Follicular Lymphoma

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83.1 Introduction

First-line therapy for patients with advanced stage follicular lymphoma (FL) in need of treatment is to administer chemoimmunotherapy followed by maintenance rituximab (RTX). With this approach approximately half of the patients will remain progression-free at 10 years. Both auto-HSCT and allo-HSCT have been employed in the management of patients with FL since the 1980s. However, the roles of both forms of HSCT have continued to evolve as both transplant and non-transplant therapies have been refined. The current indication for auto-HSCT and allo-HSCT are reviewed below.

83.2 Autologous HSCT

83.2.1 Auto-HSCT in First Response

With both the development of auto-HSCT in the 1980s and the realisation that standard-dose chemotherapy was not curative for indolent lymphoma, investigators explored the role of auto-HSCT as a consolidation strategy following first-line therapy. Promising initial studies culminated in the development of several large randomised studies where auto-HSCT was compared with either no further therapy or interferon. Whilst some of these studies demonstrated an improvement in disease control, no overall survival benefit could be demonstrated (Lenz et al. 2004; Ladetto et al. 2008). These observations combined with a growing realisation of the acute and long-term toxicities of auto-HSCT have led to the abandonment of auto-HSCT as a first-line consolidation procedure.

83.2.2 Auto-HSCT for Relapsed FL

To date, the CUP trial has been the only randomised study comparing consolidation with an auto-HSCT (using either purged or unpurged stem cells) with no further therapy in the relapse setting (Schouten et al. 2003). In this trial, 140 patients with relapsed FL were randomised between consolidation with an auto-HSCT (using either purged or unpurged stem cells) or chemotherapy alone. The 2-year PFS for the chemotherapy alone arm was 26% compared with 58% and 55% for those receiving HSCT with either purged or unpurged stem cells, respectively. Further there was an overall survival advantage in favour of the two transplant arms (Schouten et al. 2003).

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More recently the EBMT-LYM-1 study prospectively examined the role of purging and maintenance with Rituximab (RTX) peri-HSCT in RTX naïve patients with relapsed FL (Pettengell et al. 2013). In this study all patients underwent an auto-HSCT, and no benefit could be demonstrated for in vivo purging. However, the study did demonstrate that for patients receiving RTX maintenance, the PFS was in excess of 50%. A number of other studies have also reported long-term follow-up of auto-HSCT in relapsed FL and describe a 10-year PFS ranging between 31 and 50% (Kornacker et al. 2009; Montoto et al. 2007). Taken together these results demonstrate that between 25 and 50% of patients experience prolonged PFS following an auto-HSCT for relapsed FL suggesting that this is a curative procedure for a significant minority of patients.

Although promising it is important to recognise both the acute and long-term toxicities associated with auto-HSCT which continues to limit the application of this therapy. Whilst early TRM may be relatively low in younger patients, there is evidence that for patients over the age of 60, the TRM may be in excess of 10% (Sánchez-Ortega et al. 2016). Given that the median age of patients with relapsing FL is 69 an auto-HSCT will be associated with a significant TRM for the majority of patients. An additional concern is the late risk of developing secondary malignancies including MDS/AML. In a prospective randomised study, patients undergoing an auto-HSCT for FL had a significantly higher rate of both solid malignancies and MDS/AML compared to patients not receiving HSCT (Gyan e al. 2009). Further, in a population-based study of more than 7000 patients undergoing auto-HSCT, the risk of secondary malignancies was 1.4 times greater and the risk of MDS/AML 20.6 times greater than the general population (Bilmon et al. 2014). It is unclear whether the type of conditioning therapy used for an auto-HSCT influences the risk of secondary malignancy and MDS/AML. Evaluation of the bone marrow for clonal haematopoiesis and cytogenetic abnormalities may enable the identification of patients at a greater risk of developing MDS/AML following an auto-HSCT. For these patients alternative relapse therapies may be more suitable.

83.2.3 The Role of Purging, Conditioning Regimen and Maintenance

The BM is infiltrated in approximately 75% of FL patients at diagnosis, and consequently a number of investigators have studied the role of marrow purging in auto-HSCT (Gonzalez-Barca et al. 2000). However, no clear benefit for purging could be demonstrated in prospective studies (Schouten et al. 2003; Pettengell et al. 2013), and there was some evidence that purging resulted in significant additional immune suppression (IS). Consequently, purging remains an experimental procedure in auto-HSCT for FL.

There is a wide variety of different conditioning regimens that may be employed for auto-HSCT in FL but a paucity of randomised trials comparing the efficacy and toxicity of these different regimens. The BEAM (BCNU, VP, Ara-C, MEL) regimen has become the most widely used regimen prior to auto-HSCT in malignant lymphoma and has been adopted in many countries. A number of investigators have looked to improve upon BEAM by including RTX and dexamethasone, substituting BCNU with bendamustine (Visani et al. 2014), or incorporating bortezomib, mitoxantrone or fotemustine. Several groups have also incorporated radioimmunotherapy (RIT) into the conditioning regimen prior to auto-HSCT in NHL. In one small randomised trial comparing Zevalin and BEAM (Z-BEAM) with BEAM in relapsed/refractory B NHL, there was a survival advantage in the Zevalin arm (Shimoni et al. 2012).

Auto-HSCT in FL, Key Points

- Auto-HSCT should not be employed in first response.
- Auto-HSCT should be considered in patients with relapsed disease responding to reinduction therapy.
- Auto-HCT achieves a 5-year PFS of approximately 50% and may be curative in a significant minority of patients.
- There is no proven role for purging strategies.
- Maintenance rituximab for four infusions should be considered post auto-HSCT.

83.3 Allogeneic HSCT

Allo-HSCT offers several advantages over auto-HSCT in FL: the provision of a graft uncontaminated by lymphoma cells or exposed to mutagenic agents and the development of an allogeneic GVL effect. Early studies employed MAC regimens and demonstrated that cure could be achieved in a significant proportion of patients (Peniket et al. 2003; van Besien et al. 2003). In retrospective studies comparing allo- with auto-HSCT, MAC allo-HSCT was associated with a lower relapse rate but a higher TRM and consequently a similar OS. In an attempt to reduce the toxicity of allo-HSCT, RIC allo-HSCT has been developed (Robinson et al. 2002). A number of groups have demonstrated the safety and efficacy of RIC allo-HSCT and demonstrated that this type of transplant may be employed in older patients with significant comorbidities and in those patients who have undergone a prior auto-HSCT. Following a RIC allo-HSCT, the relapse rate is typically below 30%, whether performed as a first transplant procedure (Robinson et al. 2013) or following a previous auto-HSCT (Robinson et al. 2016) and the 5-year PFS rates range from 50 to 85%.

83.3.1 Conditioning Regimen Intensity

It is currently unclear whether a RIC or a MAC allo-HSCT offers superior outcomes in FL. A retrospective registry study demonstrated that the two approaches to allo-HSCT resulted in similar outcomes in the sibling donor setting (3-year OS for the MAC and RIC were 71% and 62% (P = 0.15), respectively) (Hari et al. 2008). However, the EBMT reported that in the unrelated donor setting, RIC allo-HSCT was associated with a lower NRM and significantly longer PFS and OS when compared with MAC allo-HSCT (Avivi et al. 2009). The median age at relapse of FL is 69, and therefore the majority of patients that may be considered for an allo-HSCT will be considered too old for MAC regimens, and many authorities therefore recommend a RIC allo-HSCT for FL. However, in younger patients (<50 years old) and without significant comorbidities, more intensive regimens may also be considered.

83.3.2 Donor Source for Allo-HSCT and TCD

The outcomes of both matched sibling donor (MSD) and MUD allo-HSCT in FL are broadly similar. A recent large retrospective study conducted by the EBMT and the CIBMTR demonstrated that the PFS and OS following MSD and MUD were similar (Sureda et al. 2018). For patients lacking a MSD or MUD, either a cord blood or haploidentical family donor may now be considered. The feasibility of umbilical cord blood (Rodrigues et al. 2009; Brunstein et al. 2009) and haplo-HSCT (with PT-CY) (Dietrich et al. 2016) in NHL (including FL) has been reported. However, the toxicity of both CBT and haplo-HSCT is significant, and it remains to be established whether either type of alternative donor source is superior to MSD and MUD.

TCD of the graft is a well-established method to reduce the incidence of GVHD post-transplant but runs the risk of eliminating allo-reactive T cells that will mediate the GVL effect and consequently result in a higher relapse rate. The risk of relapse may be offset by employing donor lymphocyte infusion (DLI), and with this approach, the 4 years PFS and relapse risk was 76% and 24%, respectively, and the incidence of GVHD was low (Thomson et al. 2010), suggesting that this approach may also be an option for allo-HSCT in FL.

Allo-HSCT for FL, Key Points

- Allo-HSCT should only be considered in patients with relapsed disease.
- Reduced intensity conditioning regimens are most appropriate for patients over the age of 50 or with significant comorbidities.
- Patients under 50 years may be considered for more intensive regimens.
- Matched sibling, matched unrelated, haploidentical and cord blood stem cell sources may be considered.
- T-cell depletion may be employed but should be combined with chimerism directed donor lymphocyte infusions.

83.4 Patient Selection for HSCT in FL

As discussed above HSCT options are no longer considered in first response and are reserved for patients with relapsed disease. However, patients with relapsed FL represent a highly heterogeneous population, and a HSCT will not be appropriate for many patients. Therefore, numerous factors have to be taken into consideration when selecting patients for a HSCT procedure. Patient-related factors such as age, comorbidities, performance status, organ function, the HSCT comorbidity index (HSCT-CI) (Sorror et al. 2005) and patients' personal views will determine if a patient is fit to undergo a transplant and what the likely TRM rate will be. Certain features relating to the patient's lymphoma are prognostic in the relapsed setting, and transplantation should only be considered in patients where the lymphoma is considered to considerably shorten survival. Patients that relapse within 2 years of the first-line therapy (Casulo et al. 2015) and those with high-grade transformation at relapse (Sarkozy et al. 2016) have been shown to have poor survival, and these patients should be considered for a HSCT procedure once adequate disease control has been obtained. Patients with a high FLIPPI score at relapse and those with multiple relapses may also have a poor prognosis, and these patients may also be considered for transplant options. It is important, however, to carefully counsel the patients regarding both the transplant and non-transplant therapies that are currently available of which there are many.

83.5 Auto-HSCT or Allo-HSCT as a First Transplant Procedure

The decision whether to employ either auto- or allo-HSCT in relapsed FL remains challenging. There has been only one prospective randomised study addressing this issue, which was unfortunately closed early due to poor accrual (Tomblyn et al. 2011). An EBMT retrospective comparison demonstrated that the PFS at 5 years was 57% for patients receiving an allo-HSCT compared with 48% for those receiving an auto-HSCT, but overall survival was similar with both types of transplant (Robinson et al. 2013). It is therefore currently not clear which SCT option is superior for relapsed FL, and in the absence of definitive data, the decision regarding an auto- or allo-HSCT needs to be taken on an individual patient basis. Given the excellent results recently reported with auto-HSCT (Pettengell et al. 2013), the relatively low toxicity and the potential for cure a number of authorities now recommend an auto-HSCT as the first transplant of choice and that an allo-HSCT should be reserved for patients relapsing after an auto-HSCT.

83.6 Allo-HSCT in Patients Relapsing After Auto-HSCT

The largest series of patients undergoing a RIC allo-HSCT after the failure of an auto-HSCT was reported by the EBMT. The NRM at 2 years was significant (27%), but the 5-year PFS and OS were 48% and 51%, respectively (Robinson et al. 2016). The duration of response following the allo-HSCT was also significantly longer than after the auto-HSCT illustrating the potential of the allogeneic GVL effect in this disease. This data demonstrates that a RIC allo-HSCT can act as an effective salvage strategy in this setting although the toxicity was significant. There is also a risk that patients may fail to respond to reinduction therapy, and therefore would not be eligible for an allo-HSCT.

Patient Selection Key Points

- Only patients with (a) early relapse or (b) high-grade transformation after first-line therapy or (c) multiple relapses should be considered for HSCT consolidation.
- The superiority of either auto-HSCT or allo-HSCT has not been established.
- Auto-HSCT may cure some patients and is associated with lower toxicity compared to allo-HSCT.

- RIC allo-HSCT may cure patients that relapse after an auto-HSCT.
- Many authorities recommend an auto-HSCT as the first transplant procedure of choice.

83.7 Conclusions

Both auto- and allo-HSCT have an established role in the treatment of relapsed FL, and both forms of transplant can deliver curative therapy to patients with otherwise poor prognosis disease. Patient selection for transplant therapy is critical, and a current understanding of the rapidly evolving field of alternative non-transplant lymphoma therapies is mandatory. The treatment paradigm for FL will change over the coming years as novel agents are incorporated into clinical practice, and the place of these agents relative to transplantation will evolve.

References

Avivi I, Montoto S, Canals C, et al. Matched unrelated donor stem cell transplant in 131 patients with follicular lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Br J Haematol. 2009;147:719–28.

Bilmon IA, Ashton LJ, Le Marsney RE, et al. Second cancer risk in adults receiving autologous haematopoietic SCT for cancer: a population-based cohort study. Bone Marrow Transplant. 2014;49:691–8.

Brunstein CG, Cantero S, Cao Q, et al. Promising progression-free survival for patients low and intermediate grade lymphoid malignancies after nonmyeloablative umbilical cord blood transplantation. Biol Blood Marrow Transplant. 2009;15:214–22.

Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National Lympho Care Study. J Clin Oncol. 2015;33:2516–22.

Dietrich S, Finel H, Martinez C, et al. Post-transplant cyclophosphamide-based haplo-identical transplantation as alternative to matched sibling or unrelated donor transplantation for non-Hodgkin lymphoma: a registry study by the European society for blood and marrow transplantation. Leukemia. 2016;30:2086–9.

Gonzalez-Barca E, Fernandez de Sevilla A, Domingo-Claros A, et al. Autologous stem cell transplantation (ASCT) with immunologically purged progenitor cells in patients with advanced stage follicular lymphoma after early partial or complete remission: toxicity, follow-up of minimal residual disease and survival. Bone Marrow Transplant. 2000;26:1051–6.

Gyan E, Foussard C, Bertrand P, et al. High-dose therapy followed by autologous purged stem cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by the GOELAMS with final results after a median follow-up of 9 years. Blood. 2009;113(5):995–1001.

Hari P, Carreras J, Zhang MJ, et al. Allogeneic transplants in follicular lymphoma: higher risk of disease progression after reduced-intensity compared to myeloablative conditioning. Biol Blood Marrow Transplant. 2008;14:236–45.

Kornacker M, Stumm J, Pott C, et al. Characteristics of relapse after autologous stem-cell transplantation for follicular lymphoma: a long-term follow-up. Ann Oncol. 2009;20:722–8.

Ladetto M, De Marco F, Benedetti F, et al. Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. Blood. 2008;111:4004–13.

Lenz G, Dreyling M, Schiegnitz E, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. Blood. 2004;104:2667–74.

Montoto S, Canals C, Rohatiner AZS, et al. Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study (LFTU of autoSCT). Leukemia. 2007;21:2324–31.

Peniket AJ, Ruiz de Elvira MC, Taghipour G, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplant. 2003;31:667–78.

Pettengell R, Schmitz N, Gisselbrecht C, et al. Rituximab purging and/or maintenance in patients undergoing autologous transplantation for relapsed follicular lymphoma: a prospective randomized trial from the lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol. 2013;31:1624–30.

Robinson SP, Boumendil A, Finel H, et al. Reduced intensity allogeneic stem cell transplantation for follicular lymphoma relapsing after an autologous transplant achieves durable long term disease control. An analysis from the Lymphoma Working Party of the EBMT. Ann Oncol. 2016;27:1088.

Robinson SP, Canals C, Luang JJ, et al. The outcome of reduced intensity allogeneic stem cell transplantation and autologous stem cell transplantation when performed as a first transplant strategy in relapsed follicular lymphoma: an analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplant. 2013;48:1409–14.

Robinson SP, Goldstone AH, Mackinnon S, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Blood. 2002;100:4310–6.

Rodrigues CA, Sanz G, Brunstein CG, et al. Analysis of risk factors for outcomes after unrelated cord blood transplantation in adults with lymphoid malignancies: a study by the Eurocord-Netcord and lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol. 2009;27:256–63.

Sánchez-Ortega I, Basak GW, Beohou E, et al. Autologous hematopoietic cell transplantation in elderly patients aged 65 and older: a retrospective analysis by the complications and quality of life working party of the EBMT. Blood. 2016;128(22):678.

Sarkozy C, Trneny M, Xerri L, et al. Risk factors and outcomes for patients with follicular lymphoma who had histologic transformation after response to first-line immunochemotherapy in the PRIMA trial. J Clin Oncol. 2016;34:2575–82.

Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. J Clin Oncol. 2003;21:3918–27.

Shimoni A, Avivi I, Rowe JM, et al. A randomized study comparing yttrium-90 ibritumomab tiuxetan (Zevalin) and high-dose BEAM chemotherapy versus BEAM alone as the conditioning regimen before autologous stem cell transplantation in patients with aggressive lymphoma. Cancer. 2012;118:4706–14.

Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106:2912–9.

Sureda A, Zhang M-J, Dreger P, et al. Allogeneic hematopoietic stem cell transplantation for relapsed follicular lymphoma. A combined analysis on behalf of the Lymphoma Working Party of the EBMT and the Lymphoma Committee of the CIBMTR. Cancer. 2018;124:1733–42.

Thomson KJ, Morris EC, Milligan D, et al. T-cell-depleted reduced-intensity transplantation followed by donor leukocyte infusions to promote graft-versus-lymphoma activity results in excellent long-term survival in patients with multiply relapsed follicular lymphoma. J Clin Oncol. 2010;28(23):3695–700.

Tomblyn MR, Ewell M, Bredeson C, et al. Autologous versus reduced-intensity allogeneic hematopoietic cell transplantation for patients with chemosensitive follicular non-Hodgkin lymphoma beyond first complete response or first partial response. Biol Blood Marrow Transplant. 2011;17:1051–7.

van Besien K, Loberiza FR, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood. 2003;102:3521–9.

Visani G, Stefani PM, Capria S, et al. Bendamustine, etoposide, cytarabine, melphalan, and autologous stem cell rescue produce a 72% 3-year PFS in resistant lymphoma. Blood. 2014;124:3029–31.