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The role of stem-cell transplantation in the treatment of marginal zone lymphoma

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A B S T R A C T

High-dose chemotherapy and autologous stem-cell transplantation (ASCT) is standard therapy in relapsed/refractory aggressive lymphoma. The optimal therapy of relapsed/refractory disseminated marginal-zone lymphoma (MZL) has not been defined. Limited data on ASCT in this setting suggests outcomes are similar to what is expected in follicular lymphoma. International guidelines suggest that ASCT should be considered in follicular lymphoma in second or subsequent remission, in particular in high-risk disease, or following disease transformation. These guidelines can be extrapolated to MZL. ASCT is not considered curative but a subset of patients achieve very long remissions. The major concern is the occurrence of secondary malignancies possibly related to total-body irradiation. Allogeneic SCT is usually considered after failure of ASCT, but can also be considered upfront in younger patients seeking curative approach. The introduction of novel/targeted therapies may change the role and timing SCT may have in the treatment algorithm of indolent lymphomas.

Introduction

Marginal zone lymphomas (MZL) are a group of indolent B-cell lymphomas that originate from memory B-lymphocytes normally present in the marginal zone or the external compartment of secondary lymphoid follicles. The 2008 World Health Organization defined 3 subtypes; extra-nodal MZL (EMZL) of mucosa-associated lymphatic tissue (MALT) type, splenic MZL (SMZL) and nodal MZL (NMZL) [1]. The different subtypes share immunophenotypic and some genetic features, but the clinical and molecular characteristics are different [2–5]. MZL account for approximately 10% of all non-Hodgkin's lymphomas (NHL), with 70%, 20% and 10% belonging to the three subtypes, respectively. MALT lymphomas arises in organs that are associated with chronic infections or autoimmune disorders [3]. The most common site is the stomach where it is frequently associated with Helicobacter Pylori infection. They often present in stage IE disease with symptoms related to the organ involved. Disseminated disease at presentation is relatively rare. SMZL present with splenomegaly, cytopenia, bone-marrow involvement and lymphocytosis and frequently with autoimmune features. SMZL is often associated with hepatitis C infection [4]. NMZL present with disseminated lymphadenopathy but with no involvement of the spleen or extra-nodal sites. It resembles follicular lymphoma and may also be associated with hepatitis C infection [5].

Marked improvement has been achieved in last years in the management of indolent lymphoma including MZL. Treatment of MZL depends on the occurrence of symptoms, the associated infection, the bulk and dissemination of the disease. Several

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groups have published guidelines for treatment [6–8]. The first-line treatment of gastric MALT lymphoma is antibiotics for irradiation of Helicobacter Pylori. Patients with localized disease who do not respond or relapse after antibiotic therapy can be treated with either radiation therapy or rituximab–chemotherapy combinations. Patients with advanced disease who require therapy are treated similarly to follicular lymphoma. Patients with SMZL and hepatitis C infection who do not require immediate therapy can be treated with anti-viral therapy. Symptomatic patients may be treated with splenectomy, rituximab alone or immuno-chemotherapy. Patients with relapsed or disseminated disease are often treated with immuno-chemotherapy. NMZL is treated similarly to follicular lymphoma. Patients with localized disease can be offered radiation therapy. Asymptomatic patients with low tumor bulk can be watched until progression while patients with high tumor burden can be treated by rituximab–chemotherapy combinations.

The optimal therapy for patients with relapsed or refractory disseminated MZL has not been defined. Both autologous and allogeneic stem cell transplantation (SCT) are often considered in this setting, but there is no specific data to support transplantation in this disease. Moreover, the introduction of novel agents such as novel monoclonal antibodies, proteasome inhibitors, immune-modulatory agents, B-cell receptor pathway targeting agents, BCL-2 inhibitors, epigenetic modulators and combinations, further increase the controversy on the role and timing of SCT in indolent NHL [9]. This review will discuss the limited data of SCT in MZL in the wider context of the data on SCT for other indolent lymphomas and in particular follicular lymphoma.

Stem cell transplantation in marginal-zone lymphoma

There are only two reports of autologous SCT (ASCT) in patients with MZL [10,11]. The Dana Farber Cancer Institute reported the first series of 11 patients with MZL given high-dose chemotherapy and ASCT [10]. Six patients had MALT, 1 had NMZL and 4 had SMZL. The median age was 47 years (range, 37–59). All patients had disseminated MZL following multiple lines of chemotherapy (a median of 2) but were still chemo-sensitive at the time of ASCT, although only 36% were in CR and 36% had overt marrow involvement. The study did not include transformed disease. Patients were treated during the years 1994–1999 and were given high-dose cyclophosphamide and total body irradiation (TBI) with purged bone marrow support. The median progression-free survival (PFS) and overall survival (OS) were 52 and 58 months, respectively. Two patients died early due to transplant related complications. One died of therapy-related myelodysplastic syndrome (MDS). Three patients relapsed and died. Most relapses were at prior sites of disease and one had transformation to aggressive lymphoma. Five patients remained in continuous CR with a median follow-up of 52 months. Of note, 5 patients had second malignancies. The major prognostic factor for adverse outcome was older age.

The group at the University of Nebraska reported a second series of 14 patients with MALT ($n = 7$), NMZL ($n = 5$) and SMZL ($n = 5$) given ASCT during the years 1992–2008 [11]. The conditioning regimen was cyclophosphamide and TBI or BEAC/BEAM. The median age was 48 years (range, 29–62). All patients had chemo-sensitive disease with a median number of 2 prior regimens, but only 4 were previously given rituximab. With a median follow-up of 138 months, 5 remained alive and relapse-free. Three had early transplant-related mortality, all in heavily pre-treated patients and all treated in early years. Only 2 relapsed, but 3 had secondary cancers (2 MDS). The median PFS and OS rates were 108 and 120 months, respectively.

A much larger study was reported by the EBMT lymphoma group together with two Italian lymphoma groups, so far only in an abstract form [12]. The study included 199 patients, transplanted between 1994 and 2013, 111 patients (56%) with MALT lymphoma, 33 patients (16%) with SMZL and 55 patients with NMZL (28%). The median age at transplantation was 56 years (range, 25–71 years). The median number of prior therapies was 1 (range 1–8), including rituximab in 74%. The vast majority had chemo-sensitive disease at SCT. TBI was used in only 8%. With a median follow-up of 4.1 years, the 5-year cumulative incidence of relapse and non-relapse mortality (NRM) were 38% and 9%, respectively. The 5-year PFS and OS rates were 53% and 73%, respectively. Multivariate analysis revealed age >65 years to be associated with shorter PFS and OS while the MALT subtype was associated with better outcome. Prior rituximab had no statistically significant effect on transplant outcome. The risk of secondary malignancies was 6.8%.

There is no specific data on allogeneic SCT in the treatment of relapsed or refractory MZL.

This limited and partly old data, suggest that high-dose chemotherapy and ASCT can allow long-term PFS in a subset of patients with advanced and multiply relapsed chemo-sensitive MZL. NRM was relatively high in the old series, but this is expected to be much reduced in the more modern era of ASCT and with more stringent eligibility criteria. NRM in NHL is expected to be in the range of 2–5% [13]. The patients were relatively young, but ASCT can be safely given to older patients in the current era [14]. However, as will be further discussed the relatively high rates of second malignancies is a concern and there may be a role of TBI used in the conditioning. In all, the results of ASCT in MZL seem similar to what is reported in other indolent lymphoma and in particular follicular lymphoma. In the absence of further data the treatment algorithm used for follicular lymphoma can be extrapolated to MZL [15,16].

Stem-cell transplantation for indolent lymphoma

High-dose chemotherapy and ASCT is the standard of care for relapsed/refractory chemo-sensitive diffuse large B-cell lymphoma [17]. The use of rituximab, has dramatically changed the outcome of patients with aggressive lymphoma, increasing both response and survival rates. However, despite this progress a significant proportion of patients are still refractory or relapse after frontline rituximab-containing therapy. Moreover, it is increasingly more difficult to rescue these

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