Second high-dose chemotherapy intensification followed by hematopoietic stem cell transplantation applying a novel high-dose topotecan-based regimen in an adult Wilms' tumor patient: case report

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High-dose chemotherapy and hematopietic stem cell support remains a valuable treatment option for the rare patient population with relapsed Wilms' tumor. Here we report the case of a 22-year-old male patient treated with two cycles of high-dose chemotherapy at relapse after nephrectomy and adjuvant chemotherapy; the first cycle with melphalan–etoposide–carboplatin and the second with a novel preparative regimen incorporating high-dose topotecan (topotecan–cyclophosphamide–melphalan). A detailed discussion and literature review pertaining to that case is provided. ***Anti-Cancer Drugs*** **22:111–114 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Wilms' tumor (WT) is a highly curable childhood malignancy, with cure rates of 80–90% [1]. Disease relapse is often related to a poor outcome depending on various prognostic factors [2]. Various approaches have been investigated for treating this small cohort of children, including new combinations such as ifosfamide, etoposide, and carboplatin (ICE) [3], and final consolidation with high-dose chemotherapy (HDC) and autologous hematopoietic stem cell transplantation (HSCT) [4–7]. WT is extremely rare in adults; however, although therapeutic approaches are very similar to those applied in the pediatric population, prognosis is reported to be worse. As the number of relapsed pediatric patients remains low, experience with HDC and HSCT has been limited to a small series [4–7]. Moreover, experience with tandem and/or double HSCT has been even more limited [7]. Here we report the case of a young adult patient with relapsed WT who was managed with salvage ICE chemotherapy followed by two cycles of HDC→autologous HSCT, with the second cycle adopting a novel HDC regimen that has not been applied, to our knowledge, in WT patients, incorporating high-dose topotecan.

Case report

A 22-year-old Caucasian male patient presented at the 'Metaxa' Cancer Hospital with a recently resected stage II WT of the right kidney for further treatment. Histology was compatible with a tumor that had penetrated the renal capsule and had favorable features. He underwent six cycles of adjuvant chemotherapy with actinomycin-D and vincristine for 18 weeks. After completion of adjuvant chemotherapy, he had no evidence of disease until 9 months, when a computed tomographic (CT) scan of the abdomen showed a 4.1×3.1 cm left para-aortic mass. He received salvage chemotherapy with carboplatin (area under the curve 6) on day 1, and ifosfamide 2.0 g/m^2, and etoposide 120 mg/m^2, both on days 1–3, with granulocyte colony-stimulating factor (G-CSF, filgrastim) support. On day 14, 11×10^6 CD34/kg were harvested from peripheral blood after a single, large volume leukapheresis. Another three cycles of chemotherapy were administered, leading to partial response (PR), followed by consolidation with HDC, melphalan–etoposide–carboplatin at specific doses and schedule as shown in Fig. 1, with autologous HSC infused on day 0 (5.5×10^6 CD34/kg) (+G-CSF from day +1). Hematologic recovery was as follows: neutrophils $\geq 500/\mu$l on day +9 and untransfused platelet count $\geq 20\,000/\mu$l on day +13. Febrile neutropenia was managed with broad-spectrum intravenous antibiotics. Nonhematologic toxicities were grade 2 mucositis and gastrointestinal (GI) toxicity (grade 2 diarrhea). On day +20, a CT scan of the abdomen/pelvis showed complete disappearance of the abdominal mass. Although he was supposed to undergo a second HDC cycle (Fig. 1), he did not return. Six months later, he was readmitted with disease relapse. A CT scan of the abdomen/pelvis showed multiple, small (≤ 1 cm) hepatic nodules, confluent

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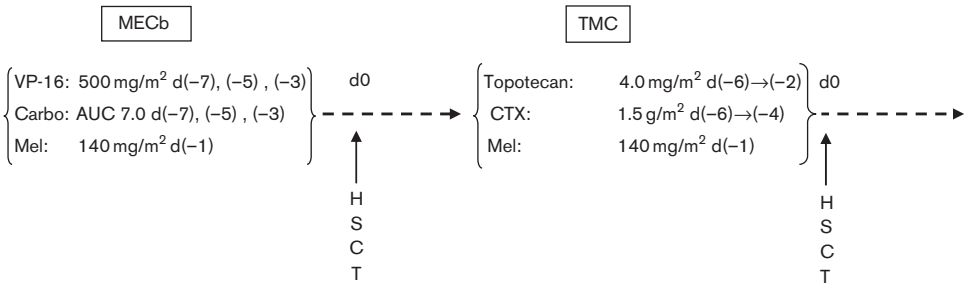
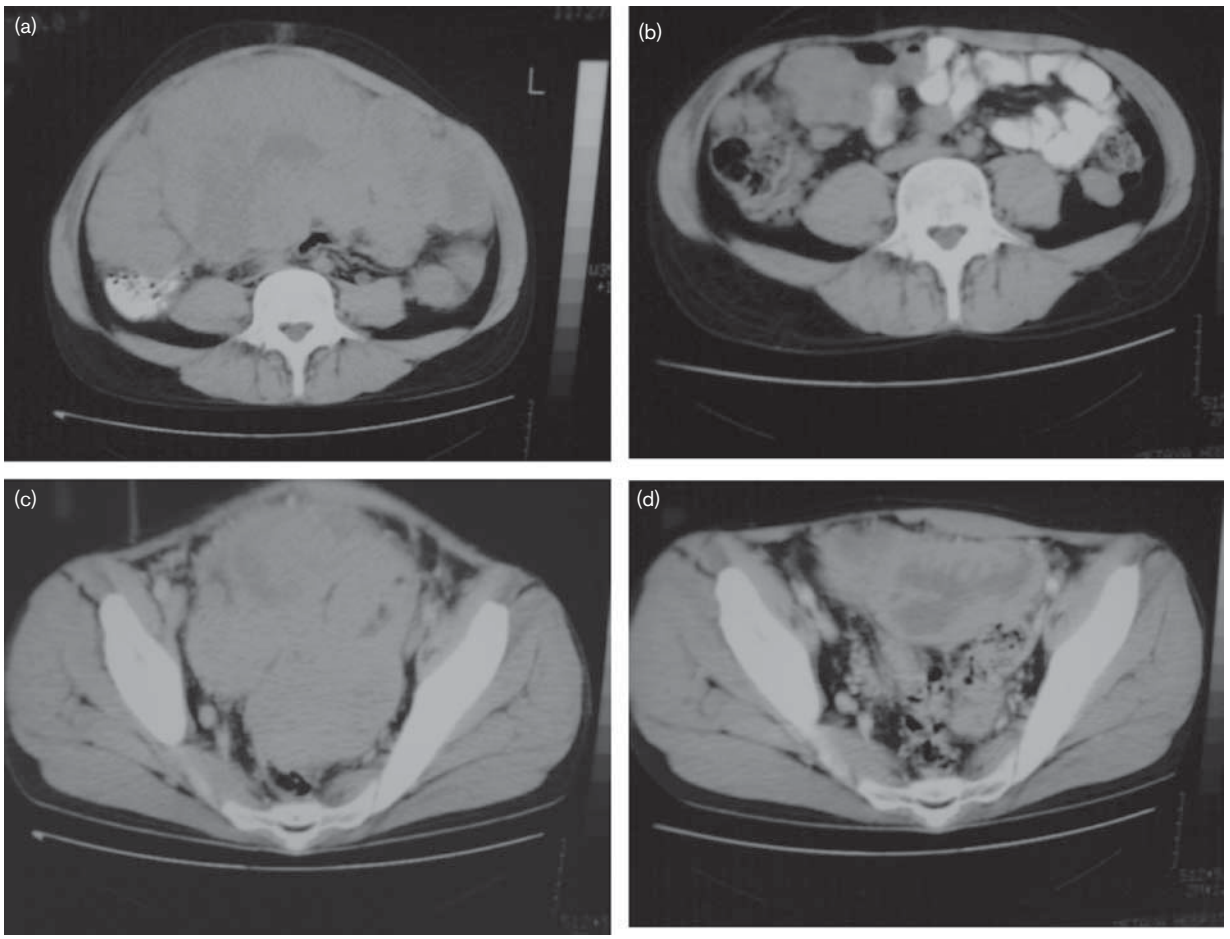
Fig. 1



Schedule of the tandem autologous hematopoietic stem cell transplantation (HSCT) initially with MECb followed by topotecan–cyclophosphamide–melphalan (TMC). Carbo, carboplatin; CTX, cyclophosphamide; Mel, melphalan; VP-16, etoposide.

Fig. 2



Tumor mass in the lower abdomen at relapse (a) before and (b) after, and disease extent in the pelvis (c) before and (d) after the second cycle of high-dose chemotherapy followed by hematopoietic stem cell transplantation.

lymph node blocks (up to 18 cm) both in the abdomen and pelvis, displacing the bowel. He received salvage chemotherapy with cyclophosphamide (CTX) and topotecan. After three cycles, he experienced a minor response not qualifying for PR, and he proceeded to HDC with a regimen consisting of topotecan–CTX–melphalan (for doses and schedule see Fig. 1). Autologous HSCs were infused on day 0 (5.5×10^6 CD34/kg) (+ G-CSF from day

+ 1). He developed grade 2 GI toxicity, epistaxis, grade 3 anemia, and febrile neutropenia, which were managed successfully. Hematologic recovery was for neutrophils $\geq 500/\mu l$ on day + 8 and untransfused platelet count $\geq 20\,000/\mu l$ on day + 12. On day + 30, a CT scan of the abdomen showed a PR (Fig. 2). Four months after the second HDC regimen, he relapsed in the abdomen. He received further treatment with paclitaxel–ifosfamide–cisplatin and bevacizumab $\times 4$ leading to PR. However, after four cycles of paclitaxel–ifosfamide–cisplatin, renal function deteriorated (grade 2) and further treatment was withheld. Three months later, he relapsed and died of inoperable intra-abdominal disease leading to intestinal obstruction. He had survived for 16 months after the second HDC topotecan–cyclophosphamide–melphalan (TMC) and HSCT cycle and for 12 months after the last relapse.

Discussion

Until now, all studies evaluating the role of HDC and HSCT in WT were derived from the pediatric population. As anticipated, no clear indications to HSCT exist as a result of the high cure rate and mostly favorable prognosis in the majority of patients after conventional front-line chemotherapy.

Very few reports regarding the application of HSCT in patients with poor prognosis, mostly relapsed WT, have been published. The first was by Garaventa *et al.* [4] and comprised 25 children enrolled in the European Group for Blood and Marrow Transplantation database. Event-free survival (EFS) was 34%, and eight of 17 children who achieved complete response (CR) were alive and disease free. Pein *et al.* [5] reported on 29 patients with relapsed WT. The preparative regimen was MECb. This study constituted the largest single-center series and showed a disease-free survival and overall survival (OS) of 50 and 60%, respectively. Kremens *et al.* [6] reported their results in 23 children with relapsed WT, applying MECb as the conditioning regimen in the majority. A 48% EFS was reported. The most recent series was reported by Campbell *et al.* [7] comprising 13 children, with CR in six and PR in seven, after salvage therapy at the time of HDC (four patients received two tandem HDC cycles). The 4-year EFS and OS rates were 60 and 73%, respectively. The Italian Association of Pediatric Hematology–Oncology reported their results in 20 children with high-risk relapsed WT treated with ICE as salvage chemotherapy followed by HDC and HSCT in 15. At 3 years, EFS and OS were 55 and 56%, respectively, and a survival benefit could be observed in patients achieving CR before the transplant [8].

The European Group for Blood and Marrow Transplantation Pediatric Disease Working Party presented data on 343 transplants in 305 patients with WT between 1985 and 2005. Several preparative HDC regimens were applied, mostly containing melphalan (MECb, 56 patients). Overall, the 4-year OS for those transplanted in second CR was 40% [9]. Only one adult WT case undergoing two cycles of HDC and HSCT has been reported in the literature so far [10].

Here we report another adult WT case treated with two cycles of HDC and HSCT. Although the first HDC cycle consisted of the commonly applied MECb, the second cycle was an entirely novel HDC regimen in this setting, incorporating high-dose TMC. TMC has been developed and tested in patients with relapsed ovarian cancer [11]. A phase I study, with escalated doses of topotecan, showed that CTX 1.0 g/m^2 days 1–3, topotecan at 4.0 mg/m^2 days 1–5, and melphalan 70 mg/m^2 days 5–6, could be combined safely and constituted the maximum tolerated dose of the regimen with up to grade 2 nonhematologic toxicity. In this report, we modified the regimen by increasing the dose of CTX to 1.5 g/m^2 on days 1–3, kept the dosage of topotecan as above, and melphalan 140 mg/m^2 on day 6. This modified TMC regimen proved to be tolerable, resulting in grade 2 mucosal and GI toxicity. Although it was planned to be administered in a tandem manner 2–3 months after the first MECb cycle, it was finally given as consolidation after three cycles of CTX and topotecan because of patient nonadherence, which led to a minor response. TMC proved to be highly cytoreductive, leading to PR maintained for 4 months without any other treatment. The theoretical basis for incorporating high-dose topotecan in alkylating agent-based HDC regimens applied in relapsed WT relies on its proven activity at conventional doses as salvage therapy in combination with CTX [12].

Therefore, the above case shows the feasibility of administering double HDC intensification aided by HSCT, in the rare adult patient population with relapsed WT, with a newly described HDC regimen in this disease, incorporating high-dose topotecan that seems to be safe and active, and could be further evaluated in relapsed WT.

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