EUROPEAN HEMATOLOGY ASSOCIATION

Immunotherapy in lymphoma - Section 3

Is transplantation in lymphoma still needed in the era of immunotherapy?

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Take-home messages

- The introduction of check point inhibitors in the treatment landscape of patients with lymphomas might potentially change the profile of patients being candidates for this procedure; number of patients treated with check point inhibitors is still low and follow up limited.
- Allotransplant related toxicity seems to be modified / increased by the prior use of check point inhibitors in these patients
- Transplant related outcomes in patients pre-treated with check point inhibitors do not seem to be worse than those of historical controls.

Introduction

Hematopoietic stem cell transplantation (HSCT), autologous or allogeneic, is used with increasing frequency in Europe where in 2014 over 40 000 transplants were reported for the first time.[1-6] Transplant-related mortality remains high between 10 and 20% in allogeneic HSCT and although much lower, ~1% for autologous HSCT, high-dose chemotherapy is toxic and demanding for patients. Progress has been made over the years reducing non-relapse mortality (NRM) by ~50% with the introduction of reduced intensity conditioning (RIC) protocols, better HLA typing and donor selection as well as better anti infection compounds and supportive care, but toxicity in HSCT is still a challenge.[7,8] Auto-HSCT remains the standard of care for patients with chemosensitive relapse of diffuse large B cell lymphoma (DLBCL) in the rituximab era.[9-11] For follicular lymphoma patients in first chemosensitive relapse, high-dose chemotherapy followed by high-dose chemotherapy is often regarded as treatment of choice.[9-12] For Hodgkin lymphoma in first chemosensitive relapse or refractory to first-line therapy, HDCT is also standard as shown by two prospective clinical trials.[13,14] Allo-HSCT can provide long-term disease control in up to 40% of patients with DLBCL who have failed auto-HSCT, in particular if performed in chemosensitive disease.[15,16] In FL patients, allo-HSCT is reserved as a potentially curative option for those patients who have failed auto-HSCT or multiple therapy lines, or who have become refractory.[11,12,17] Prospective phase II trials as well as retrospective cohort comparisons and registry analyses suggest that allo-HSCT can prolong survival in selected patients when compared with the limited non-transplant options in HL failing auto-HSCT but responding to salvage therapy.[18-20]

Drug development is accelerating and many new drugs have been developed and marketed for hematologic malignancies in the past few years. Some of the more targeted drugs have limited toxicity and it is of interest to examine whether these have changed the use of HSCT for selected indications. At the same time, accessibility to targeted drugs is an issue in some countries. A specific very-effective drug may replace HSCT and lead to decreased use of this technology, whereas another drug may enhance HSCT use and function as a 'bridge to transplant'.

Amongst many others, antibodies targeting programmed death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein-4 (CTLAP-4) are being investigated in lymphoid malignancies with varying levels of activity and an interesting toxicity profile. Anti-PD-1 antibodies such as nivolumab and pembrolizumab show encouraging response rates particularly in classical HL. Results in FL and DLBCL so far are less impressive. Results of a phase II trial in relapsed/refractory classical HL patients who had relapsed after auto-HSCT and brentuximab vedotin, showed an overall response rate (ORR) of 66% based on central review and of 72% based on investigator evaluation after a median follow-up of 8.9 months.[21] As the first immune checkpoint inhibitor in lymphoma, nivolumab was approved for the treatment of relapsed or refractory classical Hodgkin lymphoma by both, the Food and Drug Administration and the European Medical Agency in 2016.

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The possibility to combine both, autologous and allogeneic stem cell transplantation with checkpoint inhibitors is of potential clinical interest. This can be done in different settings namely post auto-HSCT, before allogeneic transplant and after the allogenic procedure. Check point inhibitors function by amplyfing effector T cell responses, and therefore combined therapy with allo-HSCT may have a synergistic anti-tumor effect (GvT), but may also result in increased toxicity with increased graft versus host disease (GvHD).

The post auto-HSCT setting is an attractive one for immune-directed therapy because of several reasons: the existence of a state of minimal residual disease and additionally, the conditioning regimen delivered alters the immune system in a way that may make check point inhibitors more effective. A phase II study of patients with DLBCL evaluated the potential benefits of adding three doses of pidilimumab one to three months after auto-HSCT. Progression free survival (PFS) at 18 months was 72%, which compared favorably to 52% seen in the control group. PFS for patients with PET positive disease before transplantation was 72% and patients with active disease after transplant had a response rate of 51%.[22] These early results have prompted the development of several prospective ongoing clinical trials in HL and DLBCL in this setting.

In the pre-allogeneic setting, most information comes from relapsed HL patients. Some potential candidates for an allogeneic procedure have previously received PD-1 inhibitors, most frequently nivolumab. The immunomodulatory effects and long half-life of check point inhibitors may alter the outcomes and toxicity profile of allo-HSCT in these patients. Residual blockade of inhibitory checkpoints at the time of transplant may result in a potentially enhanced GvT effect, but also increased immunological side effects such as GVHD. Animal models demonstrate that PD-1 blockade after allo-HSCT may augment GvT responses,[23] but could also result in higher rates of acute GVHD and higher mortality related to GHVD.[24] Clinical experience in this setting is still limited and comes basically from a retrospective multicer analysis including 39 patients who received pembrolizumab or nivolumab for the treatment of refractory / relapsed HL or NHL and subsequently underwent allo-HSCT.[25] Clinical characteristics are depicted in Table 1. With

Table 1. Clinical characteristics of lymphoma patients receiving allo-HSCT after check point inhibitors exposure*.

Patient characteristics	N = 39 (%)
Gender Male / Female	20 (51%) / 19 (49%)
Age at allo-HSCT in years (median, range)	34 (21 - 67)
Histological diagnosis HL / NHL	31 (79%) / 8 (29%)
Prior lines of therapy (median, range)	4 (2 - 8)
Prior auto-HSCT	32 (82%)
PD-1 inhibitor received Nivolumab / Pembrolizumab	28 (72%) / 11 (28%)
Cycles of PD-1 inhibitor received (median, range)	8 (3 - 27)
Time interval between last PD-1 treatment and allo-HSCT in days (median, range)	62 (7 - 260)
Source of stem cells Peripheral blood / Bone Marrow	28 (72%) / 11 (28%)
Donor type MRD / MUD / Haplo / mmURD	9 (23%) / 12 (31%) / 14 (36%) / 4 (10%)
Disease status before allo-HSCT CR / PR / SD / PD	25 (64%) / 11 (28%) 2 (5%) / 1 (3%)
Conditioning regimen RIC / MAC	38 (97%) / 1 (3%)

Allo-HSCT. Allogeneic stem cell transplantation; HL. Hodgkin's lymphoma; NHL. Non-Hodgkin's lymphoma; MRD. Matched related donor; MUD. Matched unrelated donor; Haplo. Haploidentical donor; mmURD. Mismatched unrelated donor; CR. Complete remission; PR. Partial remission; SD. Stable disease; PD. Progressive disease; RIC. Reduced intensitity conditioning; MAC. Myeloablative conditioning. Adapted from Merryman et al. Blood 2017;9:1380-88; with permission.

a median follow-up for survivors of 12 months, 1-year overall survival and PFS were of 89% and 76%, respectively, while the 1-year cumulative incidence of relapse and NRM were 14% and 11%, respectively. One-year cumulative incidence of grade 2-4, 3-4 and grade 4 acute GVHD were 44%, 23% and 13%, respectively. 1-year cumulative incidence of cGVHD was 41%. Three patients (8% of the series) developed severe hepatic sinusoidal obstruction syndrome despite having received a RIC protocol with one fatality 51 days after transplant. In addition, 7 patients (18%) developed a prolonged febrile syndrome beginning one to seven weeks after transplant. In terms of predictors of survival, non-relapse mortality and GVHD, patients receiving 8 or more doses of PD-1 inhibitors (the median number of doses in this group of patients) had an improved 1-year PFS in comparison to those receiving less doses; there were no differences between both groups of patients regarding overall survival and NRM. Time interval between the last dose of PD-1 inhibitors and allo-HSCT did not significantly impact outcome. Moreover, transplant-related outcomes were not significantly modified by donor and graft characteristics. Although there are still many questions regarding the role and appropppriateness of allo-HSCT after PD-1 blockade, the results of this retrospective study might suggest that this approach is feasible in adequately selected patients and may be associated with increased immune toxicity but also good disease control.

The largest experience presented today using nivolumab for relapse after transplant includes 20 patients with HL.[26] Nivolumab was started at a median time of 23 months after allo-HSCT and patients could not have a prior history of grade 4 aGvHD or extensive chronic GvHD as well as no need for immunosuppressive therapy for the last 4 weeks. 1-yr PFS and 1-yr OS in this series were 58.2% and 78.4%, respectively. Clearly, larger prospective experience is needed to better describe the safety and efficacy of check-point inhibitors after allo-SCT.

In summary, these preliminary findings suggest that it is possible to combine HSCT with check point inhibitors in the relapsed / refractory lymphoma landscape. Nevertheless, we are still left with more questions than answers; these questions need to be explored through well designed prospective clinical trials in order to better define biomarkers that may predict toxicity in this setting and the best way to combine both strategies in order to maximize effectiveness and mitigate toxicity. On the other hand, the incorporation of these novel agents in lymphoma therapy may eventually overcome the actual HSCT indications in these diseases.

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