

Autologous bone marrow transplantation in patients relapsed one year after R-CHOP?

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Introduction

I have studied and worked with non-Hodgkin lymphoma (NHL) for at least 16 years in the *Hospital das Clínicas* and *Instituto do Câncer do Estado de São Paulo* of the *Faculdade de Medicina da Universidade de São Paulo* (FMUSP).

Last year we attended 300 new patients with NHL and 49.5% (almost 150 patients) had diffuse large B-cell lymphoma (DLBCL)⁽¹⁾. This is in agreement with the literature that describes DLBCL as the most common subtype of NHL (30% to 35%).

Over the last four decades there has been a significant increase in the 5-year survival of patients with DLBCL. This is due to the development of anthracycline-based polychemotherapy regimens such as is used in the CHOP protocol and more recently, with the incorporation of immunotherapy with the monoclonal antibody anti-CD20 (rituximab) in the CHOP-regimen. However, 10% to 15% of DLBCL patients remain unable to acquire complete remission (CR) even in the rituximab era and 30% to 50% of the patients that acquire a first CR will relapse⁽²⁾. As we have almost 150 patients per year with DLBCL in our service, we can assume that about 60 patients per year will have refractory or relapsed disease. Hence, we have a huge challenge every year with the main question being what is the best approach to offer to relapsed DLBCL patients? The unquestionable answer to this question is that patients have to be salvaged with a second line regimen and it is always possible to consolidate the patient with autologous stem cell transplantation (ASCT). In this article I will try to examine the level of evidence of this approach and to introduce the experience I acquired over these 16 years of NHL.

Diagnosis and restaging relapsed diffuse large B-cell lymphoma patients

If patients present clinical features or findings by imaging that are suggestive of relapsed disease, they should be submitted to biopsy for confirmation. Confounding conditions such as infection and carcinoma should be discarded. Additionally, the histology must be reanalyzed in relapsed disease because it can change and this information is essential for the best management of the patient. If relapsed lymphoma is confirmed, patients should be restaged. They have to be submitted to the same exams recommended at diagnosis such as CT, PET/CT, bone marrow biopsy and others such as brain nuclear magnetic resonance and cerebrospinal fluid analysis depending on the symptoms.

Patients relapsed within the first five years after CR are defined as early relapse and after five years as late relapse. Patients with refractory disease present worse prognosis in salvage therapy than patients with relapsed disease. The prognostic factors of the relapse must also be investigated and the molecular subtype of DLBCL must be identified.

Treatment for relapsed diffuse large B-cell lymphoma

In our institution we use consolidation using ASCT as the first choice for patients with relapsed DLBCL.

The first randomized prospective study carried out to specifically test the role of the ASCT in DLBCL was the PARMA study. In this trial, patients with relapsed and chemotherapy-sensitive DLBCL were randomized to salvage chemotherapy with a cisplatin and cytarabine-based regimen alone or in combination with ASCT. The disease free survival (DFS) and overall survival (OS) were significantly higher in the transplantation arm compared with the chemotherapy alone arm (46% and 53% vs. 12% and 32%, respectively). However, patients resistant to chemotherapy presented significantly worse prognoses than chemotherapy-sensitive patients [1-year progression free survival (PFS) of 22% vs. 5-year PFS 43%]. However, this study only enrolled under 60-year-old patients⁽³⁾.

A second analysis of the PARMA study was performed to evaluate the international prognostic index (IPI)⁽⁴⁾ for DLBCL at relapse. The overall responses (ORs) of patients after 2 cycles of dexamethasone, cytarabine and cisplatin (DHAP) were 77%, 54%, 55% and

42% in patients with IPIs of 0, 1, 2 and 3, respectively (p-value = 0.02). Thereafter, the CR rates were 33%, 29%, 20% and 0% for the same groups (p-value = 0.03). The OS rates at 5 years were 46%, 25%, 25% and 11%, respectively (p-value = 0.001). After the first 2 cycles of DHAP there was a second randomization where patients were selected to receive 2 more cycles of DHAP or ASCT. The IPI at relapse was highly correlated to the OS in patients treated in the DHAP arm (5-year OS of 48%, 21%, 33% and 0% for IPI 0, 1, 2 and 3, respectively; p-value = 0.006) but not in the ASCT arm (5-year OS of 51%, 47%, 50% and 50% for IPI 0, 1, 2 and 3, respectively; p-value 0.90). Patients with an IPI higher than 0 presented greater benefit to ASCT, but there was no significant benefit in patients with IPI = 0 compared to consolidation with DHAP alone (p-value = 0.50). It is important that ASCT is available in face of age and co-morbidities⁽⁵⁾.

Recently, another multicenter phase 2 trial, the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) compared the rituximab, ifosfamide, carboplatin and etoposide (R-ICE) with rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP) protocols for salvage therapy of patients with relapsed DLBCL. The second end point was to evaluate the role of rituximab maintenance after ASCT. Different to the PARMA study, the CORAL trial also enrolled patients with relapsed and refractory DLBCL after the CHOP or R-CHOP regimens. Patients were first randomized for salvage with R-ICE and R-DHAP. Also the impact of previous use of rituximab, of relapsed vs. refractory disease, and relapse before or after 12 months of induction therapy should be taken into account⁽⁶⁾.

After 3 cycles of R-ICE or R-DHAP, chemosensitive patients were consolidated with ASCT after etoposide, cytarabine and melphalan (BEAM) conditioning. Thereafter patients were selected by a second randomization for maintenance with rituximab or observation. The authors found no differences between R-DHAP or R-ICE as salvage for DLBCL patients (OR = 63%) and 50% for ASCT. Moreover, the OS and DFS after ASCT were similar for both groups treated with R-DHAP or R-ICE. Patients treated with rituximab as first line showed lower response to salvage therapy than patients not treated with rituximab before (51% vs. 83%; p-value = 0.001). The 3-year event free survival (EFS) was 21% for patients exposed to rituximab and 47% for rituximab-naïve patients. Patients that presented relapse less than 1 year after induction therapy also had poor outcomes similar to those observed for patients refractory to the salvage regimen. In this last group of patients the outcome was very poor with a minimal probability of cure⁽⁶⁾.

The European Blood and Bone Transplantation Registry published a retrospective study with 470 patients to evaluate the impact of ASCT in patients in a second CR after salvage therapy. In this study 351 (74%) patients were rituximab-naïve before ASCT and 119 (25%) received rituximab before ASCT. The median duration of the first CR was 11 months and the median time from diagnosis to ASCT was 24 months. The most common conditioning regimen was BEAM (67%). After ASCT, the 5-year OS was 63% (95% confidence interval: 58%-67%) and 5-year DFS was 48% (95% confidence interval: 43%-53%). The main predictive factor for DFS was the duration of the first CR (median: 51 months vs. 11 months; p-value < 0.001).

Patients relapsed within 1 year of the first CR had the worst prognosis (median: 6 months vs. 47 months; p-value < 0.001)⁽⁷⁾. According to the literature ASCT provides a significant benefit for survival and it is recommended as part of salvage therapy for patients with chemosensitive relapsed DLBCL with an evidence level 1+ characterized by existence of well-conducted meta analyses or systematic reviews of randomized controlled trials^(3,6,8,9). However, there is no randomized trial evaluating the best conditioning regimen for ASCT; the most common used are 1-3-bis-chloroethyl-nitrosurea (BCNU), BEAM and cyclophosphamide, carmustine, etoposide (CBV). Radiotherapy may be used in bulky lesions as consolidation after ASCT and maintenance with rituximab after ASCT increases PFS but not the OS. However, as prolonged cytopenias and increased infections have been reported with this strategy it is not recommended outside of clinical trials. On the other hand the role of ASCT for refractory DLBCL is limited and these patients must be enrolled in clinical trials. The recommended standard source of hematopoietic stem cells for ASCT is the peripheral blood (PBSCT) instead of bone marrow because it is related with lower rate of death due to infection⁽⁹⁾. A randomized study comparing autologous PBSCT versus BMT for aggressive lymphomas (61% DLBCL) showed that patients who underwent autologous PBSCT had a significantly longer OS, but not EFS in relation to autologous BMT patients⁽¹⁰⁾.

Therapy of relapsed diffuse large B-cell lymphoma in patients ineligible for autologous stem cell transplantation

According to the literature, the outcomes of relapsed DLBCL are worse for over 60-year-old patients than for younger patients. The PARMA study did not enroll over 60-year-old patients and there are no comparative data for ASCT versus non-transplantation as salvage therapy in this patient group. A retrospectively study evaluated 2612 patients with DLBCL submitted to ASCT; 463 (18%) patients were older than 60 years (median: 63 years). When compared to the 2149 patients younger than 60 years old, the elderly patients more frequently received at least two treatment lines (76% vs. 57%; p-value < 0.001), were less commonly in first CR at the time of transplantation (23% vs. 30%; p-value = 0.005) and there was a longer time between diagnosis and transplant (median time 14 months vs. 7.5 months; p-value < 0.001). Non-relapse mortality was higher in elderly patients at 100 days (4.4% vs. 2.8%), at 1 year (8.7% vs. 4.7%) and at 3 years (10.8% vs. 6.5%; p-value = 0.002). With a median follow-up of 12 months for surviving patients in the elderly group and 15 months for the younger group, the risk of relapse was 38% and 32%, respectively (p-value = 0.006). The PFS was 51% and 62%, respectively at 3 years (p-value < 0.001) and the OS was 60% vs. 70%, respectively at 3 years (p-value < 0.001). Outcomes from some studies provide evidence on the use of ASCT as salvage for over 60-year-old patients. We can conclude that age greater than 60 years in itself is not a contraindication for ASCT. There is no upper age defined to limit ASCT, but outcomes, such as transplant-related mortality, relapse and survival, in older adults are not as good as in younger patients^(11,12).

The PARMA and CORAL trials showed that relapsed DLBCL patients not submitted to ASCT present a low chance of survival at five years. Usually these patients are older and the toxicity is high, causing a high level of morbidity and mortality. These patients have to be treated palliatively trying to maintain the best quality of life usually with oral agents or radiotherapy for localized disease.

Survival predictive factors in relapsed diffuse large B-cell lymphoma

Two main predictive indexes have been developed to discriminate how patients are more able to acquire CR and their chance of relapse. The first one was the IPI. Based on five factors (age, Ann Arbor stage, serum lactate dehydrogenase level, performance status and number of extranodal sites) this index is today used throughout the world. In the IPI, there are four groups of risk that can predict different 5-year survival rates. In patients with low risk IPI (0-1) the 5-year survival rate is 73%, in intermediate-low risk (IPI 1-2) it is 51% and for intermediate-high (IPI = 3) and high risk (IPI \geq 4) the 5-year survival rates are 43% and 26%, respectively⁽⁴⁾. The IPI remains an important survival predictive index for relapsed DLBCL⁽⁵⁾.

Another important and robust predictive factor for survival in DLBCL is based on the gene signature of the tumor cells that identify two molecular subgroups of DLBCL. The germinal center DLBCL (GC-DLBCL) subtype show tumor cells with a gene signature similar to that found in B-cells from the normal germinal center and the activated B-cell (ABC) or post-germinal center DLBCL (Non-GC) a subtype that has a gene profile usually found in normal activated B-cells. Patients with the GC-DLBCL subtype present significantly higher survival rates compared to patients with the non-GC-DLBCL subtype treated with CHOP or R-CHOP⁽²⁾.

As showed by the CORAL trial, the cell of origin of DLBCL remains a prognostic factor for relapsed/refractory patients. Germinal center B (GCB)-like DLBCL was significantly associated with a better PFS in the R-DHAP arm. However, the presence of the c-MYC gene rearrangement was significantly correlated with worse PFS (p-value = 0.02) and worse OS (p-value = 0.04). Prior exposure to rituximab (p-value = 0.0052), a high risk of age-adjusted IPI (p-value = 0.039), and FoxP1 expression (p-value = 0.047) were also related to worse prognoses in relapsed/refractory DLBCL⁽¹³⁾.

The results of a (18)F-fluoro-deoxyglucose positron emission tomography (FDG-PET) scan after at least two cycles of salvage chemotherapy and before ASCT are correlated with predictive factor for relapsed/refractory DLBCL. A study showed that FDG-PET-negative patients before ASCT had better PFS and OS after ASCT. A positive FDG-PET scan after salvage chemotherapy and prior to ASCT indicated an extremely poor chance of durable response after ASCT⁽¹⁴⁾.

The main messages

ASCT is the best option for patients with chemosensitive relapse DLBCL, is associated with a significant survival benefit and is recommended as part of salvage therapy for these patients.

The age higher than 60 years is not an absolute contraindication for ASCT. But, ASCT outcomes as well as transplant-related mortality, relapse and survival in older adults are not as good as in younger patients.

ASCT using peripheral blood is not associated with survival benefit or improved tumor control in comparison to bone marrow. However, ASCT using peripheral blood is safer and easier to use with faster engraftment and lower rate of death due to infection, hence peripheral blood is the standard for autologous stem cell source.

There is not sufficient evidence to recommend maintenance with rituximab outside a clinical trial after ASCT.

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