

HSCT FOR HODGKIN LYMPHOMA

Alessandra Paz¹, Rosane Bittencourt², Decio Lerner³, Camila Manca⁴, Mair Souza⁵, Otavio Baiocchi⁶, Philip Bachour⁷, Leila Pessoa de Melo⁸, Samir Kanaan Nabhan⁹

1 Chief Hematologist Hematology and HSCT Service HCPA-UFRGS - 2 Responsible hematologist Autologous TCTH program at HCPA_UFRGS - 3 Chief Hematologist at the Bone Marrow Transplant Center (CEMO) - INCA - 4 Hematologist TCTH Service Base Hospital of São Jose dor Rio Preto - 5 Hematologist TCTH Hospital Amaral Carvalho de Jau - 6 Hematologist UNIFESP and Hospital Alemão Oswaldo Cruz - 7 Hematologist UNIFESP and coordinator of the Hematology Service and BMT Hospital Alemão Oswaldo Cruz - 8- Hematologist Medical Director of the Hematology Service of São Jose dos Campos 9 Hematologist Medical Supervisor of the TMO Unit oncology and hematology of the HC-UFPR Complex

Correspondence to? Alessandra Paz: alepaz@hcpa.edu.br

ABSTRACT

Over the past few decades, advances in combination of chemotherapy and radiotherapy have significantly improved treatment for patients with classic Hodgkin's lymphoma (cHL). Currently, more than 80% of patients aged <60 years, and mainly with localized disease, have an enormous chance of cure. However, the prognosis of patients with primary refractory disease or those who reach a complete remission (CR) and eventually relapse remains poor. Autologous stem cell transplantation (ASCT) is the standard treatment for most patients with relapsed or refractory HLC (R/R) when compared to conventional chemotherapy with a significant proportion of cured patients but 50% of them still relapse. Allogeneic transplantation is potentially the only curative therapy and since new agents such as brentuximab vedotin, nivolumab and more recently, pembrolizumab have been used before allogeneic transplant, we noticed an improved response to the procedure.

INITIAL APPROACH

After staging with the Lugano Classification, disease is, in general, classified into 3 groups: favorable localized (stages I and II, without risk factor), unfavorable localized (stages I and II with one or more risk factors) and advanced disease (stages III and IV, and some specific cases IIBX) ^[1,2,3,4,5,6,7,8,9] The risk factors, based on characteristics of subgroups of patients with a worse prognosis in clinical trials are: (A) bulky mediastinal mass, (B) extranodal disease, (C) erythrocyte sedimentation rate and (D) ≥ 3 nodal sites. The IPS, which stands for International Prognostic System, defines advanced disease as a risk; patients over the age of 45 years; male; stage IV; hemoglobin < 10.5g / L; albumin < 4g / L; leukocytes > 15×10^9 /L and lymphocytes < 600×10^9 / L . ^[8,9,10]

PET-CT with FDG is recommended both at the initial evaluation and end of treatment, its result should always be reported using the Deauville score. If possible, it can be performed after 2 or 3 cycles of chemotherapy as an interim PET for early prognosis definition. Bone marrow biopsy is useful in patients

without access to PET-CT at diagnosis, or special cases (such as in presence of cytopenias, for example).^[7,9] Response Assessment: PET-CT ^[8,9,10] Deauville scores 1 and 2 are considered negative and scores 4 and 5 are positive (active lymphoproliferative disease). Although patients with score 3 may have a good prognosis, it is recommended that if there is a plan to reduce treatment intensity, it is considered an inadequate response for safety.^[7,9,10]

We will not address first-line treatment in this article as this is not the focus of this SBTMO consensus.

AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) - IA

Management of R/R cHL includes a mandatory new biopsy if relapse occurs >12 months from the end of first-line treatment and it is highly recommended if relapse is suspected <12 months or in primary refractory disease.^[11]

The two immediate and simultaneous measures for R/R cHL consist of enrolling patient in a transplant center and initiating salvage chemotherapy. Chemo sensitive patients are those who achieve a response rate greater than 50%, with different drug-based protocols. Patients with primary refractoriness or recurrence in less than 1 year after first-line treatment have a worse prognosis.^[12] Linch and colleagues demonstrate a clear improvement in disease-free survival (DFS) for the BEAM scheme associated with ASCT.^[13,14,15,16,17,18] PET-CT is an important prognostic factor and when negative in pre-HSCT it is associated with a higher event-free survival rate.^[19,20] The Chemo rescue more frequently used are DHAP, ES-HAP,ICE with Overall Response(OR) 89%,67%,88% respectively. Gencitabine schemas are GDP,CVD e IGV with OR 62%,70 and 88%.

Anti CD30 Brentuximabe Vedotim isolated for patients that have used 2 or more

chemo schemas have been 50% OR. Combinations with Brentuximab Vedotina (BV), monoclonal antibody anti cd30 associated with several chemotherapy schemes such as: BV-DHAP has been emerging as possibilities of rescue with very encouraging results in substitution to conventional chemotherapy thanks to high rates of complete metabolic response before transplantation^[20,21,23,24].

MOBILIZATION

Different methods for mobilization are employed and there is no uniformity or significant divergences between the techniques used: a) isolated application of G-CSF in standardized doses of 10 mg and 20 mg/kg/day.^[25, 26,27] b) Cyclophosphamide + Growth Factor. Cyclophosphamide in a single dose, 1 to 2 g/m² 7 days before starting the application of G-CSF in the standard dose of 10 mg/Kg/day for 5 days.^[28,29,32,33] c) Plerixafor: Fixed dose of 20 mg or 0.24 mg/Kg of body weight for patients weighing ≤ 83 Kg, or 0.24 mg/Kg for patients over 83 kg. It should be applied after 4 days of G-CSF at a dose of 10 mg/Kg/day 6 to 11 hours before apheresis, for 1 to 4 consecutive days.^[30,31,34]

CONDITIONING SCHEMES

There are few studies to evaluate different conditioning schemes for ASCT in cHL. The BEAM scheme, Carmustine based, has always been the most used and many European groups emphasized its high antitumor response with acceptable toxicity.^[27] However, in 2015 Carmustine left the international market due to the limited availability of the alcoholic solvent necessary for its preparation. The transitory scarcity of Melphalan must also always be considered when choosing the best scheme. Table 1 show schemes that can be used with acceptable toxicity and acceptable relapse rates.

SCHEME	DRUGS
LACE35	Lomustine/Cytarabin/Cyclophofamide/Etoposide
LEAM36	Lomustine/Etoposide/Cytarabin/Melphalan
TEAM37	Thiotepa/Etoposide/Cytarabin/Melphalan
BUEM37	Busulfan/Etoposide/Melphlan
GEMBUMEL37	Gencitabine/Busulfan/Melphalan
BUCYE37	Bussulfan/Cyclophosfamide/Etoposide
Benda-EAM37	Bendamustin/Etoposide/Cytarabin/Melphalan

POST-AUTOLOGOUS CONSOLIDATION OR MAINTENANCE

Recent studies validated the risk factors for post-autologous relapse and which patients may benefit from post-transplant irradiation.^{21,22} These prognostic factors may characterize patients at higher risk of relapse after ASCT: primary refractory disease, relapse in the first 12 months after first-line treatment or after 12 months with extranodal disease or B symptoms, need for > 2 rescue lines or PR/SD before transplantation. Patients with 2 or more factors have high risk relapsed.^{20,22,23} The AETHERA study, a randomized phase III study, evaluated post-autologous consolidation therapy by comparing Brentuximab vedotin versus placebo in patients at high risk of relapse or primarily refractory and after a 5 year median follow up confirmed the DFS benefit of this strategy.²³

ALLOGENIC TRANSPLANTATION

Reduced intensity conditioning (RIC) - III C

Allogeneic hematopoietic stem cell transplantation remains the only potentially curative strategy for patients with cHL who relapse after ASCT due to graft versus lymphoma effect. However, quality of life and mortality unrelated to relapse is still significant for patients who develop acute or chronic graft versus host disease (GVHD) and severe opportunistic infections. But role and timing for an allogeneic transplantation has been questioned in recent years with the availability of new agents.^{38,39,40}

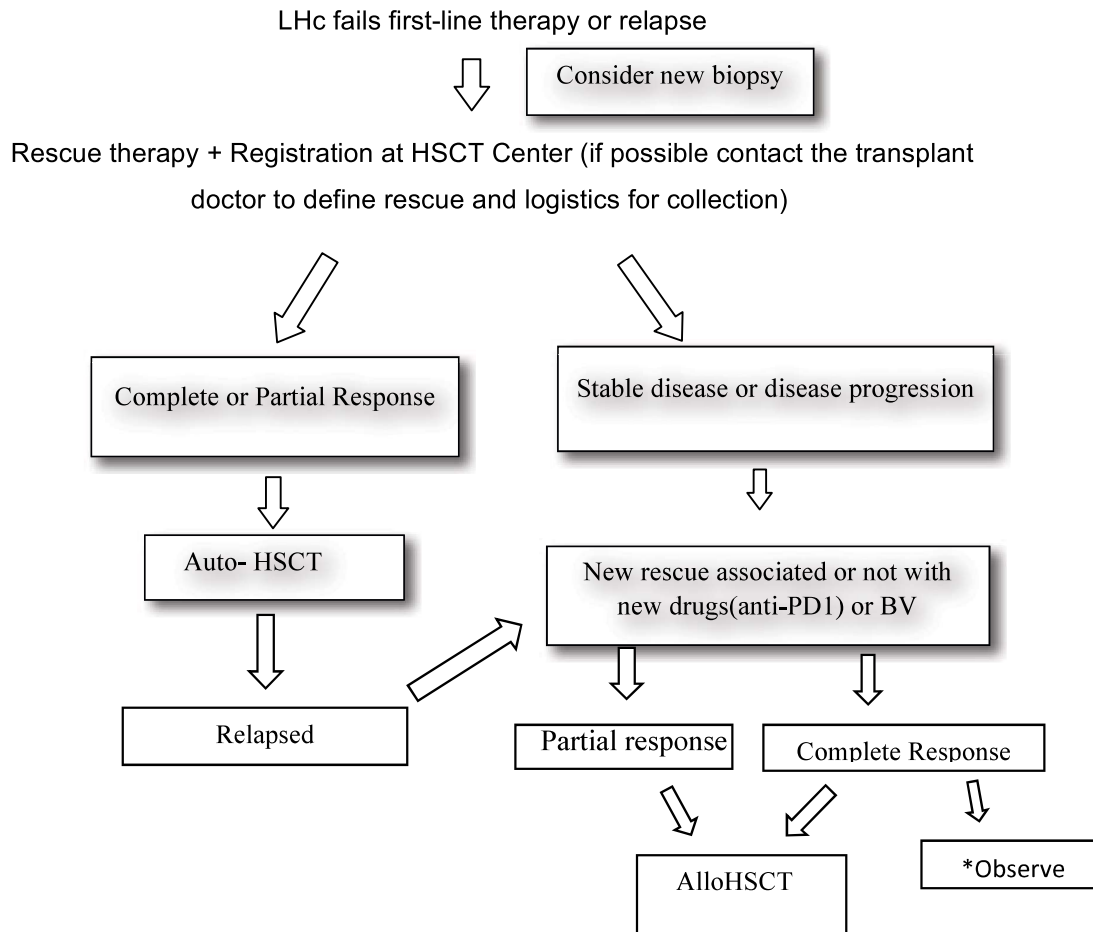
Despite the absence of randomized clinical trials, allogeneic HSCT with reduced intensity conditioning (RIC) with an HLA match or haploidentical related donor, and with an unrelated donor has been a therapeutic option for the treatment of patients with relapsed post-autologous LH or with no response to rescue therapies.⁴¹ RIC HSCT is considered the best choice by the American society because it allows a drastic reduction in mortality related to the procedure, however, the relapse rates still remain high.^{42,43} The complete response before HSCT was an important differential for the increase in lymphoma-free and global survival, emphasized in the publication by Sarina and collaborators.⁴⁴

In 2018, Gaudio et al. demonstrated through a multicenter retrospective study, no difference in OS (35%) and DFS (34%) between related and unrelated donors. Main risk factor for relapse was disease activity at time of HSCT.⁴⁵ The only prospective phase 2 study that evaluated low intensity allogeneic HSCT with 92 patients with LHc showed a TRM of 15% in 1 year and DFS and OS in 4 years completely different in the global population, 18% and 41 % respectively, and in transplant patients with a disease classified as chemosensitizable was 40% and 60%.⁴⁶

Currently, the use of monoclonal anti-CD30 antibody, Brentuximab vedotin (BV) has achieved remission rates of around 50% in patients, including those considered refractory to other rescue schemes.⁴⁷ BV and anti-PD1 inhibitors are increasingly used before allogeneic HSCT in order to achieve deeper responses before the procedure.^{47,48,49} Anti -PD1 inhibitors can be a alternative to relapsed patients after allo HSCT, but the used must be caution because GVHD risk⁵⁰

There is no consensus regarding the ideal conditioning regimen for RIC HSCT. Fludarabine with alkylating agents are the most used ones. In unrelated HSCT, the association of thymoglobulin is recommended for in vivo depletion of T lymphocytes. The vast majority of patients do not have a full match sibling or unrelated donor and, therefore, haploidentical transplantation has gained strength, especially after the use of cyclophosphamide 50mg/Kg/day (D +3 and D +4) post-transplant for depletion of allo T cells in vivo. Several retrospective studies have shown no significant differences in OS or PFS between transplant modalities with haploidentical donors when compared with matched sibling or unrelated donors.^{51,52,53,54} In some studies, haploidentical HSCT has also been associated with a lower rate of chronic GVHD. Main advantages of haploidentical donor are a faster search, good tolerability and a lower rate of chronic GVHD, but there are considerable disadvantages such as graft failure, acute GVHD and also a delayed immune reconstitution or risk of recurrence. In conclusion, the available evidence of haploidentical transplantation for recurrent / refractory Hodgkin's lymphoma after autologous HSCT is encouraging and this may, in fact, be an excellent option for patients without an available HLA donor.⁵⁵

Algorithm for early referral of LH patients to the HSCT center



*Checkpoints inhibitors seem very effective with promising survival results, however the follow up still too short, to final decision of whether to allograft a patient relapse after auto-HSCT might rely on the risk profile of the underlying disease as well a transplant-related risk.

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