Hematopoietic stem cell transplantation for extracranial germ cell tumors

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ABSTRACT

Malignant extracranial germ cell tumors (GCT) are uncommon in the pediatric population. Most affected children can achieve cure using conventional chemotherapy combined with appropriate local control. The role of high-dose chemotherapy with autologous stem cell transplantation (HDCT/ASCT) in GCT has been studied mainly in adult cohorts. In this article, we reviewed the current evidence and indications for HDCT/ASCT in the management of pediatric GCT.

Keywords: Neoplasms, Germ Cell and Embryonal. Stem Cell Transplantation. Pediatrics.

INTRODUCTION

Malignant extracranial germ cell tumors (GCT) are rare tumors in pediatric patients[1,2]. About 80% of children with extracranial GCTs can be cured with conventional treatment, consisting of cisplatin-based chemotherapy combined with appropriate local control[3–6]. Although rare, in cases of relapse or refractory tumors, second-line therapies are required. Salvage therapies include conventional chemotherapy and high-dose chemotherapy with autologous stem cell transplantation (HDCT/ASCT)[7]. However, there are limited data on the salvage treatment and prognostic factors of pediatric patients with relapsed/refractory (R/R) GCT[8–10].

HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION INDICATIONS IN EXTRACRANIAL GERM CELL TUMORS

HDCT/ASCT is a therapeutic option mainly investigated in adult patients with GCT, either as first-line or salvage treatment. There are only a few data on its use in pediatric patients with GCT[10–14].

HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION AS FIRST-LINE THERAPY

In adult patients, HDCT/ASCT as first-line treatment for high-risk patients had shown survival benefits in early reports, but four large and randomized studies showed no improvement in survival results[15–18]. However, in one of these trials, there was a trend towards better response with HDCT/ASCT in patients with unsatisfactory tumor marker decline[17]. Based on this result, the current protocol of the Latin American Germ Cell Pediatric Oncology Cooperative Group[19] has suggested considering HDCT/ASCT for those patients with high-risk metastatic GCT, with a slow decline in tumor markers after the first two cycles of chemotherapy.

Recently, a retrospective analysis of the large database of patients with primary mediastinal non-seminoma germ cell tumor registered in the European Society for Blood and Marrow Transplantation (EBMT) showed that HDCT/ASCT may represent a therapeutic option for these patients, after the first relapse or even as a front-line treatment[20].

HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION AS SALVAGE THERAPY

The standard rescue treatment for R/R GCT includes either conventional dose chemotherapy (CDCT) or HDCT/ASCT. One of the most used CDCT for salvage is the TIP regimen (paclitaxel, ifosfamide and cisplatin)[21].

For adult patients, HDCT/ASCT is the second-line treatment of choice in many institutions, despite the lack of positive randomized trials. The most meaningful data regarding HDCT/ASCT for patients with R/R GCT come from retrospective studies[7]. There is only one phase III trial comparing HDCT/ASCT *versus* CDCT in relapsed GCT that showed no difference in disease-free or overall survival[22]. However, this study has been criticized by the methodology and the toxic conditioning regimen utilized. Superiority of HDCT *versus* CDCT is currently being analyzed in a multicentric randomized trial—Alliance A031102 TIGER trial (Clinical Trials NCT02375204)—, which compares CDCT with TIP and HDCT/ASCT using mobilizing paclitaxel plus ifosfamide followed by high-dose carboplatin and etoposide (TI-CE) as first salvage treatment in relapsed or refractory GCT. This trial will hopefully answer the question about differences in efficacy and toxicities of CDCT *versus* HDCT salvage treatment[23].

Reports by the Indiana University and the Memorial Sloan Kettering Cancer Center showed good answers with HDCT/ASCT even in third-line and platinum-refractory patients, suggesting that in the absence of safety concerns, no subgroup of patients is so unfavorable that consideration of HDCT/ASCT should be excluded[24,25].

PEDIATRIC PATIENTS

Studies with HDCT/ASCT in pediatric patients with GCT are still scarce and mostly retrospective. De Giorgi *et al.*[11] reviewed the EBMT experience with HDCT/ASCT in 23 children with relapsed extragonadal GCT, including nine patients with GCT of the central nervous system, and described a median follow-up of 66 months, in which 8/14 (57%) patients with extracranial GCT remained in remission. HDCT protocols reported in the analysis were variable, and no toxic deaths were observed. More recently, Ussowicz *et al.*[12] reported a series of 18 children with GCT who underwent HDCT/ASCT after relapse or unsatisfactory response to first-line chemotherapy. Chemotherapy regimens MEC1 (carboplatin 1,500 mg/m^2, etoposide 1,800 mg/m^2, and melphalan 140 mg/m^2) and MEC2 (carboplatin 800 mg/m^2, etoposide 800 mg/m^2, and melphalan 140 mg/m^2) were each used in nine patients. No deaths related to toxicity were reported, but due to severe mucositis with life threatening bleeding or sepsis following the MEC1 protocol, HDCT dose was reduced (MEC2). The five-year overall survival and event-free survival (EFS) were of 76 and 70.8%, respectively. Regarding overall survival or EFS, no statistically significant difference was noted between MEC1 and MEC2 protocols[12].

Recently, our group reported the experience of two Brazilian pediatric centers with HDCT/ASCT in 34 children and adolescents with extracranial GCT. Most patients (73%) received carboplatin, etoposide and melphalan (CEM) as HDCT regimen. The five-year overall survival considering all patients was 47.1%. However, it is

important to note that 10/34 patients had progressive disease before starting HDCT/ASCT, for whom the five-year EFS was 0%. Regarding only patients who achieved disease control (complete or partial remission) before HDCT/ASCT, the five-year overall survival was 62.5%. HDCT/ASCT-related toxicity was high using this approach, pointing to the need for less toxic conditioning regimens. In conclusion, in our experience, heavily pretreated children and adolescents with extracranial GCT achieved considerable survival rates with HDCT/ASCT since at least partial control of their disease was possible before starting HDCT/ASCT[13]. The HDCT/ASCT indications for children with GCT are described in Table 1.

Table 1. Indications for hematopoietic stem cell transplantation in pediatric germ cell tumors.

	Autologous	Allogeneic
First-line therapy	Consider for patients with high-risk metastatic germ cell tumors, with a slow decline in tumor markers after two cycles of chemotherapy	Not recommended
Salvage therapy	Should be offered as the second- or third-line therapy, even in patients with platinum-refractory disease*	Not recommended

*However, in the Brazilian experience, HDCT/ASCT with a single conditioning regimen was not effective for children with progressive disease before starting transplant. Source: Elaborated by the authors.

CONDITIONING REGIMENS FOR EXTRACRANIAL GERM CELL TUMORS

According to reports on adult patients, there is a tendency to increasingly use sequential HDCT/ASCT in GCT, although prospective data from adequately powered randomized trials are still lacking to define the optimal number of cycles[15,18,23–25]. A randomized trial of the German group compared one cycle of HDCT/ASCT with three cycles. A third drug was added to the group that received one cycle, but the mortality was significantly higher, and the study was halted[26]. Gössi *et al.*[27], in a retrospective study, have not found differences in outcomes between two or three cycles of HDCT/ASCT, while one cycle seemed to yield inferior results. In subgroup analysis, the third cycle of HDCT/ASCT seemed to benefit patients who achieved a complete response after the first cycle. A systematic review suggested that at least two cycles of HDCT/ASCT should be offered, and a single cycle should not be used[28]. In the TIGER trial that is under way, patients assigned to the HDCT/ASCT arm will receive three cycles of carboplatin and etoposide[23]. Conditioning regimens recommendations for children with GCT are described in Table 2.

Table 2. Conditioning regimens recommendations in pediatric germ cell tumors.

	Standard
Sequential carboplatin and etoposide[13,22] (three cycles, each 21 days)	Carboplatin* 500 mg/m²/day or 16.7 mg/kg/day (< 2 years old or < 12 kg): D-4, D-3, D-2 Etoposide 400 mg/m²/day or 13.3 mg/kg/day (< 2 years old or < 12 kg): D-4, D-3, D-2
Alternatives	
Carboplatin, etoposide and melphalan[13]	Carboplatin 425 mg/m²/day or 14.2 mg/kg/day (< 2 years old or < 12 kg) or dosed with Calvert formula with AUC 4.1 (lower dosed used): D-6, D-5, D-4, D-3 Etoposide 337.5 mg/m²/day or 11.3 mg/kg/day (< 2 years old or < 12 kg): D-6, D-5, D-4, D-3 Melphalan 140 mg/m²/day or 4.7 mg/kg/day (< 2 years old or < 12 kg): D-1
MEC2[12]	Carboplatin 200 mg/m²/day or 6.7 mg/kg/day (< 2 years old or < 12 kg): D-6, D-5, D-4, D-3 Etoposide 200 mg/m²/day or 6.7 mg/kg/day (< 2 years old or < 12 kg): D-6, D-5, D-4, D-3 Melphalan 140 mg/m²/day or 4.7 mg/kg/day (< 2 years old or < 12 kg): D-1

*In the TIGER trial AUC = 8. Source: Elaborated by the authors.

POST-HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION RESIDUAL MASS

Although local control should be performed whenever possible before HDCT/ASCT, for patients who undergo HDCT/ASCT with residual tumor, surgical resection of residual masses plays an important role, contributing to the cure[29,30]. In a retrospective analysis, viable tumor cells were found in 46% of the patients, and they had

a significantly inferior outcome after surgery compared with patients with necrosis and/or mature teratoma, even if all cancer was completely resected[29].

Although radiotherapy has so far played a limited role in the treatment of extracranial GCT, the biological rationale for its use and potential implementation with systemic therapies exist and should be worthy of investigation in clinical trials[31]. The Brazilian Germ Cell Pediatric Oncology Cooperative Group has suggested consolidation with radiotherapy after HDCT/ASCT for some patients in whom complete surgical resection is not possible, especially in sacrococcygeal tumors[13].

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Villela NC, Ikeuti PS, Klinger PHS, Zanette A, Castro Junior CG and Lopes LF. **Conception and design:** Villela NC and Lopes LF. **Manuscript writing:** Villela NC, Ikeuti PS, Klinger PHS, Zanette A, Castro Junior CG and Lopes LF. **Final approval:** Villela NC and Lopes LF.

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