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REVIEW ARTICLE

Prevention and treatment of relapse after stem cell transplantation with immunotherapy

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Abstract
Relapse has become the leading cause of treatment failure after stem cell transplantation. Besides cellular therapies and novel agents, immunotherapeutic strategies have entered clinical practice in order to reduce or prevent relapse. Here, we summarize the presentations on checkpoint inhibitors, vaccination strategies, and novel antibody therapies, which were presented and discussed at the third International Workshop on Biology, Prevention, and Treatment of Relapse after Stem Cell Transplantation.

Checkpoint inhibition

Checkpoint immune inhibition in hematological malignancies—an area of flux

Targeting of the PD-1/PD-L1 axis is a transformative approach being employed in recent years in the field of oncology with unprecedented results in a host of notoriously clinically challenging solid cancers [1–5]. Subsequently, the efficacy of this approach was recapitulated to some degree in hematological malignancies, particularly in refractory Hodgkin lymphoma (HL) whose unique disease biology makes it a prime candidate for PD-1 inhibition [6–9], although emerging data in myeloma [10] and possibly leukemia [11] also hint at a prospective role for checkpoint immune inhibition in these diseases. As relapse following stem cell transplantation (SCT) is the major cause for mortality in transplanted patients, there is an unmet need for preemptive therapies to minimize the risk for relapse, and thus checkpoint immune blockade presents an attractive therapeutic avenue to pursue in this clinical setting.

Checkpoint immune blockade for prevention of relapse following SCT

From a mechanistic standpoint, emerging data suggests that PD-1 blockade synergizes with allogeneic SCT as demonstrated in a murine model of acute myeloid leukemia (AML) where the graft-versus-leukemia effect, mediated via introduction of tumor-reactive T-cell receptor genes, was enhanced by combination therapy with concurrent PD-1 blockade [12]. In the same vein, a recent preclinical study demonstrated that downregulation of PD-1 expression, using a peptide antagonist of vasoactive intestinal peptide (VIP) signaling, led to expansion of anti-leukemia $CD8^+$ effector T-cells, and increased the survival of the transplanted animals by enhancing graft-versus-leukemia activity [13]. Furthermore, blockade of VIP signaling reduced T-cell homing to target organs associated with GVHD, and thus resulted in enhanced graft-versus-leukemia effect without increasing the rate of GVHD. Adding to the complexity of the emerging picture, it seems that the efficacy of PD-1 inhibition in the context of transplantation is also dependent

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on the actual physical location of the transplanted T-cells. Interestingly, the anti-leukemia capacity of transplanted T-cells was dictated to some degree on the distinct PD-L1 expression in different tissues where for example lymph nodes were characterized by a high expression level of PD-L1 resulting in impaired tumor killing efficacy, which could be improved by anti-PD-1 treatment [14].

One of the initial attempts to capitalize on the proposed role of checkpoint immune inhibition in stimulating graft-versus-tumor effect was undertaken by Bashey et al. [15] in a cohort of 29 patients relapsing after allogeneic SCT. Using ipilimumab, a human anti-CTLA4 monoclonal antibody, at relatively low doses, they showed a very modest anti-tumor effect with only three patients responding. However, subsequent case series with higher doses of ipilimumab in AML [16], HL [17], and anaplastic large cell lymphoma [18] lend further credence to this approach. In contrast, some investigators suggest that T-cell exhaustion may not play a major role in relapsing AML patients and thus the utility of checkpoint immune inhibition after transplantation is questioned in this setting [19].

An additional salient point to consider in this context is the optimal timing to initiate preemptive PD-1 therapy following SCT. In myeloma for example, it has been well known that impaired immune reconstitution following autologous SCT is a major determinant of relapse, which is at least partially attributable to a specific population of exhausted $CD8^+$ T-cells with upregulated PD-1 expression. Indeed, relapsing myeloma patients are characterized by an increased number of these cells 3 months after SCT. Moreover, it has been shown that in vitro PD-1 inhibition of this subpopulation increased the proliferation and cytokine secretion activity of these cells, thus substantiating a case for early introduction of PD-1 inhibition post-transplant to reverse and enhance anti-tumor immunity [20].

Lastly, it is also worthwhile noting that the rapport between checkpoint immune inhibition and transplantation seems to be of a reciprocal nature as recently shown by Merryman et al. [21] who analyzed the clinical outcome of 39 transplanted lymphoma patients treated prior to allo-SCT with either pembrolizumab or nivolumab. Interestingly, compared to patients not treated with PD-1 therapy, immune reconstitution after PD-1 exposure was characterized by decreased Treg:CD4 and Treg:CD8 ratios in addition to severe and persistent depletion of PD1+ T-cells, which in the authors' opinion may have contributed to increased graft-versus-tumor responses.

We conclude by noting that the role of the PD-1 axis may not be limited only to a therapeutic role but may also aid with prognostication as PD-1 expression levels have been shown to predict mortality following SCT [22] and correlate with a positive minimal residual disease state in myeloma patients [23].

Challenges and risks with the use of checkpoint immune inhibition following SCT

Hitherto, we emphasized the potential benefit accrued by employing immune checkpoint inhibitors as a means of minimizing disease relapse following SCT, yet recent work proposes that there are significant challenges with the use of these agents in this specific patient segment. These challenges pertain to the unique immunological context, which was appreciated more than a decade ago by Blazar et al. [24] showing in a murine model of graft-versus-host disease (GVHD) the increased mortality effected by PD-1 blockade. More recently published data adds further complexity to the emerging picture by revealing that deficiency of PD-L1 mitigates GVHD via modulation of inflammatory cytokine production and metabolic pathways without affecting graft-versus-leukemia potency [25]. These preclinical data are well grounded in the clinical arena where several case series indicate that PD-1 inhibition with both nivolumab and pembrolizumab may result in worsening of chronic GVHD [26] leading even to fatal consequences [27]. In the meritorious phase 1 trial by Davids et al. [28] with ipilimumab, severe GVHD preventing further administration of the drug was seen in 4 out of 28 patients. Further, in a recently presented abstract, the efficacy and toxicity of nivolumab as a single agent in 12 HL patients relapsing after allo-SCT was examined. Notably, acute GVHD occurred in only 2 patients who both had prior history of grade II acute GVHD in the 3 months preceding nivolumab therapy [29]. In another analysis of 27 anti-PD-1 treated lymphoma patients, relapsing after allo-SCT, 10 of 27 pts (37%) developed acute GVHD, mostly of the liver and skin, resulting in three fatalities [30]. These data contrast with a recently published small series of nine patients receiving post-transplant cyclophosphamide, of which only a single patient developed GVHD following the administration of a donor lymphocyte infusion, which may in itself have caused the GVHD [31]. In aggregate, these data suggest that, as with any other immunotherapy-based approach, use of PD-1 antagonists has the potential for immune toxicity in transplanted patients.

Future directions

In the broadest sense, immune checkpoint blockade holds the potential to unleash the immune system's suppressed anti-tumor activity and enhance the efficacy of SCT in the hopes of effectively reducing relapse rates. The results of ongoing and future clinical trials (Tables 1–3) will help in establishing the exact role PD-1 blockade will assume in this clinical venue.

Table 1 Ongoing and upcoming clinical trials with immune checkpoint inhibitors after stem cell transplantation

Agent	Clinicaltrials.gov registry ID	Phase	Clinical setting
Pembrolizumab	NCT02362997	2	Pembrolizumab after autologous stem cell transplantation in patients with relapsed/refractory classical Hodgkin lymphoma, diffuse large B-cell lymphoma, and T-cell non-Hodgkin lymphoma in first remission
Nivolumab/ipilimumab	NCT02846376	1	Single-agent and combined checkpoint inhibition after allogeneic hematopoietic stem cell transplantation in AML patients at high risk for post-transplant recurrence
Nivolumab/ipilimumab	NCT02681302	1b/2a	Single-agent checkpoint inhibition after autologous stem cell transplantation in myeloma and lymphoma patients at high risk for post-transplant recurrence

AML acute myeloid leukemia

Cancer vaccines and hematopoietic stem cell transplantation

Allogeneic transplantation is uniquely curative for a subset of patients with hematologic malignancies due to the capacity of alloreactive lymphocytes to target malignant cells [32]. However, the lack of specificity of this response results in significant toxicity due to graft-versus-host disease and imperfect protection from disease relapse. Efforts to limit the risk of GVHD are associated with increase risk of relapse. While complications due to immunologic discordance between donor and recipient are obviated in patients undergoing autologous transplantation, the lack of an immunologic component targeting disease results in high rates of relapse [33]. A major area of investigation is the design of cancer vaccines: (a) to stimulate host immunity to selectively target residual disease following autologous transplantation; (b) to create a tumor-specific donor response following allogeneic transplantation that protects against relapse while minimizing risks for GVHD; and (c) to potentially induce lasting anti-tumor immunity that may replace the need for transplant.

Hematologic malignancies arise in the setting of immune dysregulation characterized by poor tumor immunogenicity and an immunosuppressive milieu that facilitates immune tolerance and disease escape [34]. Cancer vaccine strategies are designed to reverse tumor-mediated immune suppression through the enhanced presentation of tumor antigens and the subsequent activation and expansion of tumor-specific T-cells. A critical aspect of vaccine design is the identification of shared tumor-associated antigens as potential targets for immune recognition. These have included antigens derived from embryonic development (NY-ESO, WT-1, MAGE-3, survivin), aberrantly expressed proteins derived from oncogenes (MUC1) and transcription factors linked to malignant transformation (SOX2, XBP1) [35, 36]. A vital aspect of vaccine design is the capturing of tumor heterogeneity including the effective targeting of stem cell populations that are a critical reservoir contributing to disease relapse. Of note, several shared antigens such as WT1 and MUC1 are present on the leukemia stem cell [37, 38].

Neoantigens arise from mutational events intrinsic to a given patient's malignancy and are potentially recognized by high-affinity T-cells within the immune repertoire [39]. However, the immunogenicity of individual neoantigens and their recognition by the effector cell repertoire is uncertain and strategies to identify potential targets may be cumbersome. In addition, vaccination directed against an individual or groups of antigens are subject to immune escape through the downregulation of the target(s). An alternative strategy is the use of whole tumor cells as a source of antigen in which a polyclonal response can be elicited including both shared and neoantigens [40]. The use of patient-derived tumor cells in the context of a personalized vaccine may be potent but presents logistical challenges surrounding access to tumor cells and logistical hurdles for vaccine production.

Another critical aspect of vaccine design is the identification of the ideal platform for antigen presentation [41, 42]. In vivo administration of stimulatory cytokines or toll-like receptor agonists has been pursued to activate innate immunity and foster the recruitment and activation of native antigen-presenting cells. In vivo loading of DCs may also be induced via chemotherapy-induced tumor lysis and inflammation associated with radiation. Alternatively, DCs may be generated ex vivo through the cytokine-mediated maturation of plasmacytoid cells or myeloid precursor populations isolated from peripheral blood, Langerhans cells, cord blood, or bone marrow.

Vaccination following high-dose chemotherapy with stem cell rescue has been explored in patients with myeloma in which autologous transplantation is associated with enhanced disease response and prolongation of remission but not cure. High-dose chemotherapy provides a minimal disease platform that may be more effectively targeted by immune effector cells. In addition, lymphopoietic reconstitution is associated with alterations in the tumor microenvironment and disruption of tolerance mechanisms that favor the selective expansion of tumor-reactive clones [20].

Table 2 Ongoing and upcoming clinical trials with cancer vaccines and antibodies post stem cell transplantation

Agent	Clinicaltrials.gov registry ID	Phase	Clinical setting
CT7, MAGE-A3, and WT1 vaccine	NCT01995708	1	CT7/MAGE-A3/WT1 mRNA-electroporated autologous Langerhans-type dendritic cells after autologous stem cell transplantation in patients with myeloma
WT1 analog peptide vaccine	NCT01827137	1	WT1 analog peptide vaccine in patients with multiple myeloma following autologous stem cell transplantation
GM-CSF secreting autologous leukemia cell vaccination	NCT01773395	2	Adenovirus vector transferred GM-CSF secreting autologous leukemia cell vaccination (GVAX) versus placebo vaccination in patients with advanced MDS/AML after allogeneic hematopoietic stem cell transplantation
Blinatumomab	NCT02807883	2	Blinatumomab maintenance following allogeneic hematopoietic cell transplantation for patients with acute lymphoblastic leukemia
Inotuzumab ozogamicin	NCT03104491	1/2	Inotuzumab ozogamicin post-allogeneic hematopoietic cell transplant for acute lymphocytic leukemia

Table 3 Recent studies using immunotherapy to prevent relapse following transplantation

Agent	Clinical setting	Transplant modality	Phase	Results
PD-1 blockade [21]	Refractory lymphoma prior to transplant	Allogeneic	—	One-year relapse rate of 14%. Four transplant-related deaths
Ipilimumab [15]	Relapse following transplant in various hematologic cancers	Allogeneic	1	Disease response in 3/29 patients
Dendritic cell vaccination [45]	Myeloma patients following transplant	Autologous	2	Complete response and very good partial response in 78% of patients
Adoptive T-cell transfer and tumor vaccine [47]	Myeloma patients following transplant	Autologous	1/2	Median event-free survival of 20 months
GM-CSF secreting tumor vaccine [51]	High-risk AML and MDS patients following transplant	Allogeneic	1	Durable remission seen in 9/10 patients (range 12–43 months)

AML acute myeloid leukemia, *MDS* myelodysplastic syndrome, *GM-CSF* granulocyte-macrophage colony stimulating factor

Single antigen-based vaccination in the post-transplant period targeting idiotype or MAGE3 was associated with the expansion of antigen-specific T-cells in the early post-transplant period, but the impact on clinical response and outcome was uncertain. In one study comparing outcomes following post-transplant idiotype-based vaccination with a large historical cohort, vaccination appeared to be associated with an improvement in overall survival (OS), despite a lack of effect on progression-free survival [43].

The Boston group has developed a tumor vaccine in which patient myeloma cells are fused with autologous dendritic such that a broad array of shared tumor antigens and patient-specific neoantigens are potentially presented in the context of dendritic cell (DC) mediated co-stimulation [44]. Vaccination following autologous transplantation with DC/MM (Multiple Myeloma) fusions resulted in the durable expansion of myeloma-specific T-cells and the conversion of partial to complete responses such that the complete/near complete response rate nearly doubled in the late post-transplant period [45]. Significant challenges remain for post-transplant vaccination with respect to reversing intrinsic deficiencies of native effector cells and overcoming the tumor microenvironment. In one approach, vaccine therapy was coupled with infusion of T-cells activated via CD3/CD28 ligation in an effort to induce functionally competent effector cells capable of responding to stimulation in the early post-transplant period [46, 47].

The integration of vaccine strategies with immunomodulatory therapy is currently being explored as a means of enhancing post-transplant therapy and preventing reestablishing of immune tolerance. Lenalidomide therapy is associated with T-cell and NK-cell activation and enhanced responses to pneumococcal vaccine [48]. In a unique multicenter clinical trial conducted through the clinical trials network (CTN 1401), patients undergoing autologous transplantation for myeloma are being randomized to undergo DC/MM fusion vaccination in conjunction with lenalidomide maintenance as compared to lenalidomide maintenance alone (NCT02728102). Alternative strategies being explored include the use of vaccination in conjunction with checkpoint blockade partnering tumor-specific T-cell expansion with reversal of the exhausted phenotype associated with PD-1 expression.

Vaccine therapy is also being explored following allogeneic transplantation in an effort to enhance tumor-specific immunity while minimizing GVHD. Recognition of tumor-associated antigens by humoral and cellular immunity has been noted following allogeneic transplantation and is associated with protection from relapse suggesting that lymphodepletion and the introduction of donor cells facilitates the reversal of tolerance. Early phase clinical studies have demonstrated that vaccination with a WT1-based vaccine following allogeneic transplantation results in the further expansion of antigen-specific T-cells and reduction in the WT1 signal [49, 50]. However, the clinical importance of this observation is not yet clear. The use of whole cell-based vaccines after allogeneic transplantation has been explored in the context of the GVAX model in which autologous tumor cells are genetically engineered to express GM-CSF. In one study, vaccination of patients with AML demonstrated evidence of tumor-specific immunity and durable responses in 9/10 vaccinated patients [51]. In another study, 18 patients with Chronic lymphocytic leukemia (CLL) undergoing vaccination demonstrated a biasing of the T-cell response toward autologous tumor as compared to alloantigen-bearing recipient cells. Consistent with these findings, the incidence of GVHD appeared similar to a historical control and the projected 2-year PFS was an encouraging 82% [52]. Randomized studies will be needed to ascertain if the clinical outcomes result from induction of tumor-specific immunity as compared to the selection of patients able to receive the vaccine.

Finally, the use of vaccination to effectively induce tumor-specific cellular immunity replacing the need for allogeneic transplantation is being explored. Prior experience with peptide or antigen-based vaccination has yielded evidence of immunologic response but uncertain clinical benefit. Studies that combine vaccine approaches with agents that target immunosuppressive microenvironment may yield better results. In addition, understanding the importance of the impact of the immunologic milieu on disease evolution has led studies of vaccine strategies in earlier phases of disease such as in smoldering myeloma. Investigators have demonstrated that vaccination with DC/AML fusions following chemotherapy-induced remission has resulted in the sustained expansion of leukemia-specific T-cells and a 71% progression-free survival at nearly 5 years of follow-up, despite a median age of 63 [40]. A randomized trial to comparing vaccine alone, vaccination in combination with PD-L1 antibody, or best supportive care in patients with AML achieving remission following chemotherapy is currently being initiated.

Antibodies for ALL and AML

ALL

Treatment results in newly diagnosed adult ALL have improved considerably in the past decade with an increase of complete remission (CR) rates to 85–90% and OS rates to 40–50% [53]. However, the outcome of relapsed/refractory (R/R) ALL remained extremely poor. Response rates after first, second, or later salvage are around 40, 21, and 11%, respectively and 3-year survival rates reach 11, 5, and 4%, respectively. Particularly patients with early relapses

have significantly poorer reponse rates compared to late relapse [54]. Therefore, the composition of patient groups in clinical trials for R/R ALL is essential for outcomes.

In B-precursor ALL, surface antigens are frequently detected. Thus, CD19, CD22, CD20, CD33, and CD52 are present in 90–100%, 90–100%, 30–40%, 30 and 80% of the cases, respectively [55]. Therefore, immunotherapy with antibodies is a promising approach. Antibodies employs different mechanisms of action compared to chemotherapy and may therefore be active in chemotherapy-resistant patients. Not surprisingly an impressive clinical development of new compounds occurred in past decade.

CD20 antibodies have already been integrated into first-line therapy of ALL and lead to a significant improvement of long-term outcomes in CD20-positive ALL [56]. In R/R B-precursor ALL, rituximab induced remissions according to several case reports [57]. Therefore, the addition of CD20 antibodies to standard salvage regimens should be considered in R/R ALL.

Inotuzumab is a CD22-directed antibody, which is conjugated to calicheamicin. It yielded very promising CR rates in R/R ALL in phase II studies [58]. In a randomized study, inotuzumab ($N = 109$) was compared to standard of care (SOC) ($N = 109$) defined as high-dose cytarabine-based regimens. A total of 67% of the patients entered the trial in first salvage (including late relapses), 16% had a prior SCT, and patients with high peripheral blast count were excluded. The CR/CRu rate was 81% (36/45%) for inotuzumab and 29% for SOC. A total of 78% of the patients with CR/CRu in the inotuzumab arm had no detectable Minimal Residual Disease (MRD) compared to 28% in the comparator arm [59]. The median survival was 7.7 months for inotuzumab and 6.7 months for the comparator arm. A total of 41% of the patients treated with inotuzumab received a SCT subsequently. A major side effect of concern with inotuzumab is veno-occlusive disease (VOD), particularly after subsequent SCT. The incidence of VOD may depend on dose, dose density, and duration of treatment with inotuzumab, and is increased in patients receiving a conditioning regimen with double alkylators [60]. Usually an interval of 3–4 months after prior allogeneic SCT was requested in trials with inotuzumab and CD19 bispecific antibody blinatumomab. A small proportion of patients in the inotuzumab trials had received a prior SCT (16% in the inotuzumab arm). The CR rate was not different for patients with (76.5%) compared to patients without (81.5%) prior SCT. Data on survival outcomes were not reported [60].

The CD19 bispecific antibody blinatumomab has domains against CD19 and CD3, and thereby attracts T-cells to CD19-positive B-precursor ALL cells and leads to directed lysis of the target cells [61]. The antileukemic activity depends on the availability of functional patient T-cells and access to the target. In a first phase II study in R/R ALL, the optimal dosing schedule was defined and a stepwise increase after 1 week showed the lowest rate of adverse events [62]. In a subsequent phase II study, which included patients with unfavorable relapse characteristics only, the CR/CRi rate in 189 patients was 43% [63]. The median survival was 6.1 months. Around 80% of patients with CR/CRh reached a negative MRD status. Patients with a low leukemia burden (<50% blast infiltration of bone marrow) had considerably higher response rates, than patients with a higher blast infiltration (73% vs. 29% overall response rate after two treatment cycles) [63].

Based on the results of phase II trials, a large international randomized trial in R/R Ph-negative ALL was conducted comparing blinatumomab with SOC. Overall, 405 patients were included. A total of 42% of the patients entered study in first salvage (early relapses only) and 35% had a prior SCT. CR/CRi/CRp rates were 44% for blinatumomab (34/9/1.5%, respectively) versus 28% for SOC. Responses occurred mostly within one cycle of therapy. The median survival for the blinatumomab ($N = 271$)-treated patients was significantly superior with 7.7 months compared to 4.0 months for SOC ($N = 134$) [64]. A total of 24% patients received subsequent SCT. It is of note CR rate was not different in patients with prior SCT (40%) compared to those without (46%), neither was the survival (7.7 months vs. 7.7 months) [64]. Data on outcome of these patients would be of great interest as data on the role of T-cell counts and T-cell expansion especially in patients with relapsed ALL after SCT. Case reports have demonstrated that blinatumomab can induce donor T-cell activation [65, 66]. There is maybe also a rationale for combination with donor lymphocyte infusions in clinical trials [67].

Overall, both inotuzumab and blinatumomab yielded promising CR/CRi rates—but in different subsets of R/R ALL. Studies are therefore only partly comparable. More importantly, both compounds were significantly superior to SOC. However, overall median survival was still around 6–7 months, which is due to relapses without SCT or after SCT and also due to TRM. In one cohort of 26 patients pretreated with inotuzumab, the TRM reached >30% [68]. The mortality may be partly due to a higher age of the patient population, heavy pretreatment but also high-risk transplant procedures, like mismatch transplants and non-standard conditioning regimens. Overall, it remains questionable whether outcome of R/R patients can be improved substantially even with new compounds.

Treatment of ALL relapse in an earlier stage could be a promising new approach. Patients with persistent or recurrent MRD have a very poor prognosis, due to resistance to chemotherapy resulting in a high relapse rate [14, 15, 69, 70]. Patients with MRD positivity are generally in better clinical condition and clearly have a lower leukemia burden compared to cytologic relapse. This situation could be

advantageous for efficacy and safety of innovative single-drug treatments.

After a successful pilot study [71–73], an international trial with 116 patients was directed to patients with MRD above 10^{-3}, including one-third of patients with persistent MRD after a prior hematologic relapse. Seventy-eight percent showed complete MRD response [73]. The median survival was 36.5 months compared to ~6 months in R/R ALL [74]. The study also demonstrated a significant advantage in terms of OS for those patients who achieved a complete MRD response after one cycle (35.2 months) compared to those without (7.1 months) [74]. Overall, the use of blinatumomab in the MRD setting yielded favorable results in terms of responses, survival, and duration of remission, particularly if compared to the R/R setting. Whereas the majority of patients received a subsequent SCT, preliminary results indicate that some patients stayed in long-term remission without any further therapy after blinatumomab [75].

For relapse prevention in the management of ALL, the most promising approaches are optimized, pediatric-based first-line therapies including SCT in selected high-risk patients. In addition, better approaches are needed to use the new antibodies. This includes combination or sequential therapy in order to avoid upcoming resistance. Optimized maintenance strategies are required in patients with no option for SCT. New compounds may allow to renounce on high-risk transplant procedures, e.g., in older patients or patients with no matched donor. In these patients, non-transplant relapse treatments may be explored. Additional efforts are needed to elucidate mechanisms of resistance against targeted drugs. Earlier detection of upcoming relapse and treatment in the MRD setting may be one essential future approach. Overall, the most exciting perspective is the integration of new, targeted compounds into first-line therapy, which will ultimatively help to avoid relapses.

AML

In AML, the conjugated CD33 antibody gemtuzumab ozogamicin achieved FDA approval. In relapsed/refractory AML, the CR rate was 26% after a single course [76]. As for inotuzumab, the risk of VOD after subsequent SCT is of concern. Other CD33 antibodies with different conjugated toxins are under evaluation. CD123 is another interesting target in AML, particularly due to its lower expression on normal hematopoietic stem cells compared to CD33. The conjugated CD123 antibody SL-401 induced CRs in relapsed/refractory AML (summarized in Assi et al. [77]).

Overall experience with antibody therapies for relapse prevention in the context of SCT is far less developed in AML and other hematologic malignancies compared to ALL. The combination of suitable targets like CD22 and CD19 and the medical need probably fueled the development of new antibody therapies specifically in ALL also in the context of prior or subsequent SCT. The options to reduce relapse risks by new antibody therapies are also more pronounced in ALL due to the broad availability of MRD testing as a trigger for preemptive therapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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