HSCT FOR NON-HODGKIN LYMPHOMA

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DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL):

The addition of rituximab to the CHOP chemotherapy protocol (cyclophosphamide, doxorubicin, vincristine and prednisone) significantly improved the results for patients with DLBCL, the most frequent subtype of non-Hodgkin’s lymphomas (NHL) [1]. However, there is a subgroup of patients with a worse prognosis [2] identified by the international prognostic index (IPI), where survival rates remain around 50%. Efforts have been made to improve R-CHOP including increasing dose density with 14-day cycles, the use of obinutuzumab, or intensifying therapy such as the DA-EPOCH protocol, but with no definitive clinical benefits [3]. Biological agents such as ibrutinib, lenalidomide and bortezomib have also been incorporated in an attempt to improve results [4] without success. Since the pre-rituximab era studies have incorporated high-dose therapy and autologous HSCT as part of the treatment of these lymphomas in various stages of treatment: remission induction [5-7] with results favoring the therapeutic arm of conventional chemotherapy, consolidation of remission and rescue in disease recurrence [8]. Studies and recent meta-analysis incorporating autologous HSCT as consolidation, after achieving remission in intermediate and high-risk IPI patients have not yet demonstrated evidence of benefit [9-11]. Sub-analyses within these studies showed that in high-risk patients early intensification could be beneficial. In addition to IPI adverse biological characteristics such as tumor cell of origin (CGB x ABC), presence of MYC rearrangement, BCL-2 and BCL-6 (double / triple-hit) have been studied in this context with no benefit proven [12]. Aggressive NHL relapses, after initial therapy, have a poor prognosis. Rescue regimes with conventional QT, give survival rates, in two years, below 25%. The PARMA TRIAL [13] randomized study demonstrated that autologous HSCT is the treatment of choice for chemosen-
sitive recurrence. SLE rates, over 8 years, were 36% for the transplant arm and 11% for DHAP rescue. In the CORAL trial [14], less than 25% of patients who relapsed within 1 year of diagnosis achieved long-term disease-free survival with autologous HSCT. Final analysis of this study [15] confirmed the previous findings, in addition to demonstrating no benefit of maintenance with rituximab after autologous HSCT. In patients with DLBCL, the data on the results of allogeneic HSCT come from retrospective case series studies and record analyzes [16]. These studies included patients with very advanced disease, with several previous therapeutic lines, in addition to grouping diversified histologies, making it difficult to interpret the findings and take conclusions. Myeloblastic conditioning promoted lower rates of recurrence compared to autologous HSCT, but with unacceptably high mortality rates. Reduced intensity conditioning (RIC) has promoted the immune control of the tumor with increased survival rates and reduced transplanted-mortality related [17,18].

DLBCL RECOMMENDATIONS

1. Autologous HSCT is not recommended as consolidation of remission for patients with diffuse large B-cell lymphoma, regardless of the IPI subgroup (1A)
   a. Patients with partial response to R-CHOP can be considered for consolidation with ASCT
   b. Patients with Double-Hit lymphomas can be considered for consolidation with ASCT if:
      i. They have not received non-intensified regimens as initial therapy
      ii. They have not achieved Complete Response after intensified schemes
   c. DLBCL patients with secondary infiltration in the CNS can be considered for consolidation with ASCT
with schemes targeted for central nervous central primary NHL

2. Autologous HSCT is recommended as the therapy of choice for chemosensitive recurrence (1A); regardless of the time of recurrence.

a. There is no preferred recovery scheme, it is recommended that each center uses the scheme that is most familiar with

b. There is no maintenance benefit with post-transplant rituximab (1B)

3. Allogeneic HSCT is indicated in young patients with post-autologous recurrence using reduced intensity conditioning

**FOLLICULAR LYMPHOMA (FL)**

Currently, for most patients with FL without early disease-related events, survival is similar to the general population. The prognostic impact of early progression within 24 months of chemotherapy treatment (POD24), with 50% of OS in 5 years compared to 90% in patients without early progression [1-4].

The indication of early intensification in patients with FL in first remission was a matter of debate in the pre-rituximab era [5-8]. In the rituximab era, a randomized study comparing autologous HSCT and conventional chemotherapy and rituximab as the first line showed no difference in OS [9]. A meta-analysis published by Shaaf et al [10] confirmed the absence of benefit in OS rates, when comparing autologous HSCT to conventional chemotherapy with rituximab in previously untreated patients, as first-line therapy for FL.

The management of recurrence should be based on the time of recurrence, if early (POD24) or late. For young patients with POD24, consolidation with high-dose chemotherapy and autologous HSCT should be considered [11]. In the pre-rituximab era, a randomized study (CUP Trial) demonstrated superior results for autologous HSCT compared to conventional rescue in FL [12]. Data from the CIBMTR and the National LymphoCare Study (NLCS), showed that patients who relapse less than 1 year after transplant had a higher OS at five years than those who did not undergo autologous HSCT (73% versus 60%, P = 0.05). In the multivariate analysis, the early use of autologous HSCT was associated with significantly reduced mortality (RR: 0.63; 95% CI: 0.42 to, 0.94; P = 0.02) [13].

Studies enrolling patients with transformed FL (TFL) before the incorporation of immunotherapy demonstrate the efficacy of autologous HSCT [2,14-18]. A study by the Canadian bone marrow transplant group demonstrated a modest improvement in OS and PFS for patients undergoing HSCT compared to the group of patients who had received rituximab and chemotherapy [19]. In CIBMTR analysis, the OS rate was 50% in 5 years and although a small number of patients had previously used pre-transplant rituximab, it did not impact survival rates [20]. In the PRIMA study, patients with TFL who had previously used rituximab appeared to do better when undergoing autologous HSCT. A recent study with untreated TFL patients revealed a tendency towards worse OS in the group submitted to autologous HSCT [21, 22].

Data from retrospective studies [23], indicate a significantly lower risk of relapse for allogeneic HSCT when compared to autologous, but the benefit is suppressed by the high mortality rates related to the procedure with myeloablative conditioning. For allogeneic HSCT with reduced intensity conditioning (RIC), the recurrence rate is generally below 30%, whether or not preceded by an autologous HSCT, with a 5-year PFS ranging from 50 to 85% [24-28]. The results of match related donors (MSD) and unrelated (MUD) in FL are similar. For patients who do not have MSD or MUD, the use of cord blood or haplo-identical family donor may be considered [29-32].

**FL RECOMMENDATIONS**

1. Autologous HSCT is not indicated in the first line treatment of FL (1A).

2. Autologous HSCT can be considered therapy of choice in young patients with FL with early recurrence (POD24) and chemosensitive (1B).

3. Autologous HSCT should be considered in patients with TFL with chemosensitive disease, who have received therapy initially for FL (1B).

4. Allogeneic HSCT, with conditioning at reduced intensity, should be offered to patients with post-autologous recurrence and HLA-compatible donor (2C), preferably in chemosensitive disease.

**MANTLE CELL LYMPHOMA (MCL):**

Symptomatic patients or patients with a large tumor load, who have treatment indication, good performance status and permissive comorbidity profile benefit from a more intensive induction regimen with immuno-polychemotherapy through protocols that include rituximab and cytarabine. After induc-
tion treatment, consolidation in first remission with high dose chemotherapy and autologous HSCT is recommended. This recommendation is based on retrospective case series and a prospective study from the pre-rituximab era [1-7]. Progression-free survival ranged from 48 to 68% in 4 years in these studies and overall survival from 61 to 80%. The subpopulations of patients that can benefit the most are those with blastoid / pleomorphic morphology and with a high MIPI risk score. TP53 mutation carriers do not appear to benefit.

The most frequently used conditioning regime is BEAM. Alternatively, CBV, BEAC, BuCyVP [8] and BendamustinaEAM [9] have also been employed. Maintenance treatment with rituximab for 3 years after transplantation is recommended from a prospective randomized study that showed a PFS of 83% in 4 years in the Rituximab arm versus 64% in the control arm [10].

First-line regimens that include new drugs (BTK inhibitors, bortezomib, venetoclax, lenalidomide) may, in the future, replace consolidation with high doses of chemotherapy and autologous HSCT [11-13], depending on the results of prospective studies in progress.

Autologous HSCT can also be offered as a rescue treatment for chemosensitive relapses of fit patients who have not received this treatment modality as consolidation in the first line.

Evidence of an immunological effect of the graft against mantle cell lymphoma supports the indication of allogeneic HSCT in post-autologous recurrence or in first remission for selected cases [14]. Retrospective studies describe progression-free survival of 49 to 56% and overall survival of 54 to 75% in 5 years, with an incidence of 40% relapse reported in the largest series of cases, recorded by the EMBT [15-17]. The conditioning regimes most frequently used were of reduced intensity.

Mostly proposed as a rescue treatment in post-autologous recurrence [18], allogeneic HSCT can be indicated in the first line for fit patients with subtypes of poor prognosis, such as those with mutated TP53 [19], blastoid or pleomorphic variants [20].

**MCL RECOMMENDATIONS**

1. Autologous HSCT is indicated as consolidation in the treatment of MCL that reached at least PR after the 1st line of treatment in eligible patients (28).

2. Autologous HSCT can be considered as rescue therapy in patients with MCL with chemosensitive relapses who did not receive ASCT in the first line (2B).

3. Allogeneic HSCT may be indicated for the first-line treatment of MCL in fit patients with poor prognosis disease, such as those with mutated TP53 or blastoid (2C) variants.

B. Allogeneic HSCT can be indicated as a rescue treatment in patients who relapse after autologous HSCT (2C).

**PERIPHERAL T-CELL LYMPHOMAS (PTCL)**

The 2016 World Health Organization (WHO) classification recognizes up to 29 different types of PTCL [1]. The most common PTCL include peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL, ALK-positive and ALK-negative), extranodal NK/T-cell lymphoma and other rares subtypes. Most of them have an aggressive clinical course and historically dismal results [2]. Treatment in the front-line setting is mostly often done with anthracycline-based chemotherapy, which is associated with a high failure rate and frequent relapses [3]. The addition of etoposide to CHOP results in an advantage in terms of event-free survival (EFS) but the greatest benefit was observed in young patients and ALK-positive ALCL subtype [4]. Aggressive approaches have failed to bring consistent improvements in long-term survival [5]. Currently, the better understanding of the biology of these diseases and prognostic models [6] has translated into the development of novel treatment options as brentuximab-vedotin (BV) upfront chemotherapy regimen for the PTCL CD30+, histone deacetylase inhibitor (epigenetics therapies), Janus Kinase inhibitor, phosphoinositide-3-kinase inhibitors, lenalidomide, bortezomib as therapeutics strategies [7,8]. Despite the availability of newer active single agents, relapsed and refractory patients are less likely to receive these therapies and continue to have inferior outcomes and improvements in front-line therapies are needed [9,10]. The recent publication of the ECHelon-2 trial [11] has significantly changed front-line treatment paradigms for CD30+ histologies, incorporating BV in front-line therapy, which includes ALK+ and ALK–ALCL, and some AITL and PTCL-NOS, demonstrated by a statistically significant improvement in PFS and OS with a manageable safety profile.

Prospective studies have demonstrated the feasibility and benefit of autologous HSCT as part of the frontline strategy in nodal PTCLs [12,13,14]. In the
final analysis of the largest conducted prospective phase II trial including autologous HSCT in first remission, the Nordic study (NLG-T-01) [13], evaluated the outcomes of 166 patients, of which 62 were classified as having PTCL-NOS. This study demonstrated that 71% of patients completed the therapeutic sequence and 90 patients were in CR 3 months after transplantation. The overall response rate was 78%; and at a median of 60 months, although 82% of patients had advanced disease at diagnosis. The TRM was 4%. The best results were achieved for the ALK-subtype, with OS and PFS rates, in 5 years, of 70 and 61%, respectively. An EBMT registry study, with a median follow-up of 65.8 months, showed a PFS rate for patients transplanted in CR/PR was 75% compared to 32% for those transplanted with relapsed or refractory disease [15]. The COMPLETE data registry [16] was a prospective multicenter analysis of 499 patients with PTCL. Among the patients in CR following frontline therapy who underwent autologous HSCT, in nodal types, the median OS was not reached for the autologous HSCT group, versus 57.6 weeks for the non-HSCT group, with a trend of significance (p = 0.06). By subgroup, there was superior survival in patients with advanced-stage and intermediate to high-risk IPi in favor of transplant. There was improved PFS and OS specifically for AITL (2-year PFS of 68.8 vs. 41.2) and a trend for improvement in ALK−ALCL (100 vs. 83.8), but not in PTCL NOS. This study demonstrated a trend toward improvement with autologous transplantation in PTCL. High-dose chemotherapy followed by autologous HSCT may improve the outcome in PTCL, and the achievement of a first complete remission before HSCT has proven to be a strong predictor of improved outcome [17,18]. High-dose therapy followed by autologous HSCT is widely recommended for consolidation after a complete or partial remission is achieved. With regard to allogeneic versus autologous transplant, a European trial randomized patients with PTCL to allogeneic versus autologous transplant and found no difference in EFS or OS. There was increased treatment-related mortality in the allogeneic group (31%) but increased relapses (36%) in the autologous group. At this time, there is insufficient evidence to broadly support autologous HSCT as part of the frontline strategy, however, reduced toxicity of autologous HSCT with recent advances, may alter the risk to benefit risk-benefit ratio [18]. Allogeneic HSCT is not recommended frontline other than for very rare subtypes with extremely poor outcome, such as hepatosplenic T-cell lymphoma (HSTCL) [19].

Most patients with PTCL will eventually relapse. A phase 2, open-label, multicenter study evaluated the efficacy and safety of brentuximab vedotin, for relapsed/refractory CD30+ non-Hodgkin lymphomas, and objective responses were observed in 41% of patients with relapsed T-cell lymphomas, including 54% ofAITL patients [20]. There have been no prospective trials evaluating high-dose regimens of chemotherapy followed by autologous HSCT in patients with relapsed PTCL. Treatment with salvage chemotherapy and autologous HSCT may be recommended in those who are transplant eligible and did not receive a transplant in the first remission. Report of the International T-cell project demonstrated that autologous HSCT at the time of relapse was associated with a 3-year survival of 48% compared with only 18% in those without transplantation [21]. However, long-term remission rates to autologous HSCT in this setting are unsatisfactory. For the approximately 30% of patients without relapse in 2 years, the survival is significantly better (5-year OS, 78%) [22].

Allogeneic HSCT for patients with chemo-resistant relapsed/refractory PTCL, and for those who relapse following autologous HSCT, is the only potentially curative therapy. Numerous retrospective studies have been published on this topic, relapse rates ranging from 17% to 3% at 3 years to 49% at 5 years; NRM rates range from 12% at 5 years to 46% at 5 years; and OS rates range from 38% at 3 years to 57% at 5 years [23]. Recent studies have addressed this therapy [24-26]. As novel therapies for relapsed PTCL become available, it will be critical to combine them with allogeneic HSCT (as conditioning and/or maintenance therapies) to improve outcomes in patients with relapsed/refractory disease [27].

**PTCL RECOMMENDATIONS**

1. Patients with nodal PTCL, in CR/PR, should receive consolidation of remission with autologous HSCT, except ALCL ALK+ subtype (1B)

a. The remission treatment induction therapy must contain etoposide; and brentuximab-vedotin in ALCL CD30+ (2B)

b. Autologous HSCT can be considered in second chemo-sensitive remission in ALCL ALK+ (2C)

c. Primarily refractory patients should not be transplanted with autologous HSCT (2B)

d. PET positivity found at the end of induction treatment and in patients who have received autologous HSCT is a strong predictor of reduced survival

2. ATLL: Allogeneic transplantation is the only chance to cure ATLL and is recommended for aggressive
subtypes (acute, lymphoma type and chronic high risk) upfront for transplant-eligible patients (2B) [28]

3. HSTCL: For patients eligible, allogeneic transplantation is recommended as consolidation after induction therapy reaching CR or PR. Autologous transplant can be considered if a suitable donor is not available or the patient is not eligible for allogeneic transplant (2B) [29]

4. Allogeneic transplantation is the therapy of choice for patients with post-autologous recurrence disease (2C)

a. Myeloablative or non-myeloablative conditioning regimens can be used

b. Allogeneic HSCT is recommended frontline in hepatosplenic T-cell lymphoma due to its refractoriness to conventional chemotherapy regimens, aggressive clinical course and poor outcomes.

AUTOLOGOUS CONDITIONING:

The most commonly used protocols in autologous HSCT, for patients with lymphoma, include carmustine but in the current Brazilian reality, this medication is not marketed. Therefore, substitutes such as lomustine, bendamustine, busulfan or mitoxantrone are some of the alternatives to be associated with alkylating agents and topoisomerase inhibitors. [1·9]. The combination of gemcitabine with other drugs has also been used for lymphomas. [10·12]

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REFERENCES FL


REFERENCES MCL


**REFERENCES PTCL**


REFERENCES CONDITIONING


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