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Autologous stem cell transplantation in lymphomas: current indications

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Abstract

Hematopoietic stem cell transplantation is an established curative treatment for a number of conditions including malignant hematologic diseases and non-malignant congenital and acquired disorders involving the hematopoietic system and some types of solid tumors, e.g. germ cell tumors and soft tissue sarcomas. Hodgkin's disease and non-Hodgkin lymphomas can be treated and, in a large number of cases cured, by first-line chemotherapy or radiotherapy. Unlike many other malignancies, relapse is not uniformly fatal but the treatment is usually markedly myelotoxic with the high doses of chemotherapy (HDC) used in relapse. Hematopoietic reconstitution with either autologous marrow or peripheral stem cells post-chemotherapy has made HDC relatively safe, with mortality rates as low as 2% in some centers. The choice of conditiong regimen has traditionally been based on institutional experience, and several regimens are considered standard and routinely used for patients with all histologies of lymphoma. Each HDC regimen is associated with its own unique toxicities, based on the individual agents or modalities used. Novel targeted and immunotherapy approaches, including chimeric antigen receptor T-cell therapy, are currently being studied in clinical trials with promising early results, so the role of autologous stem cell transplantation in the treatment of lymphomas could be changed. The current clinical indications for HDC followed by autologous hematopoietic stem cell transplantation in lymphomas management for patients with a bad prognosis (as a consolidation therapy) or relapsed/refractory disease are reviewed in this paper.

Key words: lymphoma, high-dose chemotherapy, autologous hematopoietic stem cell transplantation

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Introduction

The World Health Organization (WHO) has categorized more than 30 unique histopathologic types of lymphomas. Approximately 88% are B-cell lymphomas. The current indications for autologous hematopoietic stem cell transplantation in some types of lymphomas [including Hodgkin lymphoma (HL)] are presented here.

Follicular lymphoma

Follicular lymphoma (FL) is a heterogeneous disease with a varying prognosis owing to differences in clinical, laboratory, and disease parameters. Although generally considered incurable, prognosis for early- and advanced-stage disease has improved because of therapeutic advances, several of which have resulted from elucidation of the biological and molecular basis of the disease. The choice of treatment for FL is highly dependent on patient and disease characteristics. Several tools are available for risk stratification, although limitations in their routine clinical use exist [1–7].

Investigators explored the role of autologous hematopoietic stem cell transplantation (ASCT) as a consolidation strategy following first-line therapy. Promising initial studies culminated in the development of several large randomized

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studies where ASCT was compared to either no further therapy or interferon alpha. While some of these studies demonstrated an improvement in disease control, no overall survival (OS) benefit could be demonstrated.

These observations, combined with a growing realisation of the acute and long-term toxicities of autologous hematopietic stem cell transplantation (auto-HSCT), have led to the abandonment of ASCT as a first-line consolidation procedure [8, 9].

Recent data suggests the strongest predictor of long-term FL outcomes is length of first remission after front-line therapy. Patients with progression of disease within 24 months of completing induction chemoimmunotherapy (POD24), which made up 19% of patients in this data set, had poorer outcomes compared to those with longer remission durations (5-year OS: 50% vs. 90%, respectively), even after adjustment for Follicular Lymphoma International Prognostic Index (FLIPI) score. The m7-FLIPI, a clinicogenetic risk score derived from a combination of the mutation status of seven candidate genes (*EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, CARD11*) together with clinical parameters [FLIPI score and Eastern Cooperative Oncology Group (ECOG) performance status], stratifies patients into a low-risk group (78% of patients) with a 5-year failure-free survival of 68% versus 25% in a high-risk group (22% of patients). m7-FLIPI was used to identify patients at risk of early relapse (POD24) using data from the German Low-Grade Lymphoma Study Group trial and the British Columbia Cancer Agency population-based registry. They confirmed that m7-FLIPI had a higher accuracy in predicting POD24 compared to FLIPI. Currently, no single treatment option exists for patients with POD24, and therapeutic approaches are generally intensification with standard agents or use of agents with novel mechanisms of action compared to front-line therapy [2–7]. Type of induction chemotherapy may influence survival of patients experiencing POD24. In the GALLIUM study, obinutuzumab-based chemotherapy was associated with a 34% reduction in the number of POD24 events. However, postprogression survival was similar in all treatment groups. Other recent analyses of POD24 after bendamustine-based induction also suggested a decreased risk of POD24 events (9–12%), with similarly poor outcomes. These findings suggest that early disease-related events after chemomimmunotherapy occur regularly and reproducibly in FL. So, the patients with POD24 are biologically distinct, possessing tumor- and/or host-related factors contributing to chemotherapy resistance, and require novel therapeutic approaches to improve poor outcomes. For fit patients aged up to 70 without an appropriate clinical trial option, aggressive treatment involving salvage chemoimmunotherapy and consolidative ASCT should be considered. This strategy can induce prolonged remissions in FL. The observation of a plateau in PFS curves suggests cure in a subset of patients, differentiating transplantation from other treatment modalities [5].

Retrospective data suggests that patients with POD24 benefit from ASCT (i.e. increased progression-free survival (PFS) and OS compared to those not receiving transplant). A recent study compared ASCT to either matched-sibling donor (MSD) or unrelated matched donor (UMD) allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients with POD24. Findings suggest that outcomes are similar with either autologous or allogeneic transplant with MSD, whereas outcomes with UMD transplant were inferior, largely due to higher transplant-related mortality [1–7].

The bone marrow is infiltrated in approximately 75% of FL patients at diagnosis, and consequently a number of investigators have studied the role of marrow purging in ASCT [10]. However, no clear benefit for purging could be demonstrated in prospective studies [11, 12], and there was some evidence that purging resulted in significant additional immunosuppression. Consequently, purging remains an experimental procedure in ASCT for FL.

There is a wide variety of different conditioning regimens that may be employed for ASCT in FL but a paucity of randomized trials comparing the efficacy and toxicity of these different regimens. The BEAM regimen had become the most widely used prior to ASCT in malignant lymphoma, and has been adopted in many countries. A number of investigators have changed conditioning schemes to improve results of BEAM by including rituximab and dexamethasone, substituting BCNU with bendamustine [13] or incorporating bortezomib, mitoxantrone or fotemustine. Several groups have also incorporated radioimmunotherapy (RIT) into the conditioning regimen prior to auto-HSCT in NHL [14].

Disease relapse following high doses of chemotherapy (HDC) and ASCT remains the principal cause of mortality in patients with relapsed or refractory lymphomas. In an effort to prevent post-ASCT relapse, a number of studies have evaluated the role of maintenance therapy, with varying success. In a randomized phase III study of FL, 280 rituximab-naive patients with chemosensitive, relapsed FL were randomized to pre-transplant rituximab purging or observation. Following transplant, patients were randomized to observation or maintenance with rituximab (MR) (375 mg/m^2 every two months for a total of four infusions). Post-ASCT MR therapy was associated with significantly higher 10-year PFS (54% vs. 37%, p =0.012), and no difference in OS was seen between the arms (73.1% vs. 67.8%, p =NS). In addition, MR therapy was associated with a nonstatistically significant increase in neutropenia in the first year of therapy. Based on the lack of benefit in OS seen in this large phase III study, MR has not been widely adopted following ASCT in FL [12, 15].

Conclusions [16]:

1) Autologous stem cell transplantation should not be used in first remission.
2) Autologous stem cell transplantation should be considered in patients with relapsed disease responding to reinduction therapy.
3) Autologous stem cell transplantation leads to a 5-year PFS of approximately 50% cases and may be curative in a significant minority of patients.
4) There is no proven role for purging strategies.
5) Maintenance rituximab for four infusions should be considered post ASCT.

Waldenström's macroglobulinemia

Small retrospective studies and a large registry analysis suggested that ASCT might improve the outcome of Waldenström's macroglobulinemia (WM) when applied as first-line consolidation. With the advent of more effective agents such as rituximab, purine analogs and bortezomib, this approach is increasingly questionable and should not be used outside clinical trials. In contrast, auto-HSCT is an option for salvage therapy in selected patients with chemosensitive disease who have not been exposed to numerous treatment lines [17].

Other indolent lymphomas

Despite improvements over the past decade in the OS of patients with indolent NHLs, these neoplsms remain largely incurable with standard therapies. Immunochemotherapy with rituximab-based regimens has become a well-established standard of care in primary and relapsed disease settings. Autologous stem cell transplantation offers a safe treatment platform, but relapse remains a significant issue. The role of transplantation in the current treatment landscape of immunochemotherapy has not been conclusively proven, and randomized trials are lacking. It is widely accepted that ASCT should no longer be performed routinely as consolidation of primary treatment, given the excellent results seen with primary immunochemotherapy. For relapsed or refractory disease, ASCT is likely to be the clinician's preferred choice, given the low non-relapse mortality (NRM) of the procedure [18].

Hodgkin lymphoma

In patients with advanced HL with poor prognostic features, the role of high-dose chemotherapy with autologous stem cell transplantation has been evaluated as part of initial therapy. Patients with advanced unfavorable HL achieving a complete or partial remission after four courses of doxorubicin-containing regimens were found to have a favorable outcome with conventional chemotherapy, and no benefit from an early intensification with HDC and ASCT was shown [19, 20].

Although the majority of patients with HL are cured with initial therapy, 10–15% of patients with early stage disease and 15–30% of patients with advanced disease have primary refractory or relapsed lymphoma [19–21]. So, despite the approval of novel therapies including brentuximab, nivolumab, and pembrolizumab, consolidation with high-dose chemotherapy and ASCT in patients responding to second line or subsequent therapy remains the standard of care in the majority of patients. Initial phase II studies suggested that HDC followed by ASCT may produce a better long-term disease-free survival than conventional chemotherapy in 30–65% of patients. Two subsequent randomized studies confirmed an improved outcome in patients with relapsed HL treated with HDC, followed by ASCT as compared to conventional salvage chemotherapeutic regimens.

In both studies, event-free survival (EFS) after three years of patients treated with HDC was over 50%. Elderly patients treated with an ASCT have increased treatment-related mortality, and commonly have an inferior EFS compared to younger patients. Some patients have relentlessly progressive disease and have been treated with tandem ASCT or allo-HSCT. Preliminary results have suggested that these therapies are feasible, but toxicity and relapses have been common [21].

Given the activity of brentuximab vedotin (BV) in patients with relapsed or refractory HL with an overall response rate (ORR) of 75% with approximately a third of patients achieving complete response (CR), the AETHERA study investigated the role of maintenance BV following ASCT. Patients with high-risk disease with primary refractory HL or relapse within 12 months of completion of frontline therapy or extranodal involvement at relapse were randomized to up to 12 months of brentuximab given every three weeks versus placebo. At 5-year follow-up, 59% of patients who received BV were progression free compared to 41% in the control arm.

The benefit was most prominent in patients with two or more of the following risk factors: relapse within 12 months or refractoriness to frontline therapy, partial response or stable disease after most recent salvage therapy, extranodal disease at relapse, B symptoms at relapse, and more than two prior salvage therapies. Common toxicities in the BV arm included peripheral neuropathy, which was reversible in the vast majority of patients, and neutropenia. This confirmed a benefit for BV therapy post-transplant in high-risk patients [22]. A much smaller study of 30 patients evaluated the use of pembrolizumab given for eight doses post-transplant in a similar cohort of patients. The primary endpoint was that pembrolizumab would improve PFS at 18 months after ASCT, from 60% to 80%. PFS at 18 months for the 28 evaluable patients was 82%, meeting the primary endpoint. However, the benefit of immune checkpoint blockade post-ASCT will need to be confirmed in a randomized trial [21]. Based on studies suggesting that

anti-programmed cell death protein 1 (anti-PD-1) monoclonal antibodies (mAb) can sensitize patients to subsequent chemotherapy, Merryman et al. [23] hypothesized that anti-PD-1 therapy before ASCT would result in acceptable outcomes among high-risk patients who progressed on, or responded insufficiently to, ≥1 salvage regimen, including chemorefractory patients who are traditionally considered poor HSCT candidates. They retrospectively identified 78 HL patients who underwent HSCT after receiving an anti-PD-1 mAb (alone or in combination) as third-line or later therapy across 22 centers. Chemorefractory disease was common in this group of patients. After a median post-ASCT follow-up of 19.6 months, 18-month PFS and OS were 81% and 96%, respectively. Favorable outcomes were observed for patients who were refractory to two consecutive therapies immediately before PD-1 blockade (18-month PFS, 78%), had a positive pre-ASCT positron emission tomography (PET) (18-month PFS, 75%), or received ≥4 systemic therapies before HSCT (18-month PFS, 73%), while PD-1 nonresponders had inferior outcomes (18-month PFS, 51%). In this high-risk cohort, ASCT after anti-PD-1 therapy was associated with excellent outcomes, even among heavily pretreated, previously chemorefractory, patients [23].

Peripheral T-cell lymphomas

Peripheral T cell lymphomas (PTCLs) are a heterogeneous group of diseases and represent approximately 10–15% of all NHLs. There are over 27 different subtypes of PTCLs and we are now beginning to understand the differences between the various subtypes beyond histologic variations. Multiagent chemotherapy with a CHOP-like regimen is the current standard of care in the frontline setting, but outcomes for PTCL patients generally remain poor. Strategies used to improve survival and reduce the risk of relapse in PTCL patients include autologous and allo-HCT. Due to the relative rarity of these diseases, the evidence supporting the use of auto-HCT and allo-HCT is based on retrospective and single-arm prospective studies. Novel targeted therapies are now being incorporated into the treatment of PTCL, and they may play important roles in improving upon current standards of care. Given recent improvements in OS and PFS in CD30+ PTCL using the drug-antibody conjugate BV, new questions arise regarding the impact of BV on consolidative ASCT, and its role as a maintenance therapy. Multiple histone deacetylase inhibitors have been approved for the treatment of relapsed/refractory PTCL, and these agents are being incorporated into HCT approaches, both in frontline and maintenance settings. Early data incorporating these agents into novel conditioning regimens has been reported, and emerging evidence suggests that chimeric antigen therapy (CAR) T cell therapies may prove effective in relapsed/refractory PTCL. The recommended treatment strategy in non-anaplastic large cell lymphoma (ALK)+ PTCL remains induction with a CHOP-like regimen followed by consolidative auto-HCT in first remission. In the relapsed/refractory setting, salvage chemotherapy followed by HCT (auto-HCT or allo-HCT depending on histologic subtype and HCT history) offers the only potential for cure or long-term remission.

Results from prospective studies suggest a substantial effect of up-front ASCT on the outcome of patients with PTCL, which should be further evaluated in randomized trials. The global conclusion of reported trials is that pre-transplantation treatment must be improved to increase the transplantation success and that one of the major challenges is knowing which patients with PTCL in first remission to select for consolidative ASCT, as patients with low International Prognostic Index (IPI), ALK+ anaplastic large cell lymphoma (ALCL) disease in remission do not need consolidation transplant. For patients with ALK+ALCL with high IPI score and poor outcomes, alternative strategies, including ASCT, should be considered. High-dose chemotherapy followed by ASCT may improve the outcome in PTCL, but the available data comes from non-randomized studies, meaning definitive recommendations cannot be made. The achievement of a first complete remission before ASCT has proven to be a strong predictor of improved outcome. Thus, any potential benefit from consolidative auto-HCT will be conferred only on those with chemo-sensitive disease. Secondly, rates of relapse after auto-HCT are significant and range from 18% to 55%. This suggests the presence of residual disease despite achievement of CR by conventional detection methods (e.g. PET). Finally, there are limited studies utilizing novel therapeutics such as BV; thus, it remains to be determined how the incorporation of novel agents may affect outcomes with HCT.

Despite these limitations, the preponderance of data demonstrates that there is an important role for autoHCT as consolidation in CR1 for patients with PTCL.

It is recommmended that all fit patients with non-ALK+ ALCL proceed with auto-HCT in CR1 upon completion of six cycles of induction CHOP-based chemotherapy. Relapses in patients with PTCL tend to be very aggressive, with poor survival and low response rates outside of ALCL; the best chance to cure patients with PTCL is in CR1 [25–27].

Outcomes for relapsed/refractory non-ALK+ PTCL are generally poor with median OS of 9.1 months. Available data suggests that patients who respond to salvage chemotherapy (i.e. those with chemo-sensitive disease) are most likely to derive benefit from ASCT. Clinical studies found that ASCT performed in earlier states of remission (i.e. CR1 ±PR1) was associated with significantly longer PFS, and that patients with refractory disease had particularly poor outcomes. Additionally, these studies suggest that a significant minority of patients with chemo-sensitive relapsed disease (i.e. CR2+/PR2+) may derive durable benefit from auto-HCT. These and other retrospective studies

indicate that prognostic scores such as the IPI/age-adjusted International Prognostic Index (aaIPI) may be useful in predicting which relapsed patients with chemosensitive disease are most likely to benefit from ASCT [25–27].

Conclusions [25–27]:

1) The recommended treatment strategy in non-ALK+ PTCL remains induction with a CHOP-like regimen followed by consolidative auto-HCT in first remission.
2) For patients with relapsed/refractory PTCL, the only potentially curative therapy is hematopoietic stem cell transplantation.
3) For patients with chemosensitive disease who attain a rapid CR to salvage therapy, particularly ALCL, ASCT in CR2 may provide curative therapy for a subset of patients (approx. 50% for ALCL, 35–40% for non-ALCL in select cases).
4) For patients with primary refractory PTCL, or PTCL that relapsed after ASCT or multiple prior lines of therapy, allo-HCT provides the only potential curative therapy with long-term survival rates of 40–50%. Due to the high risk of NRM, particularly with myeloablative conditioning in patients who have recently received ASCT or who have received extensive salvage chemotherapy, reduced-intensity regimens are preferred due to lower NRM.
5) Additional prospective trials and novel therapeutic approaches, including cellular therapy techniques, are desperately needed for this population.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma which is characterized by the chromosomal translocation t(11;14)(q13;q32) and overexpression of cyclin D1 in the vast majority of cases. Most patients present with advanced stage disease, often with extra-nodal dissemination, and have an unfavorable clinical course. Treatment with conventional chemotherapy resulted in unsatisfactory outcomes and median survival is less than three years after diagnosis of MCL [28].

The use of ASCT consolidation in first remission is supported by data published by the European and Nordic groups who noted significantly prolonged PFS with ASCT, with the European group randomizing patients to interferon versus ASCT. However, this data was attained before the widespread use of cytarabine induction regimens, maintenance rituximab in first remission, and the discovery of Bruton tyrosine kinase (BTK) inhibitors. Thus, randomized data confirming the efficacy of ASCT is greatly needed because of the number of novel strategies recently developed in MCL. The European MCL Network phase III TRIANGLE study is currently randomizing patients to an induction regimen containing the BTK inhibitor ibrutinib while also assessing whether an ibrutinib-containing induction regimen with maintenance can replace ASCT. This will be the first phase III trial to incorporate a targeted molecular therapy into the MCL induction regimen and also the first randomized study to test the efficacy of ASCT in the cytarabine and rituximab era. Post-ASCT bortezomib, although associated with an improvement in PFS, leads to significant toxicity including peripheral neuropathy and cytopenias, and therefore this approach is seldom utilized. Mature follow-up from ongoing clinical studies, along with further randomized prospective data, will help further assess toxicity and the impact of maintenance therapy post ASCT on OS [12, 29, 30]. In a phase III trial, 240 patients were randomly assigned to receive rituximab maintenance therapy or to undergo observation after autologous stem-cell transplantation. The primary endpoint was EFS (with an event defined as disease progression, relapse, death, allergy to rituximab, or severe infection) after transplantation among patients who underwent randomization. The median follow-up from randomization after transplantation was 50.2 months (range, 46.4–54.2). Starting from randomization, the rate of EFS at 4 years was 79% in the rituximab group versus 61% in the observation group (p =0.001). The rate of PFS at 4 years was 83% in the rituximab group versus 64% in the observation group (p <0.001). The rate of OS was 89% in the rituximab group versus 80% in the observation group (p =0.04). According to a Cox regression unadjusted analysis, the rate of OS at 4 years was higher in the rituximab group than in the observation group (p =0.04). Rituximab maintenance therapy after transplantation prolonged EFS, PFS, and OS among patients with mantle-cell lymphoma who were 65 years or younger at diagnosis [30].

Conclusions [28]:

1) In the ibrutynib era, autologous stem cell transplantation and rituximab maintenance still should be recommended as the standard treatment for transplant-eligible patients with MCL.
2) A second autologous stem cell transplantation does not appear to be a promising option in patients with MCL failing a first auto-HSCT. For these patients, allo-HSCT should be considered.

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphomas (DLBCL) is the most common subtype of nHL, accounting for 30–40% of all cases. There are several types of DLBCL, with most people being diagnosed with the subtype known as DLBCL or 'not otherwise specified'. First-line treatment of patients with DLBCL generally consists of rituximab (R) at standard dose (375 mg/sqm) in combination with CHOP or one of its variants such as ACVBP, CHOEP, or DA-EPOCH chemotherapy. Six cycles of R-CHOP are generally used. However, this can be reduced to four without jeopardizing treatment outcomes in patients with IPI 0 [31, 32].

Several studies have evaluated the role of consolidative high-dose therapy followed by auto-HSCT in the R era.

French [33], Italian [34], and German [35] studies failed to demonstrate an advantage of auto-HSCT over conventional chemotherapy. The only American study [36] reported an advantage of auto-HSCT in younger patients with high-risk disease (aaIPI 3); however, this study included patients treated with CHOP only and patients with T-cell lymphoma, and as a consequence was underpowered in order to show a significant advantage of auto-HSCT over R-CHOP [37]. In young patients who remain PET positive after two cycles of chemoimmunotherapy, auto-HSCT is performed in a few countries.

Autologous HSCT is still considered to be the standard treatment for patients with refractory or relapsed (R/R) DLBCL. However, in the rituximab era, the results of salvage therapy followed by auto-HSCT are less convincing than before, and the benefit of auto-HSCT, even for those patients achieving PR or CR with salvage chemotherapy and RTX, is limited [38]. In particular, patients with refractory disease or early relapse pretreated with rituximab as part of first-line therapy rarely achieve long-term remission after auto-HSCT. In the CORAL study, 3-year PFS for such patients was only 23%, although those proceeding to auto-HSCT showed 3-year PFS of 39%. Adverse prognostic factors for auto-HSCT identified in prospective studies include early relapse within 12 months of induction therapy, prior exposure to R, secondary aaIPI, poor performance status, and involvement of two or more extranodal sites at relapse [31, 38].

In the phase III CORAL study, patients with relapsed or refractory DLBCL were allocated to one of two salvage chemotherapy regimens. Those responding to therapy subsequently underwent high-dose chemotherapy followed by ASCT. Following transplant, patients were again randomized to either maintenance therapy with rituximab (MR) (375 mg/m^2 every two months for six doses) or observation. This study failed to demonstrate an improvement in 4-year EFS (52% vs. 53%) or OS (61% vs. 65%) in the MR arm compared to observation. In addition to its lack of benefit, MR was associated with increased toxicity compared to observation (30% vs. 17%), with more serious adverse events noted [12, 39].

Shortly after ASCT, there are increased circulating populations of PD-1 expressing cells, including CD45RO+ effector/memory T cells, natural killer cells and monocytes, which are integral in immune reconstitution [12, 40, 41]. It has been hypothesized that PD-1 blockade in this setting would limit tumor driven lymphocyte exhaustion *via* the PD-1 pathway and potentially lead to improvement in outcomes through eradication of residual disease. In a prospective phase II study, the anti-PD-1 monoclonal antibody pidilizumab was administered every 42 days for three cycles following ASCT in patients with R/R DLBCL, primary mediastinal B-cell lymphoma or transformed indolent B-cell lymphoma. The 16-month PFS and OS from the start of first treatment was 72% and 85%, respectively. Of particular note, in the subgroup of patients with measurable disease post ASCT, pidilizumab was associated with an ORR of 51% with 34% achieving a CR by computed tomography (CT) criteria. Overall, the therapy was well tolerated without report of significant autoimmune toxicity and no infusion reactions or treatment-related mortality [42]. Although these findings have yet to be confirmed in larger randomized studies, therapy with checkpoint inhibitors such as pidilizumab shows promise in the post-ASCT setting in DLBCL, and is the subject of active clinical studies. Although a promising option, currently MR post ASCT is not a standard of care, and should only be considered in the context of a clinical trial. Although larger confirmatory studies are needed, immune manipulation with checkpoint blockade appears to be a rational target with encouraging preliminary data [12, 31].

Conclusions [31]:

1) In the rituximab era, autologous stem cell transplantation is generally not recommended as part of first-line therapy in DLBCL, although recent data on PET-guided auto-HSCT is promising [43].
2) Auto-HSCT is still the standard of care for those DLBCL patients with chemosensitive first relapse.
3) There is no recommendation for tandem transplantation in DLBCL.

Burkitt's lymphoma

Burkitt's lymphoma (BL) accounts for around 2% of all adult NHL, with a higher incidence in patients with immunodeficiency and in patients who are human immunodeficiency virus (HIV)-positive. BL is a highly aggressive tumor with a Ki67 expression of nearly 100% requiring prompt multiagent chemotherapeutic programs. Several studies have identified risk factors for poor outcomes. Besides older age, advanced stage, and comorbidities, such risk factors are: an elevated serum lactate dehydrogenase (LDH), failure to achieve CR, anemia, central nervous system (CNS) involvement, and bone morrow (BM) infiltration. Several studies have explored the role of ASCT in first remission. In a prospective trial, the HOVON group treated 27 patients with two cycles of intensive induction followed by BEAM-conditioned ASCT for those patients achieving at least a partial remission. The 5-year EFS and OS was 73% and 81%, respectively. In a retrospective analysis of 117 patients receiving auto-HSCT as part of first-line therapy between 1984 and 1994, patients in CR at time of transplant had a 3-year OS of 72%. In the relapse situation, patients who were chemotherapy-sensitive had a 3-year OS of 37% following auto-HSCT compared to just 7% for those who were chemotherapy resistant.

In summary, auto-HSCT in BL is feasible, but there is no documented advantage compared to standard combination

chemotherapy for patients responding sufficiently to first-line treatment. Auto-HSCT may be used to optimize remission in patients with insufficient response or as bridging to allo-HSCT. In the relapse setting, given the intensive regimens usually used as first-line treatment, the difficulty lies in achieving a response good enough to proceed to auto-HSCT and to collect autologous hematopoietic stem cells; hence, auto-HSCT is rarely used in BL [44].

Lymphoblastic lymphoma

Lymphoblastic lymphoma (LBL) is an aggressive neoplasm of precursor B cells (B-LBL) or T cells (T-LBL) with features of acute leukemia. It accounts for approximately 2% of all NHL. In adults, around 90% of all LBL are T-LBL. There are only very few studies evaluating the role of auto-HSCT in LBL. In CR1, the use of auto-HSCT as a consolidation may improve relapse-free survival but has no effect on OS. In another study in 128 patients with LBL receiving auto-HSCT, response rate (RR) at 5 years was 56%. No documented role in more advanced disease >CR1 has been reported either. In conclusion, data for auto-HSCT in LBL is too sparse to reach firm conclusions [44].

Primary central nervous system lymphoma

Primary central nervous system lymphoma (PCNSL) is an extranodal NHL, which is classified as a discrete entity in the classification of the WHO. It is an aggressive malignancy that involves the brain parenchyma, spinal cord, eyes, cranial nerves and meninges. The PCNSLs constitute about 1% of all NHLs, 4% of intracranial lymphomas and 4–6% of extranodal lymphomas. The great majority (90%) of the PCNSLs are DLBCL. PCNSL is a rare disease of increasing incidence mainly affecting the elderly. The major risk factor for PCNSL is immunodeficiency, especially the HIV infection. The standard approach to PCNSL, that is high-dose methotrexate (HDMTX)-based chemotherapy followed by whole brain radiotherapy (WBRT), is associated with disappointing outcomes. Moreover, this strategy is associated with increased risk of disabling neurotoxicity, especially in elderly patients. Several drugs and strategies have been investigated to improve results and neurotolerability. Some investigators use ASCT as consolidation after primary chemotherapy and in patients with relapsed/refractory PCNSL. Current therapeutic knowledge in PCNSL management results from a limited number of single-arm phase II trials, meta-analyses and large retrospective series. Thus, several questions such as the optimal primary chemotherapy, the identification of new active drugs and the role of intrathecal chemotherapy, consolidation radiotherapy and ASCT remain unanswered. The latter is an important issue, since preliminary evidence seems to suggest a central role for this strategy in PCNSL. Some investigators showed that in refractory/relapse disease, complete remission rate (CRR) after ASCT was 40%, with 20% treatment-related mortality (TRM). Estimated 2-year RFS and OS rates were 37% and 40%, respectively. Although OS seem to be increased with ASCT in relapsed PCNSL, the difference was not significant (p =0.21). So, even with the application of ASCT in relapsed disease, the prognosis of patients with PCNSL is far from what could be hoped for [45, 46].

Conditioning regimens

There is limited data to guide the choice of HDC regimen prior to ASCT for patients with HL and NHL. 4,917 patients were studied (NHL n =3,905; HL n =1,012) who underwent ASCT from 1995 to 2008 using the most common high-dose chemotherapy schemes: BEAM (n =1,730), CBV (n =1,853), BuCy (n =789), and totalbody irradiation (TBI)-containing (n =545). CBV was divided into CBVhigh and CBVlow based on BCNU dose. One analyzed the impact of regimen on development of idiopathic pulmonary syndrome (IPS), TRM, PFS and OS). The 1-year incidence of IPS was 3–6%, and was highest in recipients of CBVhigh and TBI compared to BEAM. 1-year TRM was 4–8% and was similar between regimens. Among patients with NHL, there was a significant interaction between histology, HDT regimen, and outcome. Compared to BEAM, CBVlow was associated with lower mortality in follicular lymphoma (p <0.001), and CBVhigh with higher mortality in diffuse large B-cell lymphoma (p =0.001). For patients with HL, CBVhigh, CBVlow, BuCy and TBI were associated with higher mortality compared to BEAM (p <0.001). The impact of specific HDC regimen on post transplant survival is different depending on histology; therefore, further studies are required to define the best regimen for specific diseases [47].

Author's contributions

PR contributed all this work.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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