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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC LYMPHOMAS

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INTRODUCTION

Lymphomas are the third most common cancer of childhood in Brazil, after leukemias and central nervous system tumors[1].

The diagnosis and staging are based on clinical presentation, pathology findings with immunohistochemistry, molecular biology and radiological imaging. The treatment with multiagent chemotherapy or radiotherapy is defined according to the lymphoma subtype and risk stratification[2].

The prognosis of children and adolescents with non-Hodgkin lymphomas (NHL) and Hodgkin's lymphoma (HL) has markedly improved in the last decades, however relapsed or refractory disease is still associated with an inferior outcome. Aggressive chemotherapy followed by either autologous or allogenic hematopoietic stem cell transplantation (HSCT) is a salvage treatment strategy described in the literature, with particularities according to lymphoma subtype and to the available source of stem cells.

NON-HODGKIN LYMPHOMA

Pediatric NHL have excellent prognosis with conventional chemotherapy. Current protocols can achieve overall survival rates exceeding 80% for the most common subtypes (Burkitt and Diffuse Large B cell, Anaplastic Large cell and Lymphoblastic lymphomas).

The optimal approach for relapsed/refractory (R/R) patients, including the incorporation of new therapies, is unclear. Given the excellent results of first-line treatment in children and adolescents with NHL, clinical trials for the treatment of relapses often include heterogeneous groups of patients. This fact makes it difficult to interpret and generalize the results that are obtained.

MATURE B-CELL LYMPHOMAS

Mature B-cell lymphomas (Burkitt lymphoma – BL, and diffuse large B-cell lymphoma – DLBCL) represent the largest NHL subtype with a 90% event-free survival rates according to contemporary approaches[3]. The R/R disease prognosis is dismal, and worse prognosis factors are the first line treatment intensity, including the addition of rituximab; elevated lactate dehydrogenase (LDH), early relapses and bone marrow involvement[4].

In addition, the mature B-cell lymphoma subtype also has an impact on survival, with the DLBCL having better results when compared to BL (52%±10% x 28±3%)[5].

HSCT is considered for chemo sensitive patients, with no survival benefit for those refractory to reinduction or to first line therapy, with few anecdotal cases alive in the literature[6-,9].

Several rescue schemes are proposed, usually associated with the anti-CD20, such as high-risk blocks of BFM, R-ICE (rituximab, ifosfamide, carboplatin and etoposide), R-ICI/ICN (rituximab, ifosfamide, carboplatin, idarubicin/mitoxantrone, paclitaxel) or R-VICI (rituximab, vincristine, idarubicin, ifosfamide, carboplatin and dexamethasone). Unfortunately, progressive disease occurs in about 50% of cases during reinduction,

with better results found with the R-VICI schema (up to 20 improvement in progression free survival)[9].

It is well known that those salvage regimens are associated with severe hematological toxicities and risk of failure in mobilization and stem cell harvest. The allogeneic HSCT is an alternative to the autologous HSCT with similar outcomes and, therefore, better results than conventional chemotherapy without HSCT[8,10-13]. Most of the retrospective studies include long periods and small number of patients, not allowing conclusions regarding the Graft versus Lymphoma (GVL) effect and the potential survival advantaged associated with the allogeneic HSCT.

Although there are no prospective randomized studies exploring the best HSCT modality, there is a tendency to perform autologous transplants in DLBCL, while in BL both modalities (allogeneic and autologous) overlap, with similar results (46±5% x 44±6%)[5].

Different conditioning regimens are described for autologous transplants, mainly containing carmustine (e.g. BEAM). Since carmustine is no longer available in Brazil, busulfan-based regimens are alternatives.

For allogeneic HSCT, myeloablative regimens with Total Body Irradiation (TBI) and busulfan and Burkitt's reduced intensity conditioning including rituximab, fludarabine, thiotepa, carboplatin, mitoxantrone and paclitaxel are suggested[5,3].

LYMPHOBLASTIC LYMPHOMAS

Lymphoblastic lymphomas (LL) are the second most frequent subtype of NHL in childhood and about 10% of patients experience relapses or progression on current protocols[14]. For those patients, long-term remissions are not sustained with chemotherapy alone and bone marrow transplantation is usually recommended in patients in complete remission[15,16]. Data from the CIBMTR showed better 5-year event-free survival in patients undergoing allogeneic HSCT (40%) when compared to autologous bone marrow transplantation (4%)[12]. Thus, allogeneic HSCT based on acute lymphoblastic leukemia (ALL) principles is the standard of care for R/R LL.

LARGE ANAPLASTIC CELL LYMPHOMAS

Childhood large anaplastic cell lymphomas (ALCL) represent 10 to 15% of pediatric NHL lymphomas with survival rates ranging from 70 to 85% in different cooperative trials[17-19].

Approximately 25 to 35% of patients progress to relapsed or refractory disease. In these cases, there is no consensus on the best treatment strategy. Unlike the other NHL subgroups, salvage therapy is effective on R/R ALCL and response rates around 80% are achieved[20,21].

Bone marrow transplantation is a curative alternative for those patients and both autologous and allogeneic HSCT are addressed in the literature. Risk factors such as early relapses (< 12 months from initial diagnosis), progression during first-line therapy, involvement of bone marrow and Central Nervous System at relapse and CD3 expression on the primary tumor are associated with unfavorable outcomes in retrospective series[21,22]. Results from the CIBMTR, the Berlin-Frankfurt-Muenster group (BFM) and the Japanese group report a 5-year event-free survival of 35%, 59% and 38%, respectively[12,21,23]. Patients in CR at the time of autologous transplantation had better results when compared to patients with active disease[23].

A recent prospective trial conducted by the European group showed that late relapses could be treated with vinblastine as a single agent and that high risk disease had 65% 5-year EFS following allogeneic HSCT. The autologous transplantation arm, initially planned for patients in the intermediate risk group (CD3 negative with relapse < 1 year and who had already received vinblastine) was held after inferior outcomes results were described when compared to the allogeneic HSCT group (EFS 44% ±9%), suggesting that early relapse disease should be consolidated with allogeneic transplantation[24].

Allogeneic HSCT with myeloablative conditionings (with TBI or busulfan) and reduced intensity are described in the literature with EFS ranging from 50 to 75%[23-26].

In the recent European prospective trial published by Knorr et al, the conditioning regimen adopted for 56 ALCL relapsed patients consisted of TBI 12Gy (substituted by bussulfan in patients younger than 24months), thiotepa and etoposide.

The incorporation of new drugs, such as brentuximab vedotin and crizotinib, are explored by some cooperative groups, however the optimal approach, whether associated or not with HSCT, has not been properly established so far.

POST-TRANSPLANT MAINTENANCE THERAPY

There are few studies regarding the use of post-HSCT maintenance in NHL in the pediatric group. Tavern JA

et al published a systematic review in patients older than 18 years and no benefit was observed with the addition of rituximab in DLBCL. Check point inhibitors are promising options for future trials[27,28]. The use of Brentuximab, Crizotinib (ALK inhibitor) and Nivolumab in R/R ALCL, both as a brige to HSCT and maintanance after high dose chemotherapy have been studied, however with no conclusive results so far[29].

SUMMARY OF TREATMENT RECOMMENDATIONS FOR NHL HISTOLOGICAL SUBTYPES

In R/R NHL it is important to maintain high dose-intense treatment, avoid treatment delays and consider treatment continuation prior to full hematological recovery, especially in mature B-cell lymphomas. There is limited or no role for irradiation and surgery in these scenarios. Achieve CR prior to HSCT is associated with better survival, and early taper of immunosuppression after allogeneic HSCT may allow lower relapse rates.

Specific recommendations for each NHL subtypes are described in table 1. There are unique clinical scenarios not covered by these recommendations that may require individualized decisions.

HODGKIN LYMPHOMA

Hodgkin's lymphomas in children and adolescents, likewise pediatric NHL, have excellent survival with conventional chemotherapy associated or not with radiotherapy. Even high-risk patients at diagnosis have a good chance of cure with standard treatment and, therefore, autologous HSCT (ASCT) is not recommended as frontline therapy in pediatric HL, but it is considered for relapsed or primarily refractory diseases (R/R)[30-32].

Some risk factors have been associated with inferior outcomes for R/R patients, such as bulky disease at diagnosis, B-symptoms, extra nodal disease, first-line chemo resistance, relapses within 12 months from diagnosis, advanced stage disease at relapsed and number of previous treatment regimens. The prognostic marker that seems to be more important is the result of the fluro-deoxy-glucose positron emission tomography (FDG PET) pre HSCT with a 10-year EFS of 31% (PET positive) versus 75% (PET negative)[33-35].

Recently, a guideline was published from the EuroNet Paediatric Hodgkin Lymphoma Group[36]. According to this guideline the risk stratification at the point of relapse identifies 3 groups: low, standard and high risk groups (table 2). The low and standard risk are based on assessment of pre-salvage risk factors, and the high risk is based on response of treatment i.e., the failure to achieve a negative FDG-PET after 2 lines of salvage standard dose chemotherapy (SDCT).

The European guideline proposed that the low-risk group could be treated with SDCT plus radiotherapy consolidation only, the standard risk group could be treated with SDCT plus high dose chemotherapy and autologous stem cell transplant (HDCT/ASCT) consolidation and the high-risk group is eligible for conventional HDCT/ ASCT plus additional treatments pre and/or post HDCT/ ASCT or experimental strategies. The aim of salvage chemotherapy is to achieve a complete metabolic remission (CMR) defined as Deauville 1–3 or qPET <1.3 (in the EuroNet group the semi-quantitative "qPET" method is widely used which is a quantitative extension of the Deauville scale; Deauville 4 and 5 are respectively equivalent to qPET values of 1.3 and 2.0 and a positive PET scan is a qPET value >1.3).

Myeloablative chemotherapy with ASCT is the recommended approach for patients who develop refractory disease during therapy or relapsed disease within 1 year after completing therapy. In addition, this approach is also recommended for those who recur with extensive disease after the first year of completing therapy or for those who recur after initial therapy that included intensive (alkylating agents and anthracyclines) multiagent chemotherapy and radiation therapy[2].

Most of the conditioning regimens for ASCT include carmustine, such as BEAM (carmustine, etoposide, cytarabine and melphalan) or CBV (carmustine, etoposide and cyclophosphamide). However, as carmustine was discontinued in Brazil and in several countries as previously mentioned, there was a need to explore different regimes such as: melphalan/ etoposide; busulfan/ melphalan; gemcitabine/ busulfan/ melphalan; and alternatives to the carmustine, including bendamustine (Benda-EAM), fotemustine, lomustine (LEAM), mitoxantrone and thiotepa. There are no studies comparing the efficacy among all different conditioning regimens and therefore, there is no standard conditioning in the pediatric literature. The optimal regimen should be based on clinical status, known efficacy of previous drugs utilized, tumor localization, financial cost and regulatory approval by local authorities.

Some strategies have been adopted to improve results for high-risk R/R candidates to bone marrow

transplantation, including better salvage treatment, alternative transplant modalities, e.g. TANDEM, and post transplantation maintanence therapy.

Radiation is a well-known effective therapy for HL, however the site of irradiation and potential toxicity should be considered when it is indicated. The ideal radiation timing is controversial, although many authors recommend radiotherapy after the autologous HSCT[36].

Brentuximab vedotin (BV) (anti-CD30) can be used for salvage treatment in R/R patients, as a bridge to transplantation[37], and as a post transplant maintenance therapy[38]. In a randomized study, a 1year post-transplant maintenance with BV was associated with better disease-free survival (DFS), although no impact on overall survival was observed. Similarly, checkpoint inhibitors (PD-1) are also explored for pediatric high-risk patients, with promising results[36,37,39].

Immunotherapy remains an experimental treatment in R/ R HL in children and young people and there are clinical trials in progress. It may be considered in high risk patients that were refractory to SDCT salvage regimens. Single agent Nivolumab achieves a low CR rate and combination of Brentuximab plus Nivolumab looks more promising[36]. Pembrolizumab was well tolerated in pediatric patients and showed encouraging antitumour activity in children with relapsed or refractory Hodgkin lymphoma, similar to the experience described in adult[40,41].

TANDEM transplantation is an alternative for patients considered at high-risk for relapses after autologous HSCT. This approach consists of a myeloablative autologous HSCT followed by a non myeloablative conditioning allogeneic transplant[42].

Allogeneic HSCT can be considered for post autologous HSCT relapses, as well as in cases of failure to harvest stem cells from the bone marrow or the peripheral blood and in cases of several relapses. The conditioning regimens are either myeloablative (MAC) or reduced intensity (RIC), with an expected graft versus lymphoma effect to reduce the risk of relapse. The overall survival is comparable in both MAC and RIC approaches, with relapses more like to occur after a RIC regimen, whereas toxicity is more common following MAC strategy. The choice between RIC and MAC should consider the patient clinical status, previous treatments and the perspective of adjuvant therapy[30].

As HLA identical related or unrelated donors are only available for a subset of patients, alternative donors often need to be found. Recently, the use of T-cell-replete haploidentical stem cell transplantation (haplo-HSCT) with post-infusion cyclophosphamide (PT-Cy) in advanced hematological malignancies showed a good toxicity profile. It has been observed that haplo- HSCT act effectively against HL cells (immunological effect) and is a good choice in the treatment of poor prognosis HL in patients who do not find a HLA compatible donor[43]. Comparative studies demonstrated that Allogeneic HSCT from full-matched and haploidentical donors have similar outcomes, there is a reduced relapse rate and better overall survival with post-Cyclophosphamide haplo-HSCT[44-46].

TABLE 1. Consensus recommendation for NHL

Subtype	2nd line treatment	HSCT	Conditioning regimen
BL	2-3 courses R-ICE or R-VICI	Autologous or allogeneic	Autologous - Busulfan based regimen Allogeneic – TBI or busulfan based, Burkitt-specific RIC
DLBCL	2-3 courses R-ICE	Autologous	Busulfan based regimen
LL	Intense treatment courses analogue to high-risk ALL or relapsed ALL protocols	Allogeneic	TBI based regimen
ALCL	Vinblastine, ICE	Allogeneic for high-risk patients Vinblastine if low risk, without HSCT	TBI or busulfan based regimen

Adapted from Burkhardt B, 2021[5]

TABLE 2. Risk Stratification for First Relapsed and Refractory Classical Hodgkin Lymphoma in Children and Young People

Low Risk Group	1.Early relapse after a maximum 4 cycles of first line chemotherapy. or 2. Late relapse after a maximum of 6 cycles of first line chemotherapy. And ALL of the following • Stage at relapse is I-III • No prior RT or relapse only outside prior RT field • No excessive RT fields required in salvage
Standard risk Group	1. Primary Progressive HL 2. Early Relapse after more than 4 cycles of first line chemotherapy 3. Stage IV relapse 4. Relapse in a prior RT field 5. Relapse requiring RT in salvage that is considered as having unacceptable toxicity
High Risk Group	High risk (HR) patients are those that fail to achieve a CMR after 2 lines of SDCT on PET4. Failure to achieve a CMR prior to HDCT is associated with an inferior prognosis compared to patients that achieve a negative FDG-PET scan pre-HDCT/ASCT.

Adapted from guidelines recommendations from Euronext pediatric Hodgkin lymphoma group

TABLE 3. Consensus recommendation for HL

Recommendation	Treatment options	Conditioning regimen
ASCT: Primary refractory disease Standard or high risk relapsed who respond to salvage therapy	Salvage therapy (chemo option pre ASCT) ICE ESAHP DHAP GDP GV	BEAM or CBV* Bu Mel – low risk patients Bu Mel Gen – high risk patients LEAM Be-EAM
Post-ASCT therapy	Radiotherapy Bulky disease (>5 cm) especially if not been previously irradiated) Primary refractory disease Persistent FDG-avid disease after salvage or after ASCT Brentuximab vedotin maintenance in high-risk patients	
Allo-HCT should be used for relapse after ASCT or failure to mobilization	Options for rescue: Chemo protocol Brentuximab	RIC: Fludarabin based regimens: - Flu Mel - Flu Bu MAC regimens: - TBI based - Bu Cy
Haplo option for patients with Allo-HCT indication, without MRD.		Cy Flu and TBI 2Gy Post-cy
Tandem SCT option for High Risk patients		ASCT: MAC Allo HCT: RIC

*BCNU is not available at this moment in Brazil

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