectasides et al. [28] treated 18 patients with relapsed or cisplatin-refractory GCT with oxaliplatin plus irinotecan. Seven patients (40%) achieved a response, including four complete and three PRs (Table 2). One of the complete responders relapsed after 2.5 months, and the remaining three were continuously NED for 11+, 14+, and 19+ months. In the absence of randomized data, it is difficult to define the role of irinotecan in these combination regimens.

**Prognostic Factors with Salvage Chemotherapy**

A Norwegian report identified 164 progressing patients (testicular, 83%; extragonadal, 17%) of 795 patients treated with platinum-based first-line chemotherapy for metastatic GCTs [29]. Three prognostic factors remained in the multivariate analysis: progression-free interval, CR to induction treatment, and the level of serum β-human chorionic gonadotropin (βHCG) and α-fetoprotein (AFP) at relapse. Those patients with a progression-free interval of <2 years, less than CR to induction chemotherapy, and high markers at relapse (AFP >100 kU/l or βHCG >100 IU/l) formed a poor-prognosis group, and none of them survived beyond 3 years. Patients with up to two of these risk factors formed a good-prognosis group, with a 47% 5-year survival. A subset of patients from the good-prognosis group with a progression-free interval of ≥2 years had a 5-year survival of 61%. The earlier MSKCC report of 94 patients mirrored these data and indicated that a CR to front-line therapy, cisplatin-based salvage regimen, testis primary site, and normal serum βHCG and lactate dehydrogenase levels confer better outcomes [30]. Patients with a prior incomplete response had a particularly poor prognosis, with only 4 (9%) of 52 patients alive after a median follow-up of
approximately 3 years compared with 15 of 42 (36%) alive with a prior best response of a CR. In a report of 203 patients treated with second-line VIP or VeIP, four prognostic factors were identified: incomplete response to initial therapy, extragonadal origin, lung metastases, and elevated markers (HCG >10,000 mIU/ml or AFP >1000 ng/ml) [31]. Patients with either marker elevation or extragonadal origin and at least one other poor prognostic factor had a complete response rate of 4%, with no durable remissions, whereas patients with testicular primaries and nonelevated markers displayed a CR rate of 62% and a 3-year survival of 43%. These risk categories may differ significantly in the various populations in the phase II studies described herein, leading to different outcomes unrelated to therapy. Late-relapse GCTs defined as those that relapse beyond 2 years are a distinct chemoresistant subset that entail surgical salvage.

**BIOLOGIC AGENTS**

Although 22 of 96 specimens overexpressed the HER-2/neu protein when measured by immunohistochemistry (IHC), only three specimens showed HER-2/neu gene amplification by fluorescent in situ hybridization (FISH) [32]. There was no correlation between the results obtained by IHC and FISH. Given the lack of concordance between IHC and FISH and the low rate of HER-2/neu gene amplification in GCTs, a clinical trial of trastuzumab treatment in patients with germ cell tumors was not considered warranted. A case report, however, has reported remission induced by trastuzumab in a HER-2-expressing cisplatin-refractory patient with GCT [33]. Angiogenesis measured by microvessel density in the primary tumor significantly predicted occult nodal metastasis in clinical stage I patients [34]. In another study of 80 GCTs, including seminomas and nonseminomas, vascular endothelial growth factor expression and microvessel count were significant predictive factors for metastasis [35]. Antiangiogenic agents (thrombospondin-1 and endostatin) combined with carboplatin demonstrated the ability to suppress the progression of human germ cell tumor xenografts [36]. KIT and epidermal growth factor receptor are also expressed in a significant proportion of refractory GCTs [37]. These and other avenues for targeted therapy predicated on the biology of GCTs need to be further explored.

**SALVAGE THERAPY FOR SEMINOMAS**

**IU Experience**

A retrospective review reported 24 patients with recurrent seminoma treated with VeIP as second-line chemotherapy [38]. The minimum follow-up duration was 2 years, with a median follow-up of 7 years; 20 (83%) of 24 patients achieved a CR following VeIP alone, and one additional patient was rendered NED with the resection of residual tumor. Overall, 13 (54%) of 24 are long-term survivors with VeIP salvage chemotherapy.

**MSKCC Experience**

Twenty-seven patients with progressive recurrent seminoma were treated with salvage chemotherapy [39]. Fifteen patients received conventional cisplatin plus ifosfamide chemotherapy. Twelve patients were treated with HDCT followed by autologous stem cell rescue. Fifteen patients (56%) achieved a CR, nine with conventional cisplatin plus ifosfamide and six after HDCT. Fourteen patients (52%) were alive and NED, with 13 (48%) continuously NED at a median follow-up of 72 months.

**German Experience with Salvage HDCT**

The German group treated 13 patients with refractory or relapsed seminomas with HDCT as part of consecutive phase I/II studies [40]. Six patients had experienced treatment failure with prior cisplatin-based first-line treatments, and seven patients had also experienced failure with cisplatin-based salvage treatments. After HDCT, four patients became NED, and with a median follow-up of 4.5 years, five patients (38%) were alive. Patients with nonpulmonary visceral metastases, short relapse-free intervals, and cisplatin-refractory tumors were more likely to experience treatment failure. Given the favorable outcomes with conventional-dose second-line chemotherapy for relapsed seminomas, salvage HDCT may be considered for multiply relapsed seminomas.

**HDCT WITH STEM CELL TRANSPLANTATION**

**IU Experience**

Initial studies by IU and ECOG under the leadership of investigators at IU treated heavily pretreated and cisplatin-refractory disease with HDCT and demonstrated a poor durable remission rate of approximately 10% and high mortality of up to 21% [41, 42]. A recent updated report from IU examined 184 patients, of whom 136 were less heavily treated patients with testicular cancer treated with two cycles of (tandem) high-dose carboplatin and etoposide followed by peripheral blood stem cell transplantation or autologous bone marrow transplantation rescue as initial salvage chemotherapy [43–45]. Postchemotherapy resection of residual disease was performed in selected patients, with incomplete radiographic response associated with normalization of markers. Ninety-two patients (68%) are continuously NED after a median follow-up of 42 months.
suggesting that HDCT for minimally pretreated patients confers a superior outcome (Table 1). The update also revealed a 48% durable remission rate when HDCT was employed for third-line therapy and beyond in 48 patients, suggesting that tandem HDCT and improved modern supportive care may enhance outcomes for this population.

German Experience
Following two cycles of conventional-dose cisplatin, etoposide, and ifosfamide to assess tumor responsiveness, 74 patients with multiply-treated refractory or recurrent germ cell tumors received one cycle of high-dose carboplatin, etoposide, and ifosfamide [46]. Objective responses were obtained in 43 (63%) of 68 patients, including 21 (31%) CRs and 14 (20%) inoperable PRs with marker normalization. The probabilities of overall and event-free survival at 2 years were 44% and 35%, respectively (Table 2). Patients with disease refractory to the conventional doses administered pre-HDCT had a poor prognosis, with only 1 of 23 patients surviving event-free at 7 months after HDCT. However, 24 (53.3%) of 45 patients with disease sensitive to pre-HDCT chemotherapy displayed a probability of event-free survival at 2 years of 50%. Two patients (3%) died of toxicities. Another updated report of HDCT in 150 patients with relapsed GCTs who had received a median of two prior cisplatin regimens examined conventional-dose salvage chemotherapy followed by one cycle of HDCT [47]. The projected event-free and overall survival are 29% and 39%, respectively. Persisting toxicities occurred in approximately one third of the long-term survivors.

Eighty patients who experienced recurrence following one previous regimen received salvage treatment with three cycles of TIP followed by one cycle of HDCT with carboplatin, etoposide, and thiotepa [48]; 55 (69%) of 80 patients responded to TIP, 24 (30%) had stable disease (n = 5) or progression (n = 19), and one patient died. Only 62 (78%) of 80 patients received subsequent HDCT. Forty-one patients (66%) responded, and one patient died from multiorgan failure. Overall and event-free survivals at 3 years were 30% and 25%, respectively (Table 1). Significant grade 2 to 4 neurotoxicity was observed in approximately one third of patients.

Postchemotherapy resections of residual tumors with positive or negative markers were performed in 57 patients who had been treated with HDCT [49]. Complete resections of residual masses were achieved in 52 patients (91%). With a median follow-up of 87 months, 37 (65%) were alive, and 34 (59%) of 57 patients remained continuously NED. Patients with viable carcinoma remained continuously NED compared with 24 (77%) of 31 patients with mature teratoma and/or necrosis. The projected overall and event-free survival rates after 5 years in patients with and without viable cancer is 42% versus 84% (p < .01) and 38% versus 77% (p < .01), respectively. Therefore, complete resection should be an integral component of therapy following salvage HDCT when feasible.

MSKCC Experience
Fifty-eight patients with refractory GCT who had received up to three prior platinum-containing regimens were treated with one to two cycles of high-dose carboplatin, etoposide, and cyclophosphamide plus autologous stem cell support [50]. Twenty-three patients (40%) achieved a CR, and 12 (21%) were NED with an overall survival of 31% at a median follow-up of 28 months (Table 2). There were seven treatment-related deaths (12%). Another trial including 47 patients who had received up to three prior platinum regimens administered two cycles of paclitaxel plus ifosfamide administered 2 weeks apart with leukapheresis, followed by three cycles of high-dose carboplatin plus etoposide with stem cell support [51, 52]. Twenty-three (49%) achieved a CR to chemotherapy alone, and an additional three (6%) patients achieved a CR to chemotherapy plus surgical resection. Of those 26 patients, 6 relapsed, and 20 (43%) remain continuously NED at a median follow-up of 33 months (Table 2).

Italian Experience
A total of 84 patients with recurrent GCT stratified into good-, intermediate-, and poor-risk categories were treated with one to two courses of HDCT [53]. Most had received two to three prior cisplatin-containing regimens. Overall, 28 patients (33%) have been continuously NED. In the good-risk group, 24 patients (69%) have been continuously NED, compared with four patients (13%) in the intermediate-risk group and none in the poor-risk group. Treatment-related mortality occurred only among four patients in the poor- and intermediate-risk groups.

Dutch Experience
Patients with relatively good-risk GCTs relapsing from a first, second, or third CR induced by chemotherapy were administered conventional dose followed by two subsequent courses of HDCT containing cyclophosphamide, thiotepa, and carboplatin [54]. Thirty-five patients were treated, with the second course of HDCT administered in 25 patients. The median progression-free survival for all patients was 44 months.
Paclitaxel-Containing HDCT

The British Imperial College School of Medicine treated 36 men with GCTs with three cycles of conventional chemotherapy followed by one cycle of paclitaxel in addition to high-dose etoposide, carboplatin, and cyclophosphamide with peripheral stem cell infusion [55]. The 1-year overall survival rate for all patients was 67%, with a median follow-up of 29 months. For the 24 patients with cisplatin-sensitive disease, the 1-year overall and event-free survivals were 88% and 64%, respectively. For those with cisplatin-refractory disease, the 1-year overall survival was 25%. The City of Hope cancer center evaluated two tandem cycles of HDCT using high-dose paclitaxel, carboplatin, etoposide, and ifosfamide [56]. Thirty-one patients were evaluable, of whom two did not undergo HDCT due to rapid disease progression. Nineteen patients received both cycles of HDCT, eight progressed after cycle 1, three refused the second cycle, and one died of fungal infection during cycle 1. Twelve patients remain relapse-free at a median of 67 months. These small trials do not definitively establish the value of adding paclitaxel to the HDCT regimen.

Conventional- Versus High-Dose Chemotherapy

Plus Stem Cell Rescue

The European Group for Bone and Marrow Transplantation reported IT-94, which has been mentioned earlier in this review [13]. No significant improvements in outcome were observed with one cycle of HDCT, although the trial did not possess the power to demonstrate equivalence or detect a small difference. The subset with CR after HDCT had a significant improvement in 3-year disease-free survival (55% vs. 75%; p < .04).

The German and British MRC group performed a retrospective analysis of patients with or without one cycle of HDCT as part of their first salvage treatment and matched these patients for known prognostic factors [57]. Patients were matched on the basis of primary tumor location, response to first-line treatment, duration of this response, and serum levels of the tumor markers. Full matches on all five factors were found for 38 pairs of patients, and for an additional 17 pairs, matches on at least four factors could be identified. Hazard ratios in favor of HDCT were obtained between 0.72 and 0.84 for event-free survival and between 0.77 and 0.83 for overall survival, depending on the type of analysis. The analysis suggested a benefit from HDCT, with an estimated absolute improvement in 2-year event-free survival of 6%–12% and in overall survival of 9%–11%. However, this retrospective study is no substitute for demonstration of benefit in a prospective randomized trial. Tandem HDCT usually administered in the United States has not been compared with conventional salvage chemo-terapy, leaving its definitive value uncertain. Therefore, definitive evidence for the superiority of single or tandem HDCT over conventional salvage chemotherapy is lacking, with selection of therapy often based on the experience and biases of specific institutions. Heavily pretreated patients have historically experienced significant mortality with HDCT.

Prognostic Factors with Salvage HDCT

Three hundred ten patients treated with three cycles of VeIP/VIP followed by a single course of HDCT at four centers in the United States and Europe with more than 85% of patients having received at least two prior regimens were retrospectively evaluated by Beyer et al. [58]. Multivariate analysis identified lack of marker-negative remission with conventional salvage chemotherapy given in preparation for HDCT, primary mediastinal nonseminoma, cisplatin-refractory disease, and βHCG >1,000 U/I as independent adverse prognostic variables for failure-free survival. Three prognostic groups were identified: good-risk disease with no adverse factors, intermediate-risk disease with one to two adverse factors, and poor-risk disease with three or more factors. These groups demonstrated 2-year failure-free survivals of 51%, 27%, and 5%, respectively. IU has reported their experience with one to two cycles of VeIP/VIP followed by tandem HDCT (two courses) in 80 less-heavily pretreated men, of whom only 46% had received at least two prior regimens [59]. Patients with greater than two points in the Beyer score, platinum-refractory disease, βHCG ≥1,000 mU/ml, AFP ≥1,000 ng/ml, and primary mediastinal nonseminomas had 2-year failure-free survivals of 30%, 37%, 26%, 18%, and 0%, respectively. These risk categories may differ in the phase II studies described herein, leading to different outcomes independent of therapy.

Salvage for Relapse Following HDCT

A total of 101 GCT patients at IU who relapsed after high-dose carboplatin and etoposide were examined [60]. Median time to relapse was 10 months, and HDCT was the first salvage treatment in 29 patients and second or later salvage treatment in 72 patients. Fifty-four of 101 patients received post-HDCT treatment. Of these, 47 received chemotherapy, alone (n = 35) or in combination with surgery (n = 12). Seven patients underwent surgery alone. There were only 12 objective responses (three CRs and nine PRs) for 66 chemotherapy regimens given to 47 patients, for an overall response rate of 18.2%. Fifteen patients received platinum-based chemotherapy, with only one objective response. Chemotherapy was discontinued in 17% of cases because of toxicity. A longer interval between HDCT and post-
HDCT treatment was the only factor associated with response. Five patients (4.9%) were NED at 30, 53, 57, 85, and 93 months after relapse. Of these, three responded to oral etoposide and underwent resection of residual malignancy. All of the long-term survivors had surgery as a component of their post-HDCT regimen.

In an Austrian report of 191 patients pretreated by HDCT, 48 (25%) were subjected to post-HDCT chemotherapy for disease progression [61]. Marker-negative remission occurred in eight (17%), with a median survival of 26 weeks. Only 1 of 47 evaluable patients achieved sustained CR. On multivariate analysis, only treatment with paclitaxel and ifosfamide retained independent prognostic significance for survival.

A French retrospective report examined 32 patients who experienced progression after HDCT and most of whom received chemotherapy with or without surgery [62]. Of these, 19 had a prior marker-negative response, of whom eight patients achieved a CR with the resection of all residual disease and two achieved durable CR. Among 13 patients with marker-positive disease after HDCT, four men achieved a durable CR after salvage surgery or combined surgery and HDCT. Thus, 6 of the 32 patients with relapse or progressive disease after HDCT achieved a durable CR with the resection of all residual masses.

**Salvage Surgical Resection**

Patients with residual radiologic disease but marker-negative remission following salvage therapy need surgical resection as an integral component of therapy (which should not be termed surgical salvage therapy). Surgical salvage is attempted if patients have completely resectable disease and chemorefractory disease defined by (a) tumor-marker progression occurring after salvage chemotherapy with the lack of chemotherapeutic options or (b) tumor markers failing to normalize [63–68]. Resection of disease with tumor marker progression despite salvage chemotherapy is termed “desperation surgery.” However, few patients are suitable for complete resection in the face of resistant disease, and careful patient selection is warranted. Retrospective reports reveal an approximately 40%-50% probability of durable remissions with highly selected patients. Outcomes for 114 patients from IU with metastatic GCTs and elevated tumor markers after first- or second-line chemotherapy who underwent surgery with a minimum follow-up of 2 years were reported [68]. The 5-year overall survival was 53.9%, indicating that a subset of patients with elevated serum tumor markers after chemotherapy is curable with surgery.

**Therapy for Late Relapse**

Late relapses, defined as relapses occurring beyond 2 years and in the absence of a second primary tumor, typically are chemotherapy-refractory. Eighty-three patients evaluated at IU for relapse of GCT more than 2 years from initial therapy were reviewed [11, 69]. Forty-three of 49 patients who underwent surgery were rendered NED, and 20 (46.5%) remain continuously NED. Thirty-two patients received chemotherapy, but only six (18.8%) obtained a CR. Five of these patients remain continuously NED after chemotherapy alone, including three who were chemotherapy-naive. Eighteen of these 32 patients were successfully rendered NED by postchemotherapy surgery, and 12 remain continuously NED. Overall, 69 (85.2%) of the 81 treated patients ultimately achieved an NED state, and 38 (46.9%) remain continuously NED with median follow-up of 24.5 months.

In a German report of 418 patients who were relapse-free at 2 years after front-line therapy, 18 (4.3%) developed a late relapse [70]. The cumulative risk of late relapse was 1.1% at 5 years and 4% at 10 years, excluding patients with prior early relapses, who had risks of 9.4% and 29%, respectively. No case of late relapse was observed among patients receiving prior adjuvant chemotherapy. The risk of late relapse was lower in patients with good-risk nonseminomatous GCTs than in poor-risk patients. At a median follow-up of 38 months after treatment of late relapse, 36% are continuously NED, most of whom underwent surgical resection. Another German report retrospectively examined 122 patients (50 with seminoma and 72 with nonseminoma) with late relapse and demonstrated that surgery was associated with an increased chance of durable remission. AFP >100 U/l indicated poor prognosis [71]. The median intervals to late relapse were 42 months in seminoma and 64.5 months in nonseminoma. Particular risk groups for late relapse are nonseminoma with prior early relapse, patients receiving chemotherapy for disseminated disease at first presentation, and those with pure teratoma. MSKCC reported 29 patients with late-relapse nonseminomas, and salvage regimens included TIP, single agents, or an HDCT program [72]. The only CRs were observed in patients treated with TIP, with 7 (50%) of 14 patients treated with TIP achieving a continuous CR, six of whom underwent surgery for residual disease. Collectively, these data support surgery as the standard (despite lack of prospective evidence) for late relapse and preoperative chemotherapy may facilitate resection.

**Conclusions**

Because of the remarkable success of front-line chemotherapy for GCTs with EP or BEP followed by resection of residual masses, most patients do not require salvage therapy.

**SALVAGE SURGICAL RESECTION**

Patients with residual radiologic disease but marker-negative remission following salvage therapy need surgical resection as an integral component of therapy (which should not be termed surgical salvage therapy). Surgical salvage is attempted if patients have completely resectable disease and chemorefractory disease defined by (a) tumor-marker progression occurring after salvage chemotherapy with the lack of chemotherapeutic options or (b) tumor markers failing to normalize [63–68]. Resection of disease with tumor marker progression despite salvage chemotherapy is termed “desperation surgery.” However, few patients are suitable for complete resection in the face of resistant disease, and careful patient selection is warranted. Retrospective reports reveal an approximately 40%-50% probability of durable remissions with highly selected patients. Outcomes for 114 patients from IU with metastatic GCTs and elevated tumor markers after first- or second-line chemotherapy who underwent surgery with a minimum follow-up of 2 years were reported [68]. The 5-year overall survival was 53.9%, indicating that a subset of patients with elevated serum tumor markers after chemotherapy is curable with surgery.

**Therapy for Late Relapse**

Late relapses, defined as relapses occurring beyond 2 years and in the absence of a second primary tumor, typically are chemotherapy-refractory. Eighty-three patients evaluated at IU for relapse of GCT more than 2 years from initial therapy were reviewed [11, 69]. Forty-three of 49 patients who underwent surgery were rendered NED, and 20 (46.5%) remain continuously NED. Thirty-two patients received chemotherapy, but only six (18.8%) obtained a CR. Five of these patients remain continuously NED after chemotherapy alone, including three who were chemotherapy-naive. Eighteen of these 32 patients were successfully rendered NED by postchemotherapy surgery, and 12 remain continuously NED. Overall, 69 (85.2%) of the 81 treated patients ultimately achieved an NED state, and 38 (46.9%) remain continuously NED with median follow-up of 24.5 months.

In a German report of 418 patients who were relapse-free at 2 years after front-line therapy, 18 (4.3%) developed a late relapse [70]. The cumulative risk of late relapse was 1.1% at 5 years and 4% at 10 years, excluding patients with prior early relapses, who had risks of 9.4% and 29%, respectively. No case of late relapse was observed among patients receiving prior adjuvant chemotherapy. The risk of late relapse was lower in patients with good-risk nonseminomatous GCTs than in poor-risk patients. At a median follow-up of 38 months after treatment of late relapse, 36% are continuously NED, most of whom underwent surgical resection. Another German report retrospectively examined 122 patients (50 with seminoma and 72 with nonseminoma) with late relapse and demonstrated that surgery was associated with an increased chance of durable remission. AFP >100 U/l indicated poor prognosis [71]. The median intervals to late relapse were 42 months in seminoma and 64.5 months in nonseminoma. Particular risk groups for late relapse are nonseminoma with prior early relapse, patients receiving chemotherapy for disseminated disease at first presentation, and those with pure teratoma. MSKCC reported 29 patients with late-relapse nonseminomas, and salvage regimens included TIP, single agents, or an HDCT program [72]. The only CRs were observed in patients treated with TIP, with 7 (50%) of 14 patients treated with TIP achieving a continuous CR, six of whom underwent surgery for residual disease. Collectively, these data support surgery as the standard (despite lack of prospective evidence) for late relapse and preoperative chemotherapy may facilitate resection.

**Conclusions**

Because of the remarkable success of front-line chemotherapy for GCTs with EP or BEP followed by resection of residual masses, most patients do not require salvage therapy.
Patients with platinum-sensitive disease and testicular primaries enjoy better outcomes with salvage therapy. A single standard for salvage therapy does not exist. Typical second-line chemotherapy regimens include VeIP and TIP, with gemcitabine, paclitaxel, and oxaliplatin usually reserved for subsequent administration. Prospective studies definitively supporting salvage HDCT are lacking. Complete surgical resection of residual disease after achieving marker-negative remission is an integral component of therapy. Surgical salvage therapy retains an important role in patients with completely resectable platinum-refractory disease and those with late-relapse beyond 2 years. Given the young age of these patients and the poor outcomes for platinum-refractory disease and relapsed mediastinal non-seminomas, the discovery of novel active agents is critical. Recent insights into the biology of GCTs may facilitate further advances.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

G.S. has acted as a consultant for Pharmion and Imclone; is on the speakers bureau for Sanofi-Aventis, Pfizer, and Novartis; and receives research support from Eli Lilly and Pfizer. B.J.R. has served on the advisory board for Novartis and Bristol-Myers Squibb, both regarding drugs in prostate cancer; neither drug is discussed in this article. T.E.H. is on the speakers bureau for Bayer/Onyx, Pfizer, Amgen, Sanofi-Aventis, and Genentech; and has acted as a consultant and/or received grant/research support from Sanofi-Aventis, Chiron, Bayer, and Pfizer.

**REFERENCES**


43 Einhorn LH, Williams S, Abonour R. Salvage chemotherapy with high dose carboplatin + etoposide (HDCE) and peripheral blood stem cell transplant (PBSCT) in patients with germ cell tumors (GCT). J Clin Oncol 2006;24:4549a.


FURTHER READINGS

