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Review article

Salvage high-dose chemotherapy for germ cell tumors

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Abstract

Background: Salvage high-dose chemotherapy (HDCT) along with autologous stem cell transplant (ASCT) plays an important role in the management of patients with germ cell tumors (GCT) and progression after first-line cisplatin-based chemotherapy. In this review, the authors will discuss the history of HDCT as salvage management of patients with GCT, improvement in efficacy and safety over the past 25 years, prognostic factors for outcome, and the conflicting data on the optimal initial salvage approach.

Methods: The authors performed a PubMed search of HDCT and GCT to identify articles relevant to this review. After discussion, the articles felt to have contributed most notably to the field were selected for inclusion and summarized.

Results: Depending on patient selection and timing of HDCT, durable remission rates with salvage HDCT range between 30% and 63%. The combination of carboplatin and etoposide is the standard regimen for the high-dose cycles with more variability in the regimens used for stem cell mobilization. Adding a third agent, particularly an oxazophosphorine (cyclophosphamide and ifosfamide), may add toxicity without increasing efficacy. In addition, sequential (2 or 3 cycle) HDCT regimens appear more effective and safer than single-cycle HDCT regimens. The optimal initial salvage approach (HDCT or conventional-dose chemotherapy) remains an unanswered question and highly controversial.

Conclusions: Salvage HDCT with ASCT can cure a significant proportion of patients with GCT and progression after one or more lines of cisplatin-based chemotherapy and thus plays an important role in the contemporary management of high-risk patients.

Keywords: Germ cell tumors; Testicular cancer; High-dose chemotherapy; Autologous stem cell transplant

1. Introduction

Germ cell tumors (GCTs) are distinguished from other solid tumor malignancies by several unique features. First, they primarily affect younger rather than older patients, representing the most common malignancy among men between the ages of 15 and 40 years in developed countries [1]. Second, GCTs are typically exquisitely sensitive to cisplatin-based chemotherapy, resulting in the potential for patients to be cured even in the setting of widespread metastatic disease. Third, of the 20% to 30% of patients with advanced disease in whom progression is seen after first-line chemotherapy, a significant proportion can still be cured with salvage approaches. Curative salvage strategies include both conventional-dose chemotherapy (CDCT) and high-dose (HD) chemotherapy with autologous stem cell transplantation (HDCT/ASCT). Of particular interest is the pivotal role HDCT/ASCT plays in the management of patients with GCTs, although the benefit of this approach in nearly all other solid tumor malignancies (e.g., breast and ovarian) has not been clearly demonstrated.

This article reviews the current knowledge on HDCT/ASCT for the salvage treatment of patients with advanced GCTs. In addition, it focuses on whether it is possible to select which patients benefit from HDCT as opposed to CDCT. The data presented are based on the authors' assessment and discussion of relevant articles identified through a Pubmed search on HDCT for GCT.

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2. History of HDCT/ASCT for GCT

HDCT/ASCT was initially developed as a treatment for hematologic malignancies in the 1970s. Successful outcomes in patients with lymphoma and myeloma led investigators to test this strategy in a variety of solid tumor malignancies in the 1980s. GCTs were selected as a particularly attractive tumor type for study of HDCT/ASCT given the young age of the patient population with few serious comorbid conditions; the superior chemosensitivity of GCT compared with other solid tumor types; the dose-response relationship of agents with efficacy against GCT such as carboplatin, etoposide, and cyclophosphamide; and the fact that the primary toxicity of these agents was myelosuppression, which could potentially be overcome by ASCT.

Initial studies of HD etoposide [2] or carboplatin [3] monotherapy followed by ASCT conducted in the early and mid-1980s demonstrated activity with tolerable toxicity in patients with previously treated GCT. A pivotal phase I/II study initiated in 1986 by investigators at Indiana University combined HD carboplatin and etoposide (CE) followed by bone marrow ASCT in 33 patients with relapsed or refractory GCTs [4]. This study established a maximal tolerated dose of 1,500 mg/m^2 of carboplatin and 1,200 mg/m^2 of etoposide, each divided over 3 days before stem cell reinfusion. In this study, 2 cycles of HDCT were administered. Although 7 (21%) patients experienced treatment-related deaths, the complete response (CR) rate of 25% with durable remissions in 13% of patients was highly encouraging, considering that nearly all patients were treated in the third-line or later setting [4]. A follow-up multicenter Eastern Cooperative Oncology Group study using the same regimen conducted from 1988 to 1989 confirmed these results in 40 patients with relapsed or refractory GCTs (95% treated third line or later), with a 45% objective response rate, 20% CR rate, and 13% durable remission rate. Toxic deaths occurred in 13% of patients [5]. These 2 studies established 2 cycles of HD CE as the backbone of HDCT/ASCT programs for GCT and demonstrated the potential of this strategy to cure patients with previously treated disease.

3. Improving efficacy and reducing toxicity of HDCT/ASCT

Since these initial studies, efforts have focused on reducing toxicity and improving efficacy through a variety of means. Although initial studies exclusively used bone marrow as the source of autologous stem cells, introduction of granulocyte colony-stimulating factor in the mid-1990s, with the ability to mobilize stem cells from the bone marrow to the blood, has allowed switch to the less morbid collection of peripheral blood stem cells. In addition, use of peripheral blood stem cells is associated with a shorter duration of neutropenia and transfusion dependence [6]. Similarly, use of granulocyte colony-stimulating factor after stem cell reinfusion beginning in the mid-1990s has also led to a reduction in the duration of neutropenia [6,7], which along with improvements in antibiotics and general supportive care as well as experience in administering intensive treatment has resulted in a marked reduction in treatment-related mortality (TRM) from 21% in the initial studies to less than 3% today (Table 1) [8,9]. Toxicity has also been reduced by administration of HDCT/ASCT earlier in the salvage setting to less heavily pretreated patients (e.g., second or third line vs. fourth or fifth line).

Several strategies to improve on the efficacy of historic results with carboplatin plus etoposide combinations have been tested including: (1) increasing the doses of etoposide and carboplatin, (2) addition of a third agent, (3) use of novel agents in the mobilizing portion, (4) earlier use of HDCT and better patient selection, and (5) increasing the number of HD cycles.

Results with 2 cycles of higher doses of etoposide (2,250 mg/m^2 per cycle) and carboplatin (2,100 mg/m^2 per cycle) were reported in 2007 by Einhorn et al. Of 184 patients, 173 received both cycles of HDCT, and 116 (63%) achieved durable remissions with a median follow-up of 4 years. Only 3 (1.6%) patients died of acute treatment-related complications (Table 1). It should be noted that most patients ($n = 135$, 73%) in this series were treated in the initial salvage (second line) setting, 70% of whom achieved durable remissions. In addition, patients with late relapse or primary mediastinal nonseminomatous GCTs (PMNSGCT), factors associated with poor outcome to HDCT/ASCT, were excluded from this study [8]. Nevertheless, these results underscore the improvements in efficacy and reductions in toxicity that can be achieved with modern supportive care, use of HDCT/ASCT earlier in the disease course, improved patient selection, and escalation of etoposide and carboplatin doses.

The addition of a third drug to the carboplatin-etoposide backbone has been evaluated by several groups, with oxazophosphorines (cyclophosphamide and ifosfamide) being the most extensively studied agents. Investigators at Indiana University evaluated the combination of ifosfamide, carboplatin, and etoposide but ended the study prematurely due to nephrotoxicity experienced by 4 of the first 7 patients treated at the lowest dose level [10]. In contrast, in a German study of ifosfamide, carboplatin, and etoposide, there was no excess renal toxicity among 74 patients with GCT, and encouraging rates of 2-year event-free survival (EFS) (35%) and TRM (3%) were observed [11]. No obvious differences in supportive care or method of administration of ifosfamide explain these disparate observations.

Motzer et al. evaluated 2 cycles of the combination of cyclophosphamide 60 to 150 mg/kg with HD carboplatin 1,500 mg/m^2 and etoposide 1,200 mg/m^2 (CECy) in 58 patients with refractory GCT, defined as either an incomplete response to first-line cisplatin-based therapy or