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REVIEW ARTICLE

Prevention and treatment of relapse after stem cell transplantation in lymphoid malignancies

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Abstract

Relapse is now the major cause of treatment failure after allogeneic HSCT (alloHSCT). Many novel strategies to address this critical issue are now being developed and tested. At the 3rd International Workshop on Biology, Prevention, and Treatment of Relapse held in Hamburg, Germany in November 2016, international experts presented and discussed recent developments in the field. Some approaches may be applicable to a wide range of patients after transplant, whereas some may be very disease-specific. We present a report from the session dedicated to issues related to prevention and treatment of relapse of lymphoid malignancies after alloHSCT. This session included detailed reviews as well as forward-looking commentaries that focused on Hodgkin lymphoma, chronic lymphocytic leukemia and mantle cell lymphoma, diffuse large cell and follicular lymphoma, and multiple myeloma.

Introduction

The basic principle of allogeneic HSCT (alloHSCT) is establishing a foreign immune system in the patient for permanent suppression or eradication of recipient lympho-hematopoiesis including leukemia stem cells. This graft-versus-tumor effect is particularly potent in chronic myelogenous leukemia (CML), but has also been identified after transplant and with donor leukocyte infusions (DLI) for patients with most lymphoid malignancies, including Hodgkin and non-Hodgkin lymphomas (NHL), chronic lymphocytic leukemia (CLL), and multiple myeloma. Despite a combination of intensive conditioning and GVT activity, relapse remains the major cause of failure after alloHSCT. The 1st International workshop on the Biology, Prevention and Treatment of Relapse was held in 2009 and focused on disease-specific prevention and treatment of relapse [1, 2]. The 2nd Workshop, held in 2012 emphasized strategies that might provide a basis for the development of novel, practical clinical trials to address the problem of relapse [3]. The 3rd International Workshop on Biology, Prevention and Treatment of Relapse after Stem Cell Transplantation held in Hamburg, Germany, in November 2016 was convened to further understand issues related to biology, prevention, and treatment of relapse and to report on the most up to date progress of these initiatives since the last workshop. New agents and approaches have rapidly become available particularly for patients with lymphoid malignancies with the potential to significantly influence the ability to both prevent and treat relapse of lymphoid diseases perhaps more effectively and safer. A summary of the session dealing with results of clinical trials addressing issues related to relapse in lymphoid malignancies is presented here.

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Hodgkin lymphoma

Classical Hodgkin lymphoma (HL) represents one of the major success stories in malignant hematology [4], yet the treatment of relapsed or refractory (R/R) disease remains a significant challenge. Less than one-half of patients with R/R HL are cured with conventional salvage chemoradiotherapy followed by high-dose therapy and autologous stem cell transplantation (autologous HSCT) due in large part to relapsed disease [5, 6].

For those patients who are not candidates for autologous HSCT or experience post-transplantation relapse, options are limited. Allogeneic HSCT is considered the standard of care for young patients with HL relapsed after autologous HSCT, chemosensitive disease and a HLA compatible donor available [7–9]. With the advent of reduced intensity-conditioning protocols, non-relapse mortality (NRM) does not represent a major issue but relapse after transplant is still a major concern [10]. A significant development in the allogeneic setting has been the extended use of haploidentical donors. They have not only virtually rendered every single patient a potential candidate for a transplant but haploidentical stem cell transplant also has demonstrated interesting results in terms of low NRM and relapse rate (RR) and adequate progression-free survival (PFS) and overall survival (OS) when using the Baltimore approach with the administration of cyclophosphamide after the stem cell infusion [11–13].

Brentuximab vedotin (BV) has been proven beneficial for those patients who relapse after autologous HSCT. BV is a CD30-specific chimeric monoclonal antibody covalently coupled to several molecules of highly toxic payload, the antimitotic tubulin-inhibitor monomethyl auristatin E. In the pivotal phase 2, the efficacy and safety of BV was evaluated in patients with HL that relapsed after autologous HSCT. In this cohort of patients, tumor regression was seen in 94%, with an overall response rate (ORR) of 75%. Median PFS was 21.7 months in the 34% of patients who experienced a complete remission (CR), in contrast to 5.1 months in the 40% of patients with a partial response (PR), indicating the potential impact of remission quality on outcome [14]. Five-year follow-up of the patients included in the trial [15] demonstrated that 15 of them (13 in CR and 2 in PR) were alive and disease free at the time of evaluation; however, six of them received alloHSCT at some point, making it difficult to understand the potential capacity of BV single drug to be a curative option for a fraction of patients. More recently, consolidation strategies after autologous HSCT using up to 16 cycles of BV have demonstrated to significantly improve 3-years PFS in those patients with a high RR after transplantation [16].

The major drawback of alloHSCT for patients in relapse after the autologous HSCT is the high RR after the procedure. Therefore, improving disease control before alloHSCT consolidation may result in improved long-term outcomes. [17]. Although it is not clear that the prior use of BV significantly improves long-term outcome of alloHSCT, BV is most probably better tolerated and less toxic than conventional chemotherapy and is eventually able to bridge a significant higher proportion of patients to a curative procedure such as alloHSCT [17, 18]. In addition to that, the use of BV as a bridge to alloHSCT does not seem to modify specific transplant related toxicities

Relapse after an alloHSCT carries an exceedingly poor prognosis. BV is an effective and safe drug to be given in those patients who relapse or progress after alloHSCT as demonstrated in a retrospective analysis that examined 25 patients included in several international trials [19, 20],

Malignant cells of classical HL are characterized by genetic alterations at the 9p24.1 locus, leading to overexpression of PD-1 ligands and evasion of immune surveillance. In a phase 1b study, nivolumab, a PD-1-blocking antibody, produced a high response in patients with relapsed and refractory classical HL, with an acceptable safety profile. The results of Cohort B of the pivotal phase II prospective clinical trial Checkmate 205 indicates that nivolumab at a dose of 3 mg/kg intravaneously every other week until progression, death or unacceptable toxicity is an effective (ORR of 66%) and well tolerated approach for patients with recurrent classical HL who had failed to respond to autologous stem cell transplantation and had either relapsed after or failed to respond to BV [21]. Similar results were obtained with pembrolizumab at a flat dose of 200 mg intravaneously every 3 weeks in similar cohorts of patients (Keynote-067) [22].

Checkpoint inhibitors have been tested both before and after allogeneic HSCT. Although the four major post-transplantation outcomes are quite promising in a group of 39 patients with HL and NHL patients treated at some point with nivolumab or pembrolizumab before allogeneic HSCT, there seems to be a higher than expected incidence of transplant related toxicities such as veno-occlusive disease and post-transplant hyper-acute febrile syndrome [23]. Nivolumab has demonstrated to be a quite effective salvage therapy for patients with relapsed/progressive HL after allogeneic HSCT but also associated to a significant reactivatin of both acute and chronic GVHD specially in those patients with a prior history of severe acute GVHD and extensive chronic GVHD after transplantation [23].

In summary, the landscape of R/R HL has markedly changed in the last years and will change even more in the near future. Targeted therapy e.g., BV, is being incorporated in the post-autologous HSCT and alloHSCT settings, as consolidation treatment after autologous HSCT in patients

with high risk of relapse after the autologous HSCT and before autologous HSCT in order to increase the percentage of FDG-PET negative patients at the time of transplant. The curative potential of checkpoint inhibitors as well as the way allogeneic HSCT will be used in this disease still are open questions.

CLL

In CLL, GVT activity seems to be particularly effective in CLL. For this reason, autologous HSCT is no longer used for treating untransformed CLL. After alloHSCT, patients with active GVT as indicated by clearing minimal residual disease (MRD) subsequent to immunosuppression withdrawal or DLI have an extremely low risk of CLL recurrence [24, 25]. The predominant risk factor for an adverse transplant outlook across numerous studies has been refractory disease at alloHSCT [24, 26–30]. *TP53* abnormalities have not been associated with inferior outcome after alloHSCT in the vast majority of studies [24, 26, 28, 30, 31].

Already in the chemoimmunotherapy era the prognosis of CLL relapse post-transplant seemed not to be inferior to that of high-risk CLL in untransplanted patients [24, 32]. The advent of pathway inhibitors (PI), especially ibrutinib, an inhibitor of Bruton's tyrosine kinase, has substantially improved treatment options for CLL recurring after alloHSCT. Recent data suggest that safety and efficacy of ibrutinib given for CLL relapse after allotransplant are as good as in untransplanted patients, i.e. median progression-fee survival times of 2 years or more [32, 33]. Moreover, preliminary data indicate that ibrutinib may enhance Th1-mediated graft-versus-leukemia (GVL) effects if given on a donor chimerism scenario [34]. Furthermore, ibrutinib may have the capacity to attenuate chronic GVHD [35]. Accordingly, the outcome of post-transplant relapse in CLL patients seems to have strongly improved in recent years, with 2-year OS probabilities of > 70%, measured from the time relapse after HSCT [33, 34]. Future prospects may be further enhanced by the availability of additional PI, such as inhibitors of phosphatidynilisotol 3 kinase (PI3Ki) and BCL2 (BCL2i).

The role of DLI for treatment of clinical CLL relapse post-transplant remains unsettled. Whereas frequent and durable responses to DLI were observed in patients who had been allografted on a T-cell depletion (TCD) platform [36], the efficacy of DLI appears to be limited in patients receiving T-replete transplants [24, 32]. The use of PI as "bridge to DLI" seems to be an attractive concept worth being explored further, taking into account the immune-modulating capacity of some of these drugs [35, 37].

Taken together, with the advent of PI, treatment options and results in the setting of post alloHSCT relapse have largely improved for CLL. Given the good efficacy/ toxicity profile and the immune-modulating capacity of some of these drugs, they may improve transplant outcome by being developed for purposes such as prevention of relapse and attenuation of GVHD.

Mantle cell lymphoma

Although the introduction of high-dose Ara-C- and rituximab-based induction has significantly improved the outcome of first-line autologous HSCT in mantle cell lymphoma (MCL), virtually all patients inevitably relapse, even after having achieved MRD clearance [38]. Rituximab maintenance strategies have been proven to reduce relapse risk in this setting, but evidence that they can abandon MCL recurrence in a substantial proportion of patients after autografting is lacking [39]. More recently introduced targeted agents, such as ibrutinib and temsirolimus, have proven activity in MCL, but their efficacy in relapsed disease after conventional or high-dose induction is mostly limited. It remains to be shown if use of ibrutinib earlier in the disease course can potentially prevent relapses or even make HSCT unnecessary. So the only modality with proven long-term efficacy in patients with MCL relapse after autologous HSCT is alloHSCT [40].

The assumption that MCL is a GVT-sensitive disease is based on circumstantial evidence such as a lack of late relapses after T-replete alloHSCT [41], and the efficacy of DLI given for MCL recurrence after TCD-based transplantation [42]. Accordingly, apart from common disease-related factors such as extent of pretreatment and remission status at transplant, TCD has been identified as predictor of an increased relapse risk after alloHSCT for MCL [41–43].

In contrast to CLL, the gap between post-HSCT PFS and OS curves has been narrow in MCL with < 10% at 5 years post transplant, suggesting that salvage options for patients experiencing MCL recurrence after HSCT are limited [41, 44]. Systematic information on this issue is sparse [45]. However, preliminary data indicate that ibrutinib might gain a role in the management of MCL relapse post alloHSCT analogous to CLL [33]. In addition, other drug classes, such as MTOR inhibitors, proteasome inhibitors and imids have some efficacy in MCL and may be considered as alternative options in the post-transplant relapse setting (reviewed in ref. 46). However, with all of these agents durable control of MCL relapse will be achieved in only a small proportion of patients, if any. This dilemma may be overcome by DLI or secondary allotransplants for consolidation of otherwise short-lasting responses. This approach is basically feasible, although its results in MCL have been disappointing in the pre-PI era [47].

Diffuse large B-cell lymphoma and follicular lymphoma

The large clinical heterogeneity among the various NHL histologies prevents a detailed review of all of the specific strategies and modalities that have been employed to prevent and treat relapse after HSCT. However, a generalized and applicable overview is provided by focusing on the two most common histologies, follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL).

Early efforts to prevent relapse focused on intensifying conditioning regimens used prior to autologous and alloHSCT. However, it was found that "more was not always better" when attempting to use maximal doses of alkylating agents and radiation, as reductions in RRs were offset by increased treatment-related morbidity and mortality. As an alternative, radio-immunotherapy, yttrium-90 (90Y)–ibritumomab tiuxetan and iodine-131 (131I)–tositumomab were investigated, as they were thought to have ideal properties that would permit them to be combined with standard conditioning regimens without a significant increase in toxicities. In a phase III randomized study, 224 patients with relapsed, chemosensitive DLBCL were randomized to receive BEAM combined with either 131I-tositumomab (I-BEAM) or rituximab (R-BEAM) prior to autologous HSCT [48]. Unfortunately, there was no significant improvement in outcomes using 131I-tositumomab.

Efforts have also been made to reduce potential contamination of the autologous stem cell graft by lymphoma cells, which had been associated with higher RRs. The EBMT assessed the efficacy of rituximab as in vivo purging before transplantation and as maintenance immediately after autologous HSCT in 280 patients with relapsed FL [49]. Patients were randomly assigned to rituximab purging or observation prior to autologous HSCT and to maintenance rituximab (MR) or observation (No M). There was no difference in 10-year PFS or OS for in vivo purging, but maintenance rituximab had a significant effect on PFS with10-year PFS rates of 54% and 37% for MR and No M groups, respectively ($P = .012$). OS was not improved by either rituximab purging or maintenance.

The use of post-transplant rituximab maintenance was also evaluated in DLBCL. In the international "CORAL" trial, 477 patients with CD20 + DLBCL in first relapse or refractory to initial therapy, were randomized to either R-ICE vs. R-DHAP [50]. Responding patients proceeded to autologous HSCT, and 242 patients were randomized to either rituximab (RM) for 1 year or observation (No M). The 4-year event-free survival rates after autologous HSCT were 52% and 53% for the RM and No M groups, respectively.

These disappointing results with anti-CD20 monoclonal antibodies- in DLBCL lead to the investigation of different classes of agents in the post-transplant setting. There is evidence that thePD-1 immune checkpoint pathway may have a role in permitting NHL, including DLBCL, to evade immune surveillance. It was hypothesized that the period of post-transplant immune reconstitution may be particularly favorable for breaking immune tolerance through PD-1 blockade. Based on this hypothesis, an international phase II study of the anti-PD-1 monoclonal antibody, pidilizumab, was investigated in 66 DLBCL patients undergoing autologous HSCT, with patients receiving three doses of pidilizumab beginning 1–3 months after transplant [51]. Among the 35 patients with measurable disease, the ORR after pidilizumab was 51%. At 16 months after the first treatment, PFS was 0.72 (90% CI, 0.60–0.82); among 24 high-risk patients who remained positive on positron emission tomography after salvage chemotherapy, the 16-month PFS was 0.70 (90% CI, 0.51–0.82).

A number of different strategies have been employed to treat relapsed lymphoma after both autologous and allogeneic HSCT [1, 52]. Relative to relapse after autologous HSCT, alloHSCT is potentially curative option for appropriate patients. The European Group for Blood and Marrow Transplantation performed a retrospective analysis on 101 patients with relapsed DLBCL who underwent an alloHSCT after a previous autologous HSCT [53]. A myeloablative conditioning regimen was used in 37 patients and reduced intensity conditioning was used in 64 patients. Three-year NRM was 28.2% and the RR 30.1%. The PFS and OS was 41.7% and 53.8%, respectively. The NRM was significantly increased in patients older than 45 years of age ($P = 0.01$) and in those with an early relapse (< 12 months) after autologous HSCT ($P = 0.01$). Risk of relapse was significantly higher in patients with refractory disease at the time of alloHSCT ($P = 0.03$). No differences were seen between HLA-identical siblings and matched unrelated donors.

Similarly, the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) performed a restrospective analysis and identified 894 patients who relapsed or progressed after autologous, of which 165 patients (19%) were subsequently treated with alloHSCT [54]. A related stem cell donor and reduced intensity-conditioning regimen was used in 108 and 116 cases, respectively. Following alloHSCT, the ORR of 49%; 84 patients (51%) experienced rapid progression of disease post transplant. The NRM rate was 28%, and mortality associated with progressive disease was 25%. With a median follow-up of 24 months (2–144) at the time of this report, the OS was 39%. In multivariate analysis the only factor affecting OS was disease status at the time of alloHSCT. It appears that alloHSCT may be an appropriate option for patients with recurrent DLBCL whose disease is

still chemotherapy-sensitive and who had a prior autologous SCT.

A novel approach under intense investigation for the treatment of post-transplant NHL relapse is the use of T cells that have been genetically modified with chimeric antigen receptors (CAR), most notably against CD19. Investigators at the National Cancer Institute (NCI) administered autologous anti-CD19 CAR T cells to 15 patients with advanced B-cell malignancies (DLBCL = 9; FL = 2; CLL = 4) [55]. All patients received lympho-depleting chemotherapy (cyclophosphamide and fludarabine) prior to the anti-CD19 CAR T cells. Toxicities included cytokine release syndrome (CRS) and neurologic toxicities; there was one therapy-related death. Of 15 patients, 8 achieved CR, 4 achieved PR, one had stable lymphoma, and two were not evaluable for response. Four of seven evaluable DLBCL patients achieved CR, of which three were ongoing 9–22 months post infusion.

The University of Pennsylvania treated 28 adult patients with refractory lymphomas using autologous T cells expressing an anti-CD19 CAR [56]. Ten of the patients had undergone prior autologous HSCT, and one patient had received a prior alloHSCT. The ORR was 64%; CR occurred in 6 of 14 patients with DLBCL. Sustained remissions were achieved in 86% of patients with DLBCL. Severe CRS occurred in five patients (18%), and serious encephalopathy occurred in three patients (11%). All patients in CR by 6 months remained in remission at 7.7–37.9 months post CAR T-cell infusion.

In a phase 2, international trial, the anti-CD19 autologous CAR T-cell product axicabtagene ciloleucel (axi-cel) was used to treat 101 patients with relapsed/refractory DLBCL, primary mediastinal B-cell lymphoma, or transformed FL [57]. All patients received a lympho-depleting chemotherapy regimen of low-dose cyclophosphamide and fludarabine prior to axi-cel infusion. The ORR was 82% with a CR rate of 54%. At a median follow-up of 15.4 months, 42% of the patients continued to have a response, with 40% continuing to have a CR. The overall rate of survival at 18 months was 52%. Grade 3 or higher CRS and neurologic events occurred in 13% and 28% of the patients, respectively.

The NCI also investigated the use of anti-CD19 CAR T-cell therapy after alloHSCT. They treated 20 patients with B-cell malignancies, including ALL and lymphomas that had progressed after alloHSCT with donor-derived CAR T cells without lympho-depleting chemotherapy [58]. No patient developed GVHD. Eight patients obtained remission (CR = 6; PR = 2); the response rate was highest for ALL.

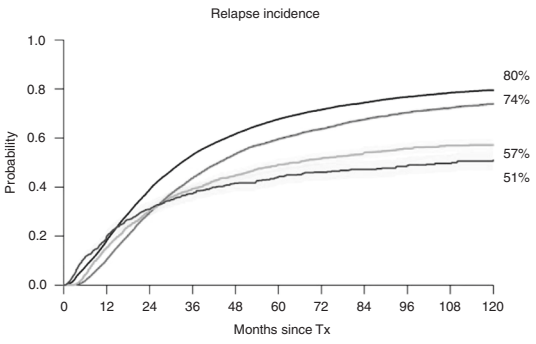
In summary, to minimize both toxicities and relapse in NHL patients undergoing HSCT, the selection of agents and intensity of preparative regimen should be based on the specific histology and the disease state. Although investigation of agents as post-transplant maintenance is reasonable, the greatest opportunity for success is in the early post-transplant period, particularly for allogeneic HSCT. Early results with CAR T cells in treating post-transplant NHL relapses are encouraging, and their use in the post-transplant setting may be ideal.

Multiple myeloma

Multiple myeloma is the most frequent indication for autologous SCT [59], but most patients will ultimately relapse. AlloHSCT has a lower risk of relapse most likely due to a graft-versus-myeloma effect but this advantage is offset by a significantly higher therapy-related mortality. Relapse remains the major cause of treatment failure after HSCT for multiple myeloma.

In EBMT database including >70,000 patients the cumulative incidence of relapse at 10 years is 80% for single autologous SCT, 74% for tandem autologous SCT, 57% for autologous/allogeneic tandem HSCT, and 51% for upfront single alloHSCT (see Fig. 1).

For relapsed patients the number of effective treatment options has markedly increased in the recent years by introduction of novel proteasome inhibitors, proteasome and immunomodulatory drug combinations, and highly effective antibodies or antibody-drug combinations [60–69]. By using triple combination therapy for relapsed patients PFS between 12 and 26 months and longer can be achieved [59, 61, 63–69]. Although a salvage autologous or alloHSCT has been shown to be effective, long-term freedom from disease was achieved only rarely [59, 67]. Therefore, the main clinical focus lays on prevention of relapse in multiple myeloma.



N at risk											
Upfront single auto	56884	34105	20855	13029	8332	5363	3542	2271	1391	877	529
Auto-auto	11507	8276	5625	3929	2807	2053	1547	1120	804	549	350
Auto-allo	1760	1214	825	621	490	386	313	245	192	152	110
Upfront single allo	964	478	331	251	195	160	125	108	80	61	49

Fig. 1 Cumulative incidence of relapse in multiple myeloma according to transplant procedure. Legend: Black, Upfront single autologous SCT. Red, Autologous SCT followed by second allogeneic SCT. Green, Autologous SCT followed by allogeneic SCT. Blue, Single autololous SCT

Intensifying the conditioning regimen for autologous SCT by adding total body irradiation or busulfan to high-dose melphalan showed contradictory results [1, 70, 71], [59, 67]. Adding bortezomib to the conditioning regimen may increase CR rate but a randomized study failed to show any benefit [72, 73] Post-transplantation consolidation therapy either with single agents or with combination therapy was investigated in numerous trials. All studies have shown an upgrade of the remission status and most of them resulted in an improved PFS, but no OS advantage could be demonstrated most likely because most trials also applied maintenance therapy [67–69].

To reduce relapse, maintenance therapy after autologous SCT has been investigated in several phase III studies [74–76]. Although nearly all studies have shown a benefit in PFS not all show a survival benefit [77–80], [65, 67–69]. Meta-analysis however showed a survival benefit for immunomodulation-based maintenance therapy and lenalidomide is now approved in the United States and Europe for maintenance after autologous SCT [67, 81].

A MRD negative status, which has been achieved in the past only by alloHSCT is now feasible by including novel agents prior and post-autologous SCT [82], [67]. A sustained status of MRD negativity is associated with long-term freedom from disease and probably also with cure [67, 83].

Multiple myeloma is the most frequent indication for autologous SCT but is also associated with the higher risk of relapse. Even in the alloHSCT setting the risk of relapse is higher than in other lymphoid or myeloid malignancies. The inclusion of novel active drugs and antibodies may help to increase remission status including MRD negativity, which will be a new endpoint for ongoing and future clinical trials.

Conclusions

We remain optimistic about the future potential to both prevent and treat relapse of lymphoid malignancies after HSCT. The development of novel targeted agents now provides a platform to more safely and appropriately treat patients before and after transplant for prevention, and at the time of recurrence as therapy for relapse. This session identified both limitations and significant advances in approaches to relapse. Over the next few years we anticipate application of targeted agents to minimize disease burden before transplant, to consolidate remission after transplant, and to provide more effective approaches as relapse therapy. Application of immune-stimulants, such as checkpoint inhibitors or CAR modified T cells will be used to enhance GVL activity, target MRD and treat fulminant relapse of these diseases. Ultimately, the development of novel relapse therapies will have a major impact on application of, and outcomes after HSCT.

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