

III. Role of allotransplantation for non-Hodgkin lymphoma and chronic lymphocytic leukemia

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With an incidence rate of ~15 per 100 000, non-Hodgkin's lymphoma (NHL) accounts for the majority of lymphoid neoplasms in Europe [1]. Although in most of these entities the results of first-line therapy are becoming more and more effective, allogeneic stem cell transplantation (alloSCT) is increasingly used in NHL. Numbers of NHL allotransplants registered with the European Society for Blood and Marrow Transplantation (EBMT) grew from 2000 to 2009 as follows: chronic lymphocytic leukemia (CLL) 160%, follicular lymphoma (FL) 62%, mantle cell lymphoma (MCL) 89%, diffuse large cell lymphoma (DLCL) 54%, T-cell lymphoma (TCL) 339%. With 354 transplants performed, CLL was the leading alloSCT indication among these five entities registered with the EBMT in 2009, followed by TCL (211), FL (199), DLCL (171) and MCL (136) (EBMT, data on file).

In contrast to autografting, where stem cells are re-infused to compensate for the hematopoietic toxicity of single-hit high-dose therapy, alloSCT represents a fundamentally different biological principle, namely the ignition of a permanent immunotherapeutic process within the recipient: the graft-versus-lymphoma (GVL) effect. Thus, three crucial questions need to be addressed for each NHL subtype in order to assess the potential benefit of alloSCT: (i) is GVL effective? (ii) can it be translated into therapeutic benefit with acceptable toxicity? (iii) which indications result from the individual efficacy/toxicity ratio?

The present overview attempts to briefly address these three key questions for the main NHL subsets CLL, FL, MCL, DLCL and TCL. Since some general issues, such as GVL/graft-versus-host disease (GVHD) principles and toxicity patterns in the reduced intensity conditioning (RIC) era, are best investigated in CLL, this entity will be described in more depth.

chronic lymphocytic leukemia

Although not curable, CLL often has an indolent behaviour with good responsiveness to cytoreductive treatment or no need for treatment at all. However, ~20% of the patients in need of treatment show an aggressive course and die within a few years of diagnosis despite early institution of intensive immunochemotherapy.

evidence for GVL activity in CLL

Evidence for GVL efficacy in CLL derives from the observation that—in contrast to autologous SCT (autoSCT) or other

intensive therapies—the relapse incidence seems to decrease over time even if the alloSCT was performed with RIC [2]. Furthermore, GVL activity in CLL is indicated by a reduced relapse risk in the presence of chronic GVHD, and an increased relapse risk associated with the use of T-cell depletion (TCD) [2]. The most compelling proof of the GVL principle in CLL, however, comes from studies analyzing the kinetics of minimal residual disease (MRD) after RIC alloSCT, demonstrating that regular achievement of MRD negativity is linked to immune intervention, such as tapering of immunosuppression or donor lymphocyte infusion (DLI). MRD negativity a year after transplant seems to be durable in >90% of patients and predictive for the absence of clinical relapse [2, 3]. Unfortunately, the GVL effect in CLL seems to be closely correlated with chronic GVHD, implying that it is essentially dependent on allogeneic effects with broader specificity rather than on CLL-specific reactivity of donor GVL effector cells [3].

efficacy and risk of alloSCT in poor-risk CLL

As reviewed in [2], long-term progression-free survival (PFS) can be achieved in 30%–60% of transplanted patients by RIC alloSCT. Where studied, patients with poor-risk CLL as defined by purine-analogue refractoriness or the presence of deletion 17p- had a similar outcome to patients without poor-risk characteristics [3]. This seems to apply also to patients whose poor risk is caused by TP53 mutations. In a study assessing the value of alemtuzumab in fludarabine-refractory CLL, the only long-term survivors were those who had been consolidated with alloSCT [4]. In conclusion (RIC) alloSCT seems to be effective in poor-risk CLL, thereby overcoming the adverse prognostic impact of purine-analogue refractoriness and deletion 17p-. However, active or unresponsive disease at the time of alloSCT still remains a predictor of an unfavorable outcome [2, 3].

Whereas non-relapse mortality (NRM) rates of up to 44% were reported in older registry analyses of myeloablative alloSCT for CLL, more recent data obtained with RIC uniformly show an NRM of between 15% and 25%. This advantage of RIC is even more remarkable as RIC cohorts are generally older and are characterized by higher comorbidity scores. It has to be stressed that in the era of RIC, where the direct toxic effect of the conditioning regimen is often moderate and NRM is essentially due to GVHD and its complications, non-relapse deaths mostly do not occur in the transplant phase but are distributed over the first 24 months

after transplantation. For instance, the 'early death' rate as defined by mortality at day +100 after SCT was <3% in the German CLL3X trial [3]. This has to be taken into account when considering the risk of dying with and without transplant.

indications of alloSCT in CLL

In 2007, the EBMT published a consensus on indications for alloSCT in CLL, stating that alloSCT is a reasonable treatment option for eligible patients with previously treated, poor-risk CLL. Criteria for 'poor-risk CLL' according to this 'EBMT Transplant Consensus' are purine-analogue refractoriness, early relapse after purine-analogue combination therapy and CLL with deletion 17p- or TP53 lesions requiring treatment [5]. Although in the meantime novel treatment modalities and a huge body of additional scientific information have become available, no significant progress has been made in terms of improving the outcome of purine-analogue-refractory CLL and 17p-deleted or TP53-mutated CLL. Therefore poor-risk CLL remains poor-risk CLL as defined in the EBMT CLL Transplant Consensus, and alloSCT the only treatment with the potential of providing long-term disease control in this condition. In addition to disease risk, patient-related risk factors, such as age and comorbidity, have to be considered when the decision about alloSCT is made [6].

follicular lymphoma

The advent of rituximab has largely improved the outcome of FL. With modern rituximab-based immunochemotherapy and rituximab maintenance, 3-year PFS after first-line therapy regularly exceeds 70%. Even after relapse, long-term disease control can be achieved by rituximab-based salvage therapy and/or autoSCT [7]. Nevertheless, a small proportion of patients do not achieve a sustained response and also fail second-line therapy. These patients have a poor prognosis and therefore qualify for more risky treatments, such as alloSCT.

evidence for GVL activity in FL

Although the published evidence is not as comprehensive as in CLL, the data available suggest that FL may be even more sensitive to GVL than CLL: DLIs are highly effective, in particular in recipients of T-depleted grafts [8]; late FL relapses after alloSCT are remarkably infrequent in comparison with other lymphoma subtypes [9]; and there is a detrimental effect of TCD on disease control [10].

efficacy and risk of alloSCT in FL

As suggested by several single-center studies [8] and registry analyses [10, 11], long-term disease control can be achieved in 40%–75% of transplanted patients by RIC alloSCT if 'current' PFS is considered, i.e. relapses that can be reverted by DLI are neglected. It seems that NRM and overall outcome are inversely correlated with disease chemosensitivity at the time of SCT. The equivalence of unrelated donors to sibling donors still needs to be shown in FL. Given the often excellent long-term efficacy of autoSCT in FL, conditioning intensity may play a particular role in this disease [7]. Indeed, in a large registry analysis patients having undergone myeloablative conditioning

tended to have superior outcome due to better disease control even after multivariate adjustment for confounders [11].

indications of alloSCT in FL

Recently, the American Society for blood and Marrow Transplantation (ASBMT) published a systematic review of SCT in FL. The bottom line for alloSCT was that no recommendations could be given due to lack of high-quality evidence [12]. This highlights the difficulty of applying scientific methodologies that are more than appropriate for standard treatments to 'orphan indications' such as alloSCT in FL. Nevertheless, in my opinion it seems to be justified to conclude that alloSCT is highly effective in FL and is associated with an NRM within the usual range if performed with RIC. Because on the one side this NRM is still substantial, and because of the good efficacy of rituximab-based salvage treatments and of autoSCT on the other side, alloSCT might be reserved for those patients who are obviously resistant to less toxic approaches, i.e. those who relapse early after salvage autoSCT or a similar effective regimen [7]. This implies that the place of alloSCT is in the third line or beyond. However, published evidence suggests that alloSCT should be applied not too late, i.e. after the disease has become completely chemorefractory [10, 11].

mantle cell lymphoma

Similar to FL, the prognosis of MCL has significantly improved over the last 15 years, at least in part due to rituximab and autoSCT. It seems, however, that these advances are mainly due to more effective first-line treatments rather than to improvements in salvage therapies. Thus, the prognosis of MCL relapse has remained poor, raising the question of whether alloSCT could have a role here.

evidence for GVL activity in MCL

Clear-cut evidence for GVL efficacy in MCL is sparse, but plateaus in the PFS curves and long-term disease control after autoSCT failure suggest that there must be a biologically relevant contribution of GVL [13, 14].

efficacy and risk of alloSCT in MCL

Most analyses of alloSCT for MCL report NRM rates that appear to be higher than in FL or CLL, even if RIC is applied [14]. Further studies are needed to find out whether this has to do with the often advanced disease course of patients with MCL at the time of alloSCT. In terms of efficacy, long-term disease control rates of ~50% have been observed in single-center series [13, 14], whereas PFS was less good in registry analyses (see abstracts by Hari et al. and Robinson et al. in this issue of *Annals of Oncology*).

indications for alloSCT in MCL

Given the poor prognosis of MCL recurrence after state-of-the-art first-line treatment, and the documented potential of alloSCT to open long-term perspectives in this situation (RIC) alloSCT appears to be a reasonable treatment option for patients relapsing after autoSCT. In contrast,

alloSCT for MCL should not be performed outside of clinical studies as first-line consolidation or in the salvage setting without previous autoSCT failure.

diffuse large cell lymphoma

Rituximab has significantly reduced the relapse risk of patients with DLCL but at the same time changed the quality of DLCL relapse: nowadays, more than two-thirds of all relapses occur within the first year after induction treatment but respond poorly to standard salvage regimen including autoSCT. Therefore alloSCT could be an option for patients with early relapse as well as for those who have DLCL recurrence after autoSCT.

GVL effects, efficacy and risk of alloSCT in DLCL

In three recent, relatively large studies on RIC allotransplants for DLCL, most of the patients had a history of a previous autoSCT [15–17]. Although NRM was regularly <30%, 3-year PFS rates hardly exceeded 40% due to relatively high relapse rates, suggesting that the GVL effect might be less pronounced in DLCL than in classical ‘indolent’ lymphomas, such as FL and CLL. However, since almost all relapses occurred during the first year after transplant, and PFS curves appeared to approach a plateau in the long term [15–17], there seems to be some immunotherapeutic benefit of alloSCT in DLCL, translating into long-term disease-free survival in a substantial proportion of patients with otherwise very unfavourable prognosis.

indications for alloSCT in DLCL

Thus, alloSCT appears to be indicated in patients with DLCL relapsing after autoSCT. Future studies should aim to assess the benefit of alloSCT as part of first salvage in comparison with autoSCT in those patients who have an early relapse or are refractory to standard induction immunochemotherapy.

T-cell lymphoma

In the absence of major therapeutic improvements in the last 15 years, the prognosis of peripheral TCL (PTCL) has remained unfavorable with the exception of Alk-positive anaplastic large cell lymphoma (Alk+ ALCL). Patients with PTCL other than Alk+ ALCL with an International Prognostic Index of low–intermediate or worse are facing a median EFS of <3 years irrespective of the intensity of the induction regimen, implying that more effective first-line and salvage strategies are needed. The prognosis of cutaneous TCL (CTCL) is better; however, patients with advanced stage CTCL have a median survival of ≤5 years.

evidence for GVL activity in TCL

In a recent registry analysis, TCL had the best outcome of all NHL subtypes after myeloblastic alloSCT from unrelated donors [9]. Moreover, impressive plateaus in the PFS curves, long-term disease control after autoSCT failure and beneficial effects of chronic GVHD on disease control strongly suggest that there is an effective contribution of GVL in both PTCL [18–20] and CTCL [21].

efficacy and risk of alloSCT in TCL

Despite an overall 2-year NRM risk of between 20% and 35%, the outcome of alloSCT for TCL appears to be quite favorable in particular in those patients who have chemosensitive disease at transplant. In this subset, 4-year survival estimates of >60% have been regularly reported in both PTCL and CTCL [18–21]. However, also in refractory patients, survival plateaus at the 30% level are observed, indicating that alloSCT might be justified in this otherwise fatal setting. Whereas donor source and conditioning intensity did not have significant impact in PTCL, RIC and sibling donors appeared to be associated with a favorable outcome in CTCL [21].

indications of alloSCT in TCL

Despite the absence of prospective trials, the available data strongly suggest that alloSCT is a promising treatment option for patients with PTCL who have failed first-line therapy. Given the very poor PFS of patients with advanced International Prognostic Index, studies addressing first-line alloSCT in this unfavorable subset seem to be worthwhile.

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