Is high-dose chemotherapy superior to conventional chemotherapy as first salvage treatment for patients with metastatic germ cell tumors?

Bassel G. Bachir, MD; Wassim Kassouf, MD, FRCSC

Department of Surgery (Urology), McGill University, Montreal, QC

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There is little prospective data on the optimal treatment of patients who fail first-line chemotherapy in advanced germ cell tumours (GCT). What makes matters more complicated is the considerable variability in what is broadly referred to as conventional dose chemotherapy (CDCT) and high-dose chemotherapy (HDCT), both considered accepted salvage chemotherapeutic regimens in advanced GCT. While other combinations have been investigated, salvage CDCT commonly consists of cisplatin plus ifosfamide and either etoposide (VIP), vinblastine (VeIP) or paclitaxel (TIP). All three have been studied prospectively, with VIP and VeIP showing complete response (CR) rates ranging from 37% to 50%. More recently, TIP has shown CR as high as 70% and as low as 19% to 41%. However, these studies have been criticized for either selecting a favourable patient population[1-3] or using suboptimal dosing of paclitaxel and/or ifosfamide.[4,5]

In HDCT, the standard is administering chemotherapy at doses of up to five times the norm, with the most commonly used drugs being carboplatin and etoposide (CE). In a retrospective series of 184 patients who received HDCT, 63% achieved a durable response with high-dose CE, either with or without a preceding cycle of VeIP. Patients who achieved remission also received adjuvant oral etoposide.[6] In contrast, in a more recent prospective study on 107 patients who received HDCT, 50% (54) achieved CR, with treatment consisting of three cycles of high-dose CE, preceded by two cycles of paclitaxel and ifosfamide given 2 weeks apart (TI-CE).[7]

Ideally, properly constructed prospective randomized trials must be set up to address the issue at hand, in view of the global differences in what constitutes HDCT and CDCT regimens, and the worldwide variability in treating this disease where HDCT may be offered as first, second or even third-line therapy. Is CDCT enough as first-line therapy in patients with advanced GCT, or should it be consolidated with HDCT? Only one prospective randomized trial has addressed this issue.[8] In the IT-94 study, CDCT patients received four cycles of VIP or VeIP, whereas HDCT patients received one cycle of high-dose CE and cyclophosphamide preceded by three cycles of VIP or VeIP. No difference in survival was noted between the two groups. However, criticisms of this study included the use of only one cycle of CE (as opposed to two or three), and the unusually high mortality rate with HDCT (7%).[8] In contrast, data based on >1600 patients from two retrospective studies have shown a significant advantage to HDCT,[9,10] with a superior advantage noted in patients receiving a sequential rather than single-cycle HDCT.[10] Answering the above question is very important, as up to 30% of patients with advanced GCT are not cured with first-line therapy.[11]

In this current study, Beausoleil and colleagues should be commended for retrospectively reviewing their patients according to the newly developed International Prognostic Factor Study Group (IPFSG) classification.[12,13] The high sensitivity of this malignancy to chemotherapy and the fact that most patients with this disease are young encourages urologists/oncologists to seek a cure even if that entails intensive chemotherapeutic regimens. Despite using only one cycle in this study, it is certainly noteworthy that the routine use of HDCT had been offered at their institution since 1990. What should also be mentioned though is the potential curative role of surgery in metastatic GCTs; up to 50% of patients may have active residual disease following salvage chemotherapy.[14] Although the authors admit that some of their patients may have had surgery,[12] it is not clear how many underwent surgery and which of the two chemotherapy treatment groups they belonged to. Although the number may have been too low to mention, analysis

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could have been significantly affected given the study's small sample size.

A multimodal approach involving physicians from several specialties, including medical oncology and surgery, should be applied. Researchers have recently proposed the TIGER trial, a prospective international multicentre randomized phase III trial of initial salvage chemotherapy comparing TIP with TI-CE in patients with GCTs.[15] Patients in this study will be stratified according to the IPFSG classification system. We look forward to the start of this trial. Until the question is finally tackled in a prospective randomized fashion, standardized therapy will remain difficult to establish.

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Correspondence: Dr. Wassim Kassouf, Division of Urology, McGill University Health Centre, 1650 Cedar Ave., Rm L8-315, Montreal, QC H3G 1A4; fax: 514-934-8297; wassim.kassouf@muhc.mcgill.ca