

Salvage chemotherapy for metastatic germ cell tumours: The known unknowns

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High-dose chemotherapy (HDCT) with autologous hematopoietic support in metastatic germ cell tumours (GCTs) has been investigated for over 25 years. Initial phase I/II studies achieved durable remissions with HDCT for a small subset of heavily pre-treated platinum-refractory patients with relapsed disease.¹⁻³ Survival for metastatic GCTs has dramatically improved from 5% in the early 1970s to about 80% today.^{4,5} This improvement has been largely attributed to the advent of cisplatin-based chemotherapy and modern surgical techniques. The outcome for the 20% to 30% of metastatic GCTs whose disease relapses following cisplatin-based chemotherapy is much less favourable. Options for salvage therapy include conventional dose cisplatin-based chemotherapy (CDCT), with paclitaxel-ifosfamide-cisplatin (TIP)⁶ or etoposide-ifosfamide-cisplatin (VIP)⁷ or HDCT with autologous stem cell transplantation (ASCT). As initial therapy for patients with poor risk chemosensitive metastatic disease, upfront HDCT compared with CDCT has demonstrated no survival advantage in randomized trials.⁸⁻¹⁰ Whether HDCT is superior to CDCT as first-line salvage therapy for patients with relapsed disease is controversial. The only randomized trial conducted in this setting (European Group for Blood and Marrow Transplantation [EBMT]-IT-94) failed to show superiority for three cycles of CDCT with VIP or vinblastine-ifosfamide-cisplatin (VeIP) followed by HDCT compared with four cycles of CDCT.¹¹ However, there were methodological limitations to this study, such as the inclusion of cyclophosphamide, a drug with minimal activity in GCT, in the high-dose chemotherapy regimen and a lack of standardization for surgical and systemic treatment following progression.

Recently, the International Prognostic Factor Study Group (IPFSG) retrospectively reviewed data from 1984 patients with relapsed GCT previously treated with cisplatin-based combination chemotherapy.¹² A five-category prognostic factor model was developed that reflected large differences in outcome, with progression-free survival (PFS) and overall survival (OS) at 2 years ranging from more than 70% in the most favourable group to less than 10% in the highest risk group. A subsequent retrospective analysis from the same group showed an improvement in PFS and OS in each prognostic group (with the exception of OS in the low-risk group) for upfront HDCT versus CDCT.¹³ In this issue of *CUAJ*, Beausoleil and colleagues provide a single institution retrospective analysis from the London Health Sciences Centre of 38 patients with relapsed GCT treated with first-line salvage chemotherapy with either four cycles of VIP/VeIP as CDCT or three cycles of VIP/VeIP followed by a single cycle carboplatin-based HDCT over a 20-year period.¹⁴ The authors' conclude that the IPFSG prognostic factor model performed similarly in their institutional dataset and that CDCT plus HDCT was superior to CDCT alone (2-year PFS 78% vs. 22%; 5-year OS 72% vs. 19%). This study demonstrates that IPFSG model is applicable to a Canadian context and provides additional support for the use of HDCT as first-line therapy for appropriately selected patients with relapsed metastatic GCT.¹⁴

Retrospective comparisons of HDCT versus CDCT alone as first-line therapy for relapsed GCT are limited by several considerations: physicians may identify healthier patients who are able to tolerate HDCT compared with CDCT alone; the CDCT comparator group includes patients who were planned to receive HDCT after initial tumour debulking with CDCT, but never received HDCT because of toxicity or an inadequate therapeutic response; and the observed differences may be due to improvements in supportive care and surgical techniques for resection of residual masses that coincide with a greater proportion of patients receiving

upfront HDCT compared with CDCT alone over time. An international randomized trial (TIGER) plans to randomize 390 patients to four cycles of CDCT with TIP compared with two cycles of paclitaxel-ifosfamide followed by three cycles of high-dose carboplatin and etoposide with autologous stem cell support (TI-CE).¹⁵ Whether this study will complete its planned accrual to definitely address this important question is unknown, as studies in metastatic GCTs have been increasingly difficult to conduct, due to the relative rarity of the patient population,¹⁶ the challenges of securing support for an international academic trial without a pharmaceutical sponsor, and the practice patterns of many institutions who have adopted HDCT as a first-line strategy based upon the existing non-randomized data.

Notwithstanding this lack of level I evidence in support of upfront HDCT for relapsed disease, there are many unanswered questions in the management of relapsed GCTs that may be addressed by non-randomized data analyses. These unanswered questions include: the optimal number of cycles of HDCT (one, two and three cycles have been used by different groups) with autologous stem cell support; if relapsing patients should proceed directly to HDCT upon diagnosis of relapse or if they should initially be treated with one to three cycles of induction CDCT to stabilize their disease and allow time to coordinate HDCT with autologous stem cell support with the transplant team; and if there are certain groups of patients with relapsed disease, such as patients with primary mediastinal non-seminoma or late (>2 years) relapse that cannot be resected surgically, whose outcome is so poor that they should not be considered candidates for HDCT. What is clear, however, is that GCTs are unique as a metastatic solid malignancy that can be cured following relapse with additional chemotherapy. This medical imperative demands that all patients with relapsed GCT be managed in centres with specialized expertise.¹⁷⁻¹⁹

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