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REVIEW ARTICLE

Transplant in Diffuse Large B-Cell Lymphoma

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Abstract: Diffuse large B-cell lymphoma is the most common type of aggressive lymphoma. Patients that don't respond to first-line therapy have a poor prognosis. Bone marrow transplant represents an effective and established salvage treatment for those patients, with curative potential. Autologous transplant uses the patient stem cell for rescue after high-dose myeloablative chemotherapy, while allogenic transplant relies on a different stem cell for a graft-versus-lymphoma effect. With distinct toxicity and capacity to induce remission, those therapies have great value in the management of patients with relapsed and refractory diffuse large B-cell lymphoma.

Descriptors: Lymphoma; Transplantation, Autologous; Transplantation, Allogenic.

INTRODUCTION

Aggressive lymphomas can be classified as a group of neoplasms of mature lymphocytes in which the overall survival is measured in months if left untreated.[1] The most common ones in clinical practice are diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, Burkitt's lymphoma, mantle-cell lymphoma, and peripheral T-cell lymphomas. This discussion focuses on DLBCL, the most prevalent type of lymphoma, and with more data.

OVERVIEW

DLBCL is the most common type of lymphoma,[2] with an estimated rate of new cases of 5.6 per 100,000 men and women per year.[3] Most patients are between 65 and 75 years old at diagnosis. As an aggressive lymphoma, patients tend to have advanced disease at presentation, with constitutional symptoms and large lymph nodes. Extranodal involvement is less frequent, but it can occur in around 30% of patients.[4]

It is considered a curable disease, with an estimate of around 60% of patients being free of disease in the long term.[5] For those patients that eventually relapse and are considered eligible, high-dose chemotherapy with stem cell rescue (or autologous transplant) is the standard therapy. However, only 50% of the relapse patients will respond to second-line treatment or have clinical conditions to support high-dose therapy. Within the primary refractory group, the prognosis is very poor, with a median overall survival of fewer than seven months.[6]

There are new treatment options for the relapsed/refractory (R/R) population of DLBCL, but the one with apparently better results is chimeric antigen receptor T cells (CAR T-cell). The ZUMA-7, phase 3 study comparing autologous transplant

and CAR T-cell in the second line for patients with R/R disease, with results recently published, can help understand where best fit this new treatment.[7] However, in most centers in the world, currently, autologous transplant is the choice for R/R DLBCL patients with curative intent.

Allogenic transplant is controversial for patients with DLBCL, although a graft-versus-lymphoma (GVL) effect has been proven. Non-relapse mortality (NRM) rates can be high as close to 30% in three years,[8] especially because of graft-versus-host disease (GVHD) and infections. Early NRM can be reduced with reduced-intensity conditioning (RIC) and better GVHD prophylaxis, and since the widespread of haploidentical platforms, almost every patient has a potential donor. The curative power of the allogenic transplant relies on a strong GVL effect, but that can take time. Therefore, the status of the disease at transplant is of great importance. Patients with a metabolic complete remission have a better outcome, but this is often difficult to achieve in chemorefractory disease and after multiple lines of therapy.

DISCUSSION OF THE CURRENT DATA

Autologous transplant

Since the PARMA trial, in the '90s, autologous transplant is considered standard salvage treatment for lymphomas.[9] Several studies addressed what should be the best second-line therapy, but always with autologous transplant as a consolidation when feasible.

The CORAL study evaluated salvage chemotherapy with R-ICE *versus* R-DHAP in DLBCL, R/R.[10] It was a prospective, randomized, multicentric, phase 3 study. About 200 patients in each group, but only 62% were previously exposed to rituximab. Response criteria with computed tomography (CTs) and bone marrow biopsy, no positron emission tomography (PET)/CT. The median age of 55 years old and most age-adjusted international prognostic index (aaIPI) of 0-1 are apparently a better prognosis group of patients. If chemosensitive, all patients underwent autologous transplant with BEAM as a conditioning regimen. Without statistical difference between arms, the 3y progression-free survival (PFS) was 37% (95% confidence interval – 95%CI 31–42), and 3y overall survival was 49% (95%CI 43–55). Only 50% of the patients received the transplant.

With the advent of CAR T-cell therapy and impressive results in multirefractory DLBCL patients, the always goal to autologous in rescue treatment is being questioned. Until more data comes to light on the comparison between those treatments in second line, autotransplant should be offered to all patients that can receive it.

Allogenic transplant

The timing of the allogeneic transplant is a constant debate. The European Society for Blood and Marrow Transplantation (EBMT) reviewed first transplants for DLBCL from 2002 to 2010, either autologous or allogenic.[11] There were 4,210 patients, 230 with an allogenic transplant (RIC for 98 pts). Results for auto, RIC allogenic transplant and myeloablative conditioning (MAC) allogenic transplant, respectively, with four years rates: NRM 7, 20 and 27%; relapse incidence 45, 40 and 38%; PFS 48, 52 and 35%; and overall survival 60, 52 and 38%. After adjustment for confounding factors, NRM was significantly worse for patients undergoing allogenic transplant whilst there was no difference in the relapse incidence.

González-Barca et al.[12] evaluated patients with relapse after autologous, between 2003 and 2013, in a multicenter and retrospective study. They selected only active therapy, excluding palliative treatment. There were 541 patients, but 164 lacked information on the chart. After excluding the palliative treatment, 256 were evaluated. The median age of 50 years old, 74% with advanced disease, time from diagnosis to autologous of 10 months (6.2-21.6), time from the first relapse to autologous of seven months (3-16), with 65% relapsing < one year from the auto. Status at autologous: complete remission 51%, partial remission 31%, stable disease/progressive disease 17%. 69 pts went for an allogenic transplant, with 65% deaths from progressive disease or transplant-related mortality. Overall survival in 3y of 36% (25.4-51.2). In a univariate analysis, the parameters associated with overall survival were elevated lactate dehydrogenase (LDH) (hazard ratio – HR=2.08, 1.49–2.86), Karnofsky performance status <80% (HR=1.69, 1.26–2.32), and time of relapse after auto > one year (HR=0.52, 0.38–0.71). When separating groups with relapse from auto > one year and < one year, respectively, 3y-overall survival 41 (31–53) *vs*. 20% (14–24).

In a large retrospective study of the EBMT's lymphoma group, between 1997 and 2006, over 100 patients were treated with allogeneic transplant for relapse after autologous.[8] Most had RIC condition (64 pts), peripheral blood as source (76 pts), and a match-related donor (MRD). The median age of 46 years old and 64 patients were Rituximab-naïve. With a median follow-up of 36 months (survivors), the 3y results were: NRM 28.2% (95%CI, 20–39), relapse risk 30.1% (95%CI 22–41), PFS 41.7% (95%CI 32–52) and OS 53.8% (95%CI 44–64). NRM was significantly worse in patients over 45y and lower PFS when relapse < 12 months from autologous transplant.

However, a frequent problem in real-life practice is getting the patient to transplant. The GITMO group reported, in a large retrospective study, less than 20% of the patients that relapse after autologous were able to receive an allogenic transplant.[13] This is over several reasons, such as progressive disease and loss of patient's performance status, but it shows that sometimes is a long way from indication to actually perform an allogeneic transplant.

The choice of a donor can be troublesome when there is no human leukocyte antigen-identical sibling. Alternative donors are nowadays established as a good option in allogenic transplants for lymphoma. Haploidentical donors with post-transplant cyclophosphamide platform for GVHD have similar outcomes than MRD and seem to be better than the umbilical cord, making it a lot easier to offer this treatment in proper time.[14,15]

CONCLUSION

With better knowledge of the disease biology, target therapies with low toxicity have been the focus of current studies. Transplant is an old treatment strategy, but still with very established results and worldwide use. Allogenic is still reserved for multi-refractory cases, as a longshot to a possible cure. The caveat of great toxicity exists, but with lower rates than before. Autologous continues to be a standard part of second-line therapy, even with the landscape of the current treatment options. In places where novel therapies are more difficult to arrive, transplants should still be very present.

AUTHORS' CONTRIBUTION

Both authors contributed equally.

DATA AVAILABILITY STATEMENT

All data were generated or analyzed in the present study.

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