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REVIEW ARTICLE

# Current status and future clinical directions in the prevention and treatment of relapse following hematopoietic transplantation for acute myeloid and lymphoblastic leukemia

Charles Craddock[1] · Dieter Hoelzer[2] · Krishna V. Komanduri[3]

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**Abstract**

In recent years we have seen a dramatic evolution of therapeutic approaches in the management of acute leukemia with hematopoietic stem cell transplantation (HCT). For both acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), alloHCT provides the best chance of long-term disease-free survival for significant subsets of patients. During this interval, we have witnessed an evolution of HCT from a therapy based on high-dose conditioning to our current understanding that its success depends both on cytoreduction and graft-versus-leukemia (GVL) effects mediated by adoptively transferred donor immune cells. Improvements in conditioning, infectious disease monitoring and management, histocompatibility testing and graft selection have successively improved outcomes, primarily due to a reduction in non-relapse mortality. Unfortunately, disease relapse remains a significant cause of treatment failure in both AML and ALL. Here, two distinguished experts, Prof. Charles Craddock and Prof. Dieter Hoelzer, reflect on the significant challenge of disease relapse following allogeneic HCT for AML and ALL, respectively. This is a review of the biology, current approaches, and future directions in the field and reflects concepts that were presented at the Third International Workshop on Biology, Prevention, and Treatment of Relapse after Stem Cell Transplantation held in Hamburg, Germany in November 2016 under the auspices of the EBMT and the ASBMT.

## Introduction

As the field of allogeneic hematopoietic stem cell transplantation (HCT) enters its seventh decade of clinical practice, we have seen a dramatic evolution of therapeutic approaches in the management of acute leukemia with HCT. For both acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), alloHCT provides the best chance of long-term disease-free survival (DFS) for significant subsets of patients. During this interval, we have witnessed an evolution of HCT from a therapy based on high-dose conditioning to our current understanding that its success depends both on cytoreduction and graft-versus-leukemia (GVL) effects mediated by adoptively transferred donor immune cells. Improvements in conditioning, infectious disease monitoring and management, histocompatibility testing and graft selection have successively improved outcomes, primarily due to a reduction in post-HCT non-relapse mortality.

Sadly, we have seen far less significant improvement in post-HCT disease relapse, with recurrence of disease remaining a significant cause of treatment failure in both AML and ALL. In this review, we hear the perspectives of two distinguished experts, Dr. Charles Craddock CBE and Prof. Dieter Hoelzer, on the significant challenge of disease relapse following allogeneic HCT for AML and ALL, respectively. Each disease-focused section reviews the biology, current approaches, and future directions in the field. This review reflects concepts that were presented at the Third International Workshop on Biology, Prevention, and Treatment of Relapse after Stem Cell Transplantation held in Hamburg, Germany in November 2016 under the

✉ Charles Craddock
Charles.craddock@uhb.nhs.uk

[1] Centre for Clinical Haematology, Queen Elizabeth Hospital, Birmingham B15 2TH, UK

[2] ONKOLOGIKUM Frankfurt|am Museumsufer, Gartenstr. 134, 60596 Frankfurt, Germany

[3] Adult Stem Cell Transplant Program, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, 1501 NW 10th Avenue, Suite 916, Miami, FL 33157, USA

auspices of the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transplantation (ASBMT).

## Significance of post-HCT relapse in AML and myelodysplasia

Disease relapse continues to represent the major cause of treatment failure in patients allografted for AML and myelodysplasia (MDS) [1]. The limited progress made in reducing the risk of disease recurrence after allogeneic stem cell transplantation (allo-SCT) contrasts with the substantial reduction in transplant-related mortality over the last two decades, and is all the more frustrating given the increasingly prominent role allografting now plays in the management of adults with AML and MDS [2, 3]. Coupled with the fact that effective salvage strategies are lacking for the majority of patients who relapse there is now real urgency that novel transplant strategies with the potential to decrease the risk of disease recurrence are examined in prospective clinical trials [4, 5].

## Biology of disease relapse in AML

Key to the rational design of novel strategies with the potential to decrease relapse post allograft must be detailed understanding of both the clinical and biological predictors of disease recurrence. The risk of disease relapse in patients allografted for AML and MDS ranges between 30 and 80% according to disease stage at transplant, presentation karyotype, and the intensity of post-transplant immunosuppression [6–9]. Higher relapse rates are consistently observed in patients transplanted using a reduced intensity conditioning (RIC) regimen compared with a myeloablative conditioning (MAC) regimen [10–13]. Importantly, the risk of disease relapse is regimen specific, whether a myeloablative or RIC protocol is utilized, emphasizing the importance of regimen-specific clinical trials in AML and MDS—an area of major unmet need [14, 15]. Retrospective analyses have also identified the level of measurable residual disease (MRD) detected pre-transplant to be a critical, and potentially manipulable, determinant of relapse risk [16]. It is to be hoped that future prospective studies will provide greater clarity concerning both the impact of distinct levels of MRD on relapse risk as well as addressing whether selective monitoring of specific cellular factions, potentially the leukemic stem/progenitor population, might increase the sensitivity of relapse prediction [17].

Disease biology is an important determinant of relapse risk as evidenced by the very high risk of recurrence in patients with either a monosomal karyotype or 17p abnormality [18, 19]. However, the significance of mutations in myeloid genes, apart from *FLT3 ITD* and *NPM1*, in predicting relapse risk post-transplant has until recently been much less well studied [20]. There are however reasons to hypothesize, given the distinct mechanisms by which intensive chemotherapy and allogeneic transplantation exert an anti-leukemic effect, that disease-specific mutations may play distinct roles in the outcome after both treatment modalities. Thus, mutations that either impact tumor kinetics or abrogate alloreactivity could plausibly modulate the potency of the GVL effect and selectively contribute to disease recurrence post-transplant. Very recent studies in both AML and MDS that have employed comprehensive next generation sequencing strategies on diagnostic material in patients have identified mutations in TP53 and the RAS pathway as independent predictors of disease relapse although the precise mechanism by which these mutations contribute to post-transplant relapse remains undetermined [21–23].

Despite its relevance to the design of novel peri- and post-transplant strategies with the potential to decrease relapse risk remarkably, little is understood of the clonal structure of recurrent disease in patients allografted for AML or MDS. Furthermore, while it is postulated that the leukemic stem/progenitor population represents the reservoir of disease relapse there are no pre- or post-transplant prospective studies evaluating this hypothesis despite its clinical implications. Studies to date identify that a sizeable proportion of patients allografted for AML demonstrate either karyotypic or molecular evolution at relapse—an observation of profound importance in the design of maintenance post-transplant strategies aimed at reducing the risk of disease relapse [21].

## Strategies to reduce the risk of AML relapse after HCT

Increased understanding of the factors determining disease relapse have permitted the development of a range of pre-, peri- and post-transplant strategies with the potential to reduce the risk of disease relapse (Fig. 1). Broadly these include reducing the disease load, as assessed by MRD status, pre-transplant, increasing conditioning regimen intensity without incurring additional toxicity and maximizing a GVL response post-transplant.

### Reduction in pre-transplant MRD status as a strategy to reduce the risk of relapse

Although pre-transplant MRD appears as an important prognostic risk factor of relapse, prospective studies are lacking and it remains to be determined whether MRD is also an important predictive factor. Importantly, patients

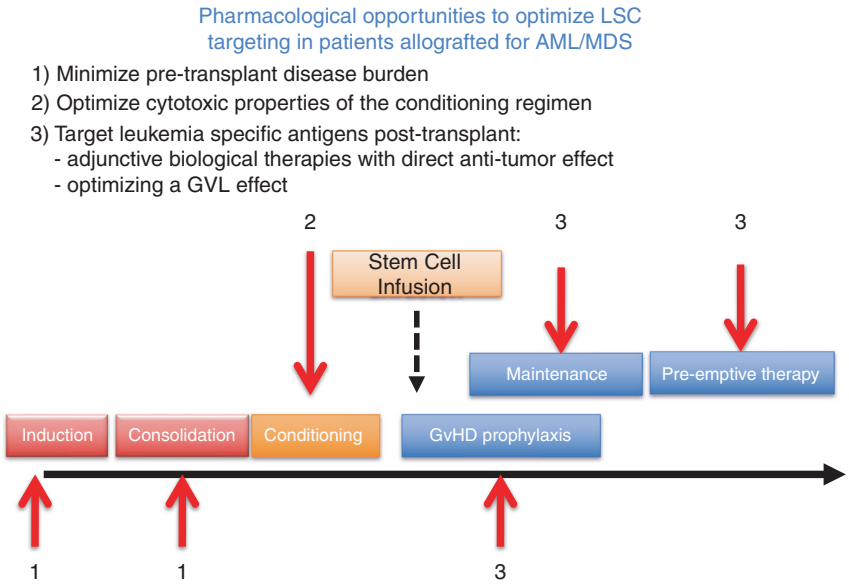


**Fig. 1** Pharmacologic opportunities to optimize leukemia stem cell targeting in patients receiving allogeneic hematopoietic cell transplants for acute myeloid leukemia and myelodysplastic syndromes

who are MRD also remain at risk of relapse post-transplant. While it is pertinent to note that retrospective registry studies have failed to demonstrate that the number of cycles of intensive chemotherapy delivered prior to either a MAC or RIC transplant impacts relapse risk of transplant outcome, none of these studies included MRD assessment [24, 25]. Consequently, there is an urgent need for prospective randomized studies that examine the impact of either an additional course of chemotherapy or dose intensification prior to transplant on both pre-transplant MRD status and relapse risk post allograft.

## Optimizing the conditioning regimen

The intensity of the conditioning regimen was first shown to be a critical determinant of relapse risk in the setting of a myeloablative Cy/TBI regimen [26, 27]. More recently retrospective registry studies and some, but not all, prospective randomized trials have demonstrated increased relapse rates in recipients of an RIC compared with a MAC regimen in patients allografted for both AML and MDS [10–12, 28]. The extent to which the attendant reduction in transplant-related mortality of an RIC allograft compensates for the increased relapse risk remains controversial and is likely influenced by both tumor-specific factors such as disease biology and pre-transplant MRD status as well as patient age and co-morbidity status. Given the central importance of the conditioning regimen in determining relapse risk and increasingly accurate prediction of patients with a high relapse risk, based on characteristics of disease biology and pre-transplant MRD status, there remains an important requirement for randomized comparisons of both MAC and RIC regimens—particularly, but not exclusively, in high-risk patients. Critical to the interpretation of such studies is a recognition that the anti-tumor properties of both RIC and MAC regimens are also critically impacted by the GVHD prophylaxis strategy adopted including the intensity of post-transplant immunosuppression and whether or not T-cell depletion is utilized. A number of modifications have been made to RIC regimens with the aim of decreasing the relapse risk notably the development of sequential conditional regimens that incorporate an additional course of cytoreductive chemotherapy immediately prior to the commencement of a conventional RIC regimen. Such an approach, best exemplified by the FLAMSA regimen, has been reported in single arm studies to reduce disease relapse in high-risk AML characterized by an adverse karyotype or primary refractoriness and the results of ongoing prospective randomized comparisons are awaited [29, 30].

## Post-transplant strategies

The observation that the elective administration of imatinib in patients allografted for chronic myeloid leukemia abolished early disease recurrence was the first demonstration that post-transplant pharmacological intervention has the potential to reduce the risk of disease recurrence [31]. More recently, the principle that maintenance therapy, administered in the first few weeks post-transplant, while patients remain in morphological remission, may have the capacity to improve transplant outcome has been extended to patients allografted for AML and MDS [32]. Conceptually, there are a number of mechanisms by which adjunctive post-transplant therapies might reduce the risk of disease recurrence. Firstly, drugs with inherent anti-leukemic activity may augment the anti-tumor activity of the transplant—particularly if they target residual leukemic stem/progenitor cells. Secondly, the simple manipulation of the

kinetics of disease relapse may give the emerging allo-immune effect a competitive advantage and thereby optimize a GVL effect. Thirdly, postponement of disease relapse permits the deferment of donor lymphocyte infusions (DLI) to a time when the risk of severe GVHD associated with early DLI is reduced. By itself this simple maneuver may be sufficient to uncouple the potential anti-tumor activity of DLI, particularly if it can be administered prior to overt relapse, from its attendant risk of severe GVHD. Finally, post-transplant pharmacological therapies may directly modify the allo-reactive response potentially through upregulation of tumor antigens by drugs such as azacitidine (AZA) or by pharmacological acceleration of T regulatory cell reconstitution post-transplant through demethylation of the FoxP3 promoter [33, 34].

One of the most promising post-transplant maintenance strategies examined in patients allografted for AML and MDS to date is the administration of sorafenib to patients allografted for FLT3 ITD-positive AML. Early phase studies have demonstrated that this FLT3 inhibitor is well tolerated and can be commenced within the first 3 months post-transplant [35, 36]. Compared with matched historical controls, there appears evidence of a reduced risk of disease relapse and these retrospective data now urgently require validation in ongoing prospective randomized trials [37]. An alternative approach of promise is peri- or post-transplant administration of the DNMT inhibitors AZA or decitabine which are also both well tolerated in this clinical setting [38, 39]. Both agents have the capacity to induce CD8+ T-cell responses to candidate tumor antigens, including MAGE antigens, which are not ordinarily observed post-transplant and prospective randomized trials of the impact of such agents on the incidence of both relapse and GVHD are now required [40]. An alternative approach with promise is the adjunctive administration of checkpoint inhibitors such as ipilimumab which have already been shown to have clinical activity in patients who have relapsed post-transplant [41, 42]. The increased availability of both targeted therapies and drugs with a broader anti-tumor activity further underlines the importance of detailed analysis of the clonal structure of relapsed disease post-allograft—with particular reference to presentation material. In this context the observation of the frequent loss of potentially druggable mutations at relapse post-transplant appears to support the exploration of maintenance strategies utilizing drug or cellular therapies with broader anti-tumor specificity as opposed to targeted therapies [21].

## Relapse in acute myeloid leukemia: Conclusions and future directions

The last decade has seen a remarkable increase in therapeutic opportunities with the potential to reduce the risk of disease relapse in patients allografted for AML and MDS. If patients are to benefit, as swiftly as possible, it is increasingly clear that a step change in the transplant community's ability to rapidly deliver prospective randomized trials is required. For this to happen resourced and incentivized trial networks of sufficient scale to permit the rapid delivery of prospective randomized trials with enhanced pharmacovigilance, embedded genomics and biomarker discovery programs, building on the inspirational work of the United States National Institutes of Health-sponsored Blood & Marrow Transplant Clinical Trials Network (BMT-CTN), will be required [43]. By accelerating the delivery of practice informing trials to regulatory standards, such networks will drive novel models of collaboration between the transplant community and the biopharmaceutical sector to the ultimate benefit of patients.

## Relapse of acute lymphoblastic leukemia: Introduction

Adults with relapsed/refractory (R/R) acute lymphoblastic leukemia have a dismal outcome. Recent published data on more than 2000 R/R ALL pts showed complete remission (CR) rate of 31–44% and an overall survival (OS) of 5−24% at ≥3 years. Adverse prognostic factors were increasing age, CNS involvement or other extramedullary manifestations [44–48].

The only chance of cure in the current era is an allogeneic SCT [49, 50]. This becomes evident from a large international reference analysis of outcomes in adults with B-precursor Ph-negative R/R ALL published in 2016 [51]. This survey included 1706 R/R patients from 11 study groups and large centers in Europe and the United States during the period between 1990 and 2013. The CR rate of first salvage was 40% (35–41%) and for second and third salvage 21 and 11%, respectively. The Overall Survival with chemotherapy only was <15% and for SCT at 3 years 28%. Prognostic factors were, apart from achievement of a CR, younger age, lower WBC at diagnosis and longer duration of CR1. These results additionally revealed that there was no superior chemotherapy-based regimen or even a standard regimen for R/R adult ALL. The rate of R/R patients to have an alloSCT differs widely from 10 to 40%.

Where do we go from here? The following sections discuss how we can advance our current standard of care including potential options to improve this situation by applying more sophisticated diagnostic approaches and novel therapies to this difficult disease.

## Minimal residual disease in ALL

Earlier detection of refractoriness to chemotherapy or an upcoming relapse is one of the options which is now

**Table 1** Expression of antigens in B-cell lineage ALL for potential antibody targeting

| Surface antigen | ALL subtypes | Antigen expression on LBC | Monoclonal antibody |
|---|---|---|---|
| CD20 | Burkitt Lymphoma/ Leukemia<br>B-precursor | 86–100%<br>30–40% | Rituximab<br>Ofatumomab |
| CD22 | B-precursorMature B-ALL | 93–98%<br>~100% | Inotuzumab Ozogamicin<br>Epratuzumab<br>Moxetumomab pasudotox |
| CD19 | B-precursorMature B-ALL | 95–<100%<br>94–<100% | T-cell activating therapies<br>- Blinatumomab<br>- Bispecific CD3/CD19<br>- CAR T cells<br>- (Chimeric Antigen Receptor modified T cells |

Hoelzer [56]

possible by the evaluation of minimal residual disease (MRD). MRD can be measured by the detection of clonally rearranged genes encoding for immunoglobulin/T-cell receptors by PCR or a leukemia-specific phenotype by using multiparameter flow cytometry. MRD negativity is thereby defined by a frequency of positive events of ($<10^{-4}$) and MRD positivity as an MRD level $>10^{-3}$ [52, 53]. Patients with a molecular failure, despite being in hematological CR or patients with a molecular relapse display a poor prognosis [54, 55].

Thus, MRD evaluation leads to a new extended and changing definition of R/R ALL patients with therapeutic consequences (e.g., alloSCT). In a retrospective analysis by the German Multicenter Study Group for Adult ALL (GMALL) early intervention at a molecular relapse resulted in a better overall survival of 55% at 3 years, compared to intervention at the time of a full hematological relapse with an OS of 26% (Hoelzer, personal communication). Thus, the current approach is to treat patients with molecular relapse with new targeted therapies, when available, with the aim to convert MRD positivity into an MRD-negative status. In addition, these patients may then become suitable candidates for a curative alloSCT.

## Immunotherapeutic approaches for ALL

Substantial progress in adult ALL has been made in the last decade by the introduction of new targeted therapies, either with tyrosine kinase inhibitors (TKI) or by immunotherapeutic approaches.

Immunologically based treatments with monoclonal antibodies or activated T cells are currently changing the treatment paradigm for ALL. In B-lineage ALL, leukemic blast cells express a variety of specific antigens, such as CD19, CD20, and CD22 (Table 1). Recently a number of therapeutic monoclonal antibodies have been developed that target these antigens [56].

### Therapies directed at CD20

The anti-CD20 monoclonal antibody rituximab is applied together with chemotherapy in different settings in adult ALL. In relapsed patients, it is often given prior to a chemo regimen particular FLAG or FLAG-IDA. However, it is not known whether the addition of rituximab improves significantly the CR rate or has any additional benefit of the outcome.

Rituximab has substantially improved the outcome of patients with de novo Burkitt leukemia/lymphoma. With repeated short cycles of intensive chemotherapy, combined with rituximab the overall survival rate has increased to >80% [57]. The 10–20% of patients with relapse have usually a very aggressive course of the disease and an allogeneic SCT would be the choice of treatment. However, it is often difficult to perform alloSCT given the time needed to find a suitable donor and to successfully apply salvage chemotherapy to obtain a CR or good PR. Given recent advances in the field, haploidentical SCT, which is more quickly feasible given the immediate availability of most haploidentical family donors, can now be accomplished with increasing success rivaling that historically only seen with matched-related alloSCT, and may be an option for those patients.

In the 30–40% CD20-positive (>20% CD20 expression) B-lineage ALL patients, the addition of rituximab to standard chemotherapy leads to an higher and faster rate of MRD negativity after induction/consolidation therapy. This clearly is transferred to an improved DFS and overall survival [58–60]. In the GMALL 07/2003 study, high-risk patients received rituximab (3×) in induction and consolidation before the planned alloSCT, though OS was not

**Table 2** Blinatumomab in children with relapsed B-precursor ALL

| Diagnosis/age/gender | Previous treatment | Response |
|---|---|---|
| HR-B prec. ALL<br>7y/m | Ch-Rel.<br>Allo SCT MUD<br>-> 3% LBC | -> MRD neg.<br>-> 2nd allo SCT hapl.<br>-> 23 mo. in Mol. CR |
| 12y/m | Ch-Rel.<br>Allo SCT MUD<br>-> 2nd/3rd rel. 21 mo<br>-> 3rd rel. 11 mo Refr. 23% LBC | -> Aplasia<br>-> Mol. neg. CR<br>-> second Allo SCT MUD<br>Relapse -> death |
| Ph+ B-prec. ALL<br>15y/m | 1st Allo SCT sib CR Rel.<br>2nd Allo SCT MUD<br>2nd relapse, 2 yrs<br>Dasa, Clofa, Ara C<br>3rd Allo SCT<br>Rel. BM+ CNS | -> MRD neg.<br>-> MRD pos. after 4 wks |

significantly improved, likely due to the patient cohort. Whether in CD20-positive relapse after SCT the addition of rituximab as monotherapy or in addition to salvage chemotherapy could have benefitted remains open. So far, there are no studies published with rituximab for patients who have relapsed following allogeneic SCT.

## Therapies directed at CD22

CD22 is an optimal target antigen since CD22 is expressed in nearly all ALL blasts. The anti-CD22 antibody most used in adult ALL is inotuzumab ozogamicin (IO), which is an antibody drug conjugate between a CD22 antibody and calicheamicin. The Ab conjugate is internalized after binding and the calicheamicin induces DNA strand breaks.

When IO was used as a single agent therapy in R/R adult ALL, a high CR rate of about 80% was obtained [60]. In the international randomized study [61] the CR rate was 81% and the MRD response 78% compared to a CR of 30% and MRD negativity of 28% in the randomized arm with standard therapy. Seventeen percent had a prior SCT and 40% received SCT after IO to achieve the overall outcome. The importance in alloSCT in achieving the outcomes in this study remains open. After IO there is an increased hepatoxicity with a VOD rate of 8–16%, which increases with the number of prior chemotherapies or with a prior SCT. IO combined with mini Hyper CVD ± rituximab in R/R patients led to a CR rate of 74 and 41% of those had an SCT. One of the promising future possibilities for IO is its combination with less intensive chemotherapy. With Mini Hyper-CVD as a frontline setting, in elderly study patients (median age 69), the CR rate was 81% and of those the MRD response was 100%, resulting in a promising 2-year RFS of 87% and an OS rate of 70% [62]. Only 6% of these elderly patients had an SCT, explained by the high age of this study. The authors of this study concluded that IO with moderately intensive chemotherapy in the frontline setting may substitute for alloSCT.

## Therapies directed at CD19

Targeting of the CD19 surface antigen is of great interest, as this antigen is expressed in all B-lineage cells, including early lymphoid precursor cells. The general paradigm of this treatment approach is to activate T cells of patients directed against CD19-expressing leukemic cells; either in vivo with the bispecific CD3/CD19 antibody (Blinatumomab) or in vitro by creating Chimeric Antigen Receptor CD19 cells (CAR-T cells).

## Blinatumomab

Blinotumomab is a novel bispecific construct that reacts simultaneously to normal CD3 T cells and CD19 ALL cells, creating a tight intercellular connection followed by T-cell–mediated cytotoxicity exerted on CD19 blast cells (BiTEmechanism) [63].

## Blinatumomab in children with relapsed B-precursor ALL

In an early study blinatumomab was applied in children with advanced ALL [64]. All children had multiple chemoresistant relapses and all of them had already one or more sibling or matched-unrelated donor alloSCT (Table 2). After blinatumomab, given as 15 $\mu g/m^2$ continuous infusion for 28 days, the response observed in all three patients treated reached MRD negativity. Two of the children received a second SCT and one remained in a molecular remission for 2 years. These study results demonstrated that

the bispecific antibody blinatumomab is active in heavily chemotherapy-pretreated and transplanted patients.

## Blinatumomab in MRD + adult ALL patients

One of the first studies with Blinatumomab in adults evaluated its potential role in eradicating MRD. Patients in this study were in hematological/morphological CR but had persistent or reappearing MRD during consolidation chemotherapy. Blinatumomab was given at a dose of 15 μg/m$^2$/day as a continued infusion for 28 days every 6 weeks. After completing cycle one, responding patients could receive up to three additional consolidation cycles or proceed to an allogeneic stem cell transplantation. In a long-term follow-up, 12 out of the 20 patients remained in CR. The estimated 3-year relapse-free survival was 60% [65, 66]. Nine patients in this study had an allogeneic SCT, but interestingly the non-transplanted patients had a similarly favorable outcome compared to the transplant group. In an international multicenter confirmatory trial, 112 MRD-positive adult patients responded as defined by conversion of MRD positivity to negativity. The overall survival rate was 36.5 months at 2.5 years and 40% received an alloSCT [67].

## Blinatumomab in relapsed/refractory adult ALL patients

The efficacy of blinatumomab in R/R ALL was explored in several studies. In a pilot study of 25 patients, 68% achieved a CR/CRi. In the international confirmatory study, 189 patients with refractory/ relapsed ALL were included. The CR/CRi rate was 43 and 80% of those achieved an MRD response [68]. Similar results were obtained in R/R elderly patients, again with a high MRD response rate of 80%. All these results were obtained in R/R B-lineage Ph-negative ALL. Interestingly, blinatumomab was also effective in R/R Ph+ B-lineage ALL and 45 patients achieved a CR/CRi including patients with the TKI-resistant mutation T35I of whom 4/10 achieved CR [69].

In a recent analysis the effect of blinatumomab was compared to historical standard therapy in adult R/R ALL [70]. The historical cohort included 694 patients compared to 189 patients receiving blinatumomab. A combined weighted summary of 189 patients with blinatumomab demonstrated a CR rate of 43% compared to 24% in the historical cohort treated with standard chemotherapy. The rate of CD19-negative relapses after blinatumomab is 10–20% irrespective of whether the patients had an alloSCT or not. While it is difficult to treat such patients, available options include Anti-CD22 Ab therapy, inotuzumab, bispecific (CD19, CD22) directed CAR-T cells or an alloSCT.

### Chimeric antigen receptor (CAR) T cells

The adoptive transfer of CAR-modified T-cells directed against CD19 is highly promising new approach for the treatment of CD19-positive childhood or adult ALL. In the first of three larger studies [71–73] the CR rate ranged from 67 to 91% with an MRD negativity in 60–81% of the CR patients. The rate of alloSCT after CAR-T-cell transfer varied from about 10 to 50%. In recent updates the benefit of an alloSCT after CAR-T 19 therapy is controversially discussed. In a recent update the outcome of SCT patients with an alloSCT after CAR-T-cell therapy was comparable to the non-transplanted patients. Thus, it has been speculated that SCT might be replaced by CAR T-cell therapy alone [74]. However, the substantial toxicity in adults, particularly the Cytokine Release Syndrome (CRS) and the potential for severe neurotoxicity, which may occasionally be fatal especially when accompanied by cerebral edema, has to be considered [75]. The CD19-negative relapse rate after CAR-T-cell therapy is 10–20%, or even higher [76]. Such relapses are difficult to treat and alloSCT remains an option in such cases.

## ALL relapse after HCT: Conclusions and future directions

- In adult MRD-positive or R/R Adult ALL, immunotherapeutic approaches may achieve higher CR rates and significantly higher MRD negativity rates, compared to traditional chemotherapy strategies.
- This would allow a higher rate of alloSCT which is so far realized in several studies. There was no increased toxicity after SCT, but also no lower relapse rate.
- In several studies, some patients receiving anti-CD22 or anti-CD19 therapy with or without an alloSCT had a similar outcome. Thus, it has been suggested that it may be possible to replace SCT with immunotherapy alone. However, it is not yet possible to identify which patients may benefit from an additional SCT. Close follow-up of MRD may help to identify such patients.
- Patients who experience CD-19-negative relapse after blinatumomab or CAR-T-cell therapy have a very poor outcome. Currently there are different treatment options under investigation, but alloSCT is certainly the best option.
- In all immunotherapeutic studies patients who had a prior SCT were included, including those who received a second SCT after immunotherapy,

apparently with no inferior outcome. Thus, we are currently moving from an occasional second SCT [77] in this setting to a more promising option.
- Overall, a key challenge that remains is to identify the optimal settings and sequential approaches for immunotherapy and alloSCT in adult ALL.

## Conclusions

Despite dramatic advances in our understanding of both AML and ALL, including significant improvements in prognostic classification, conditioning chemotherapy and supportive care following alloSCT, leukemia relapse remains a significant and daunting clinical problem. Fortunately, the availability of emerging epigenetic approaches, targeted inhibitors of leukemia cell signaling and novel immunotherapy strategies all provide hope that post-transplant relapses may be limited and/or increasingly successfully managed when they do occur. A significant challenge will be to perform cooperative trials in these relatively small patient populations that systematically identify optimal approaches to prevent and treat post-transplant relapse.

### Compliance with ethical standards

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

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