Are metastatic testicular tumours curable with high-dose chemotherapy and stem-cell rescue?

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A retrospective study has shown that haematopoietic stem cell rescue in tandem with high-dose chemotherapy should be considered a major treatment option in patients with testicular cancer following first-salvage chemotherapy and/or in cisplatin-refractory disease.

Although cisplatin-based chemotherapy cures approximately 80% of patients with newly diagnosed metastatic germ-cell tumours, the outcome in those failing initial chemotherapy is much less favourable and dependent on certain well-defined clinical factors.[1] Primary salvage options in patients who do not respond to first-line chemotherapy include conventional-dose cisplatin-based regimens, while high-dose chemotherapy (HDCT) with haematopoietic stem cell rescue has been actively investigated in the last two decades, with controversial results.[2]

Einhorn and colleagues have retrospectively analysed their experience of tandem HDCT with carboplatin and etoposide in a large series of consecutive men with metastatic testicular cancer that had progressed after receiving cisplatin-containing combination chemotherapy. This study shows 70% and 50% four-year disease-free survival in patients who received HDCT as second-line or third-line or later therapy, respectively. As it is a retrospective review, one may argue that the results are biased by patient selection. This does not seem to be the case, however, as even patients with very poor prognosis achieved long-term disease-free survival – 50% of survivors were classified high-risk by the International Germ Cell Cancer Collaborative Group classification[3] and 45% had platinum-refractory disease. It is important to note that all patients in this series received peripheral-blood progenitors as sources of haematopoietic stem cells. This strategy allowed a rapid engraftment, thereby permitting the administration of two courses of high-dose carboplatin plus etoposide with planned delays at three-week intervals and acceptable toxicity. In addition, peripheral-blood progenitors were enriched for CD34+ haematopoietic cells, a procedure which may have a role in eliminating possible cancer cells from the graft. The source of stem cells and their ex vivo manipulation may well have contributed to the positive results of the study, although there are no evidence-based data to support this hypothesis at present.

Results provided by Einhorn et al. are apparently in contradiction with data from two recently published randomised trials[4,5] that fail to demonstrate a benefit of HDCT over conventional chemotherapy in patients with a poor prognosis, albeit in earlier phases of the disease. Both studies, designed in the early 1990s during an era of great expectations for HDCT, were planned to detect an overoptimistic improvement of event-free survival. The use of bone-marrow stem cells in some patients has resulted in high transplant-related mor-

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Synopsis

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Background. Salvage therapy is used in patients with germ-cell tumours who relapse after initial chemotherapy, and often includes cisplatin combination chemotherapy or high-dose chemotherapy plus autologous haematopoietic stem-cell transplantation to rescue the bone marrow.

Objective. To investigate the efficacy of high-dose chemotherapy (HDCT) and stem-cell infusion as treatment for cisplatin-resistant metastatic testicular cancer.

Design and intervention. In this retrospective study, 184 patients with metastatic testicular cancer who had received HDCT and peripheral-blood stem-cell rescue from February 1996 to December 2004 were reviewed. Peripheral-blood stem cells were collected and purified before commencement of HDCT. Patients who had received first-line high-dose salvage chemotherapy and whose tumour had not progressed within four weeks of previous treatment were given standard doses of vinblastine, iphosphamide and cisplatin before HDCT. Patients who had already received iphosphamide-based salvage chemotherapy were given HDCT only. High-dose chemotherapy comprised two cycles of intravenous carboplatin (700 mg/m^2 of body surface area) plus etoposide (750 mg/m^2 of body surface area) given five, four and three days before the infusion of peripheral-blood stem cells. Following recovery of granulocyte and platelet counts, a second cycle of HDCT was administered.

Outcome measure. The primary outcome measure was duration of disease-free survival.

Results. The median age of patients was 31 years (range 15–58 years). All but 11 of the 184 patients received the second course of HDCT. Over a median follow-up period of 48 months (range 14–118), 116 patients remained disease free. Complete remission was noted in six patients, four after receiving paclitaxel plus gemcitabine, and two after undergoing subsequent resection of a germ-cell tumour. Among the 135 patients who received HDCT plus haematopoietic stem-cell rescue as second-line therapy, 94 were disease-free during follow-up. Of 49 patients who received treatment as third-line or later, 22 were disease-free throughout follow-up. Among the study participants, 40 patients had platinum-refractory disease, of whom 18 were disease-free during follow-up; of the 144 patients with platinum-sensitive cancer, 98 were disease-free at study completion. Approximately 74% of patients with seminoma and 60% of patients with nonseminomatous germ-cell tumours were disease-free throughout follow-up. Three drug-related deaths occurred during treatment.

Conclusion. HDCT plus haematopoietic stem-cell rescue can potentially cure patients with testicular tumours, even when used in platinum-refractory disease or as third-line or later treatment.

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tality in these studies. Nevertheless, HDCT provided statistically significant benefit in the subgroups of patients with unsatisfactory marker decline during first-line chemotherapy[4] and who achieved complete response with conventional therapy.[5] We believe that, on the basis of the robust data provided by Einhorn and colleagues, a well-designed randomised trial of haematopoietic-stem-cell transplantation and HDCT versus conventional-dose chemotherapy should be performed in patients with poor-prognostic clinical features who relapse after initial chemotherapy.

At present, there should be no debate on the use of tandem-HDCT in patients with germ-cell tumours who have failed second-line therapy.

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