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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR NEUROBLASTOMA

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Neuroblastoma (NB) is the most common extracranial solid tumor in childhood. Overall survival increased over time in this pathology from 34 to 68% for children aged 1 to 14 years. Much of this improvement is due to the implementation and adequate indication of high-dose chemotherapy with cell rescue[1]. Standard of care for patients with high-risk neuroblastoma includes multiagent chemotherapy induction, surgical tumor resection, consolidative high-dose chemotherapy with autologous stem cell transplant, posttransplant radiotherapy, and post-consolidation treatment with biological agents and immunotherapy[2]. Despite this multifaceted treatment, relapses still occur in 50% to 60% of patients in this risk group today3.

As mentioned above, the consolidation phase of high-risk regimens involves myeloablative chemotherapy and stem cell transplantation (SCT), which attempts to eradicate minimal residual disease using otherwise lethal doses of ablative chemotherapy rescued by autologous stem cells. Several large randomized controlled studies have shown an improvement in 3-year event free survival (EFS) for treatment with SCT versus conventional chemotherapy[4].

Current protocols use carboplatin/etoposide/melphalan (CEM) or busulfan/melphalan (BuMel) as conditioning regimen for SCT. Other myeloablative regimens, including CEM plus total body irradiation (CEM-TBI), cyclophosphamide-thiotepa (TC), single-agent melphalan, busulfan-melphalan-thiotepa (BuMelThio), and tandem transplantation with TC/CEM also have been used, with recent reports of improved outcomes with tandem transplantation[5-7].

The conditioning regimen for autologous transplantation should be determined based on the best result obtained within the crrent first-line treatment protocol. A prospective randomized study conducted by International Society Paediatric Oncologie Europe Neuroblastoma Group (SIOPEN) compared CEM versus BuMel conditioning regimen, after 8-10 induction cycles with high doses of platinum. Patients included in the BuMel regimen arm had improved disease-free survival and less toxicity. For this reason, BUMEL has become the standard conditioning regimen for children treated according to SIOPEN protocol[3].

Some recent data suggest that this regimen maintains its superiority when used in different treatment strategies, such as the COG group induction model that includes topoisomerase inhibitors, anthracyclines, high-dose cyclophosphamide and cisplatin.

A major concern is the accumulation of potential toxicities from these agents, including cardiotoxicity and hepatotoxicity. Recently, the results of a prospective multicenter pilot study (COG ANBL12P1) to examine the feasibility of BuMel and ASCT when administered after induction therapy according to the COG protocol were published. In it, acceptable pulmonary and hepatic toxicities were observed[7]. Within this context, additional consolidation regimen studies are underway to define the best ASCT conditioning regimen in high-risk neuroblastoma patients treated as per COG or similar protocols. Preliminary results today suggest the superiority of the BUMEL regime over the CEM also in these cases.

Regarding in tandem transplantation in neuroblastoma, several concerns regarding conditioning regimens and toxicity profile following different induction protocols still exist. Despite a trend towards improved response in some studies, the real benefit of in tandem transplantation is still being evaluated in international cooperative groups and is not routinely incorporated as a first-line treatment protocol.

Thus, it is suggested to use the conditioning regimen proposed by the patient's treatment protocol, avoiding extrapolation cases. Protocol variations must be careful and strict, not the rule.

Attention should be given to sinusoidal obstruction syndrome and thrombotic microangiopathy, conditions that may increase transplant-related mortality and are well- described complications of neuroblastoma stem cell transplantation.

While the role of autologous HSCT in neuroblastoma is well established, the use of allogeneic HSCT is controversial. Retrospective data analysis from the Center for International Blood & Marrow Transplant Research (CIBMTR) indicates that allogeneic HSCT may be useful in patients who have not previously undergone autologous HSCT. In those patients previously transplanted with autologous cells, the benefit of allogeneic HSCT after ASCT is dismal8. Recently, haploidentical stem cell transplantation is being evaluated in children with refractory/relapsing neuroblastoma[9], but the number of patients evaluated is still too small to assess the real benefit of this practice.

Postconsolidation therapy is designed to treat potential MRD after SCT, and consist of use of anti-GD2 therapy and isotretinoin. It is associated with improved 2-year event-free survival by 20% and overal survival by 11% in patients in high-risk neuroblastoma[10]. In 2021 Brazil has approved dinutuximab beta for use in this high risk patients, although the high costs of this medication will limit its routine use in near future.

Radiation therapy to consolidate local control after surgical resection of the primary tumor should be used. The optimal dose of radiation therapy has not been determined. Extensive lymph node irradiation, regardless of the extent of surgical resection preceding SCT did not provide a benefit to patients for local progression or OS[11].

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