Consensus in stem cell transplantation for pediatric solid tumors

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ABSTRACT

Solid tumors in the pediatric population are preferred treated in clinical national or international protocols, in which the work of pediatric oncology cooperative groups guides the therapeutic standards and advancements. The role of high-dose chemotherapy (HDC) and hematopoietic cell transplant (HCT) in the pediatric population is usually reserved for patients or subgroups of patients who have diseases with poor prognosis and sometimes are refractory to the best available treatment, in combination to conventional chemotherapy, surgical procedure, and radiation. The Pediatric Group of the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy has revised its current consensus, providing updated recommendations for indications and conditioning protocols. This updated guidance emphasizes that, while HDC/HCT is an important tool for specific high-risk malignancies, several tumors continue to have no indication for autologous transplantation based on current evidence.

Keywords: Stem Cell Transplantation. Ewing Sarcoma. Wilms Tumor. Solid tumors. Child.

INTRODUCTION

Solid tumors in the pediatric population are preferentially treated according to clinical national or international protocols. Although the published results have not proven an unequivocal benefit for most indications yet, children and adolescents with solid tumors can undergo auto-hematopoietic *cell transplant* (HCT) following high-dose chemotherapy as a clinical option or within research protocols, preferably as part of first-line treatment strategies[1].

Desmoplastic small round cell tumor

Desmoplastic small round cell tumor (DSRCT) is an extremely rare and aggressive sarcoma that affects mainly adolescents and young adults, usually diagnosed in advanced stages. Clinical presentation by abdominal mass that originates in the serosal surfaces with synchronous peritoneal metastases and synchronous extraperitoneal metastases (90 and 50% of cases)[2,3].

Current management of the disease includes a combination of chemotherapy, radiation, and aggressive surgical resection. Despite advances in multimodal therapy, the outcome remains poor since most patients develop high rates of disease recurrence or die in three years[2,4,5]. The most effective chemotherapeutic regimen is still debated, but most are based on those used to treat other small round cell sarcomas, with a combination of an anthracycline, alkylating agent, and vinca alkaloid[2].

In various studies, high-dose chemotherapy was followed by autologous stem cell transplantation, with unclear results. Although overall survival has increased since the initial literature reviews, disease-free outcomes remain poor for patients with DSRCT, even with the incorporation of HCT[6].

Ewing family tumors

Ewing sarcoma is a malignant tumor of bone and soft tissue that most often occurs in adolescents and young adults and requires complex multidisciplinary management with chemotherapy, surgery, and radiation. The treatment of Ewing sarcoma has evolved over the past four decades through collaborative efforts and sequential therapeutic clinical trials. The improvement in chemotherapeutic regimens combined with advances in local control measures have resulted in treatment that leads to a cure for most patients who have localized disease, whereas cure rates remain low for those who have metastatic and recurrent disease[7].

Many retrospective, single-institution case series demonstrate the efficacy of high-dose chemotherapy (HDC)-HCT in patients with relapsed or metastatic Ewing sarcoma. Furthermore, in nearly all cases, these studies show favorable outcomes for the subset of patients with less advanced disease who had an optimal response to neoadjuvant chemotherapy, achieved local control, and were in either complete or partial remission at the time of HDC-HCT[7].

The EURO-EWING 99 study investigated the role of HDC-HCT in newly diagnosed Ewing sarcoma in high-risk patients. One arm studied patients with localized, high-risk disease (defined as tumor volume > 200 mL or a poor histologic response at the time of local control with > 10% viable tumor cells in the resection specimen). Patients received neoadjuvant chemotherapy and then were randomized to receive either HDC-HCT with a busulfan/melphalan conditioning regimen or seven additional cycles of chemotherapy. Patients who received HDC-HCT had a statistically significant improvement in eight-year event-free survival (60.7 *versus* 47.1%; $p = 0.026$) and overall survival (64.5 *versus* 55.6%; $p = 0.028$). The other arm investigated patients who had isolated pulmonary or pleural metastatic Ewing sarcoma and were randomized to receive busulfan/melphalan HDC-HCT *versus* chemotherapy plus whole-lung irradiation. There was no statistically significant difference in outcomes between arms with significantly increased toxicity on the HDC-HCT group[8,9]. BuMel is feasible across all age groups, but it was associated with a higher risk of severe acute toxicity than chemotherapy arm, particularly hematological, gastrointestinal, liver, sinusoidal occlusive syndrome, and infections[10,11].

The Ewing 2008 R3 study examined 109 patients who had Ewing sarcoma with disseminated disease, excluding patients who had isolated pulmonary metastases, treated with chemotherapy, and then randomized to a consolidation with treosulfan/melphalan HDC-HCT *versus* no further treatment. There was no difference in event-free survival, although a significant benefit was seen in 41 patients who were younger than 14 years old (three-year event-free survival, 39.3 *versus* 9% in the control group; $p = 0.016$)[12].

Treatment of relapsed/refractory Ewing sarcoma remains a clinical challenge; the five-year survival rate is less than 15%, and most patients suffer a subsequent episode of progressive disease within six months of initial relapse. The clinical value of HDC + HCT in patients with relapsed/refractory Ewing sarcoma is not established because of the lack of randomized or prospective data, although some patients with chemotherapy-responsive disease appear to achieve benefit from HDC + autologous HCT[13,14].

Wilms tumor

Most patients with Wilms tumors have good overall survival outcomes. Despite the relatively small number of patients with relapsed Wilms tumors, limiting the randomization of subgroups, there is relevant information extracted from literature reports favoring the use of HDC + HCT. A meta-analysis study suggested that patients with initial stage III or IV and isolated pulmonary relapse within one year of diagnosis are the most benefited by HDC + HCT[15,16].

A review of 234 transplanted children found similar findings, suggesting that HDC + HCT has a positive impact on survival in patients with advanced early stage, unfavorable histology, previous exposure to more than four chemotherapeutic agents, in second relapse, or with disease progressing after first relapse. Very high-risk patients can be evaluated to be transplanted in the first line[17].

There are no robust studies on better conditioning, but melphalan used alone seems to be an adequate regimen[18,19]. A review of the European Group for Blood and Marrow Transplantation Solid Tumors Paediatric Diseases Working Party data showed that survival was overlapping (or even higher) for patients receiving melphalan as a single agent when compared with other regimens. In addition, preliminary results from the UKW-R protocol demonstrated that melphalan as a single agent was well tolerated and effective[20,21].

Relapsed Wilms tumors in the International Society of Paediatric *Oncology* (SIOP) context is classified into three risk groups (AA, BB, CC), and primarily based upon the upfront treatment, as this was a strong prognostic factor in retrospective studies. In this context, group BB are treated with chemotherapy followed by HDT with melphalan and HCT[22].

In the current SIOP group study, a benefit in the use of HDC + HCT has been shown regarding conventional chemotherapy, in patients relapsed with anaplasia, histology with blastematous predominance, treated with more than three drugs and in second relapses. The results, however, have not been published yet, but they were presented orally in SIOP Congress 2024.

Tables 1 and 2 summarize the indications and conditioning regimens.

Diseases like osteosarcoma, rhabdomyosarcoma, and hepatoblastoma had no new data, and transplant is not indicated except in clinical trials[23].

Table 1. Disease and indication.

Diagnosis	Transplant indication	Autologous	Allogeneic
Ewing tumor	High risk[#]	Yes	No
	Relapsed	Yes	No
Wilms tumor	High risk[##]	Yes	No
	Relapsed	Yes	No

[#] Tumor volume > 200 mL or a poor histologic response at the time of local control with > 10% viable tumor cells in the resection specimen, disseminated disease, excluding patients who had isolated pulmonary metastases; [##]according to the institutional treatment protocol. Source: Elaborated by the authors.

Table 2. Conditioning regimens.

Disease		References
Ewing tumor	Bu dose per kg* in 3 h D-6 to D-3 Mel 140 mg/m^2 D-2	10
Wilms tumor	Until 12 kg melphalan 6.6 mg/kg D-2 > 12 kg melphalan 200 mg/m^2 D-2	24

*Dose per kg for every-24-hour Busulfan administration: < 9 kg: 4 mg/kg, 9 ≤ 16 kg: 4.8 mg/kg; 16 ≤ 23 kg: 4.4 mg/kg; 23–34 kg: 3.8 mg/kg; > 34 kg: 3.2 mg/kg. Whenever available target AUC of 4,500 µMol•min/L. Source: Elaborated by the authors.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Kuwahara C, Franco S, Milaré L, Castro Junior CG and Seber A. **Conception and design:** Kuwahara C, Franco S, Milaré L, Castro Junior CG and Seber A. **Analysis and interpretation of data:** Kuwahara C, Franco S, Milaré L, Castro Junior CG and Seber A. **Technical procedures:** Kuwahara C, Franco S, Milaré L, Castro Junior CG and Seber A. **Manuscript writing:** Kuwahara C, Franco S, Milaré L, Castro Junior CG and Seber A. **Final approval:** Kuwahara C.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

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