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REPORT

NCI First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: Report from the Committee on the Epidemiology and Natural History of Relapse following Allogeneic Cell Transplantation

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Allogeneic hematopoietic stem cell transplantation (alloHSCT) is increasingly being used for treatment of hematologic malignancies, and the immunologic graft-versus-tumor effect (GVT) provides its therapeutic effectiveness. Disease relapse remains a cause of treatment failure in a significant proportion of patients undergoing alloHSCT without improvements over the last 2-3 decades. We summarize here current data and outline future research regarding the epidemiology, risk factors, and outcomes of relapse after alloHSCT. Although some factors (eg, disease status at alloHSCT or graft-versus-host disease [GVHD] effects) are common, other disease-specific factors may be unique. The impact of reduced-intensity regimens on relapse and survival still need to be assessed using contemporary supportive care and comparable patient populations. The outcome of patients relapsing after an alloHSCT generally remains poor even though interventions including donor leukocyte infusions can benefit some patients. Trials examining targeted therapies along with improved safety of alloHSCT may result in improved outcomes, yet selection bias necessitates prospective assessment to gauge the real contribution of any new therapies. Ongoing chronic GVHD (cGVHD) or other residual post-alloHSCT morbidities may limit the applicability of new therapies. Developing strategies to promptly identify patients as alloHSCT candidates, while malignancy is in a more treatable stage, could decrease relapses rates after alloHSCT. Better understanding and monitoring of minimal residual disease posttransplant could lead to novel preemptive treatments of relapse. Analyses of larger cohorts through multicenter collaborations or registries remain essential to probe questions not amenable to single center or prospective studies. Studies need to provide data with detail on disease status, prior treatments, biologic markers, and posttransplant events. Stringent statistical methods to study relapse remain an important area of research. The opportunities for improvement in prevention and management of post-alloHSCT relapse are apparent, but clinical discipline in their careful study remains important.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is increasingly being used for treatment of hematologic malignancies and the immunologic graft-versus-tumor effect (GVT) provides its therapeutic effectiveness. During the past 2 decades, peripheral blood stem cells (PBSCs) have replaced bone marrow (BM) as the graft source for the majority of alloHSCT recipients, and increasingly, alternate donor sources

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including unrelated donors (URD) and umbilical cord blood (UCB) are being used. There is an increasing shift toward nonmyeloablative (NMA) or reduced-intensity conditioning (RIC) regimens designed to limit treatment-related mortality (TRM) and expand HSCT opportunities for older patients and those with clinical comorbidities. Through all these advances, malignant relapse remains the main barrier to more successful alloHSCT. We summarize current data and outline future research regarding the epidemiology, risk factors, and outcomes of relapse after alloHSCT.

GRAFT-VERSUS-HOST DISEASE (GVHD) AND ITS IMPACT ON RELAPSE

GVHD and Graft-versus-Leukemia (GVL)

The clinical syndrome of GVHD is strongly linked to the allogeneic antineoplastic effect of HSCT therapy, the GVL or GVT effect [1]. Although separable in experimental murine studies, in humans, the distinction between GVHD and GVT is less apparent. Numerous reports have suggested reduced risk of relapse in patients with mild to moderate GVHD, but mortality from severe GVHD precludes a survival benefit despite its accompanying GVT [1]. In acute leukemias, chronic myelogenous leukemia (CML), and indolent lymphoproliferative diseases (e.g., chronic lymphocytic leukemia and follicular lymphoma), a potent GVT effect is recognized. Particularly in the leukemias, clinical evidence suggests that the protective GVL effect accompanies even mild or moderate GVHD [2]. Sufficient alloreactivity to induce complete donor chimerism may augment the GVL effect even in the absence of clinical GVHD symptoms, although a threshold or biomarker to identify sufficient donor-derived alloreactivity to prevent recurrence is not defined. Strategies to prevent GVHD, including ex vivo or in vivo T cell depletion, therefore, must be tempered by concern about lessening the antineoplastic effect of the allograft.

Impact of chronic GVHD (cGVHD) on Relapse

Several observational studies demonstrate that cGVHD is associated with lower relapse rates [1,3-11]. However, the biologic mechanisms of this important GVT effect are poorly understood and are hampered by imprecision of the GVHD diagnosis. In 2254 patients with either acute myelogenous leukemia (AML) or acute lymphocytic leukemia (ALL) in first complete remission (CR1) or CML in chronic phase, cGVHD or acute GVHD (aGVHD) plus cGVHD led to lower relative risks of relapse compared to patients without GVHD (relative risk [RR] = 0.43, $P = .01$ and RR = 0.33, $P = .0001$, respectively). Relapse rates with identical twin donors or T cell-depleted grafts were higher (RR = 2.09, $P = .005$ and RR = 1.76, $P = .002$, respectively) [1]. Similar findings were not confirmed in lymphoma patients receiving AlloHSCT [12]. Recent analyses by the Center for International Blood and Marrow Transplant Research (CIBMTR) confirmed that cGVHD (but not aGVHD) was associated with lower relapse risk in all leukemias (AML: RR = 0.75, ALL: RR = 0.69, and CML: RR = 0.67) [2], but because of increased TRM, it did not improve leukemia-free survival (LFS). Leukemia relapses were uncommon after the development of cGVHD (8%-9%; RR range: 0.5-0.6; $P < .01$), but increasing severity of cGVHD neither delayed nor lessened the risk of relapse. Patients with mild cGVHD had the best LFS [4,8,9]. In 322 patients who received RIC alloHSCT, grade II to IV aGVHD had no impact on the risk of disease relapse/progression, whereas extensive (but not limited) cGVHD reduced risks of disease relapse/progression (hazard ratio [HR] = 0.4; $P = 0.006$) [13]. The antitumor effects of cGVHD may contribute to the success of RIC transplants [14,15].

GVL and Alternative Donors

Enhanced alloreactivity accompanying greater donor:recipient HLA disparity has long been postulated to yield a more potent GVL effect and lesser risks of relapse [16]. Formal comparisons of URD and matched sibling transplants, recently published from the CIBMTR, contradict this conventional wisdom [2,17]. Two reports, 1 examining leukemias and 1 in chronic phase CML, observed a higher incidence of GVHD with greater HLA disparity, but no augmented GVL effect [2,17]. It, therefore, remains to be demonstrated that relapse risks can be reduced by selecting a disparate and thus more alloreactive donor, at least through HLA allele level matching. Additional genetic inputs associated with natural killer (NK) alloreactivity (killer cell immunoglobulin-like receptor [KIR] ligand matching, KIR ligand absence, or KIR genotyping) may further modify this effect, but GVL is not augmented by greater HLA disparity [18-20].

In 1072 UCB transplant patients, 28% developed cGVHD, and multivariate analysis demonstrated a reduced relapse rate and improved disease-free (DFS) and overall survival (OS) (RR 0.65, 0.64, and 0.71 respectively) [21]. Generally, UCB grafts have not led to higher relapse risks [22]. Recent data suggest reduced relapse using double versus single cord grafts in acute leukemias, and a prospective United States Blood and Marrow Transplant Clinical Trials Network (BMT CTN) trial is testing this in pediatric leukemia [23].

Future Research

Along with GVL potency, the biologic characteristics of a specific malignancy may also affect cGVHD-related GVT [10]. cGVHD is not a single disease, but an autoimmune syndrome driven by diverse immune

processes; thus, dissection of the biologic components of cGVHD associated with GVT needs analysis of both the cGVHD and the antitumor response [24]. Active cGVHD could limit the progression of relapsed cancer, but its associated comorbidity may preclude use of donor leukocyte (a.k.a. lymphocyte) infusion (DLI) or other immune mediators. Understanding this biology may identify new therapies.

GVHD PROPHYLAXIS AND RELAPSE

Graft-versus-host disease prophylaxis in alloHSCT with unmanipulated grafts often includes immunosuppressive agents that prevent or attenuate aGVHD. Calcineurin inhibitors (e.g., cyclosporine [CsA] or tacrolimus) plus methotrexate (MTX) successfully limit aGVHD, although this combination was associated with higher rates of disease relapse [25-28], particularly using higher doses of calcineurin inhibitors [29].

Graft manipulation with ex vivo T cell depletion successfully reduces rates of aGVHD, but increments in disease relapse have been observed [30-32]. A prospective trial comparing T cell depletion with pharmacologic GVHD prophylaxis in URD alloHSCT demonstrated faster engraftment, lower rates of aGVHD, but higher cytomegalovirus infections and a significant increase in CML relapse [33]. The particular sensitivity of CML to GVL highlights the deleterious effect of potent T cell depletion on relapse, although in some diseases, GVL can be maintained [34].

Lymphocyte-specific antibodies such as antithymocyte globulin (ATG) and alemtuzumab may reduce the risk of GVHD, and are often used with URD alloHSCT. This in vivo T cell depletion can improve URD alloHSCT because of lower TRM and less aGVHD [35-40]. Alemtuzumab-based prophylaxis was associated with increased risk of relapse and death from viral reactivation in patients with myelodysplastic syndromes (MDS) and AML, with relapse responsible for 60% of deaths [41]. Alemtuzumab or ATG in the RIC regimen may increase relapse in multiple myeloma [42,43]. Other comparative studies including different diseases did not demonstrate excessive relapse rates using ATG or alemtuzumab [36,44,45].

Future Research

Tacrolimus (TAC) instead of CsA or mycophenolate mofetil (MMF) or sirolimus replacing MTX may show promise as GVHD prophylaxis without many side effects frequently seen with CsA/MTX combinations [46-50]. Prospective testing of TAC plus MTX combinations for related and URD alloHSCT led to less grade II-IV aGVHD without differences in cGVHD or disease relapse, but no improvements in survival [48,51]. MMF plus CsA or TAC is widely used with RIC, although only limited data citing the efficacy and impact on relapse are available. Small studies with MMF or with added prednisone do not report increased disease relapse [49,52]. Sirolimus/TAC ± MTX did not alter relapse [47]. Some preclinical data suggests that sirolimus in the absence of CsA or TAC is permissive for regulatory T cells (Tregs), which can modulate the alloreactive response [53]. Limiting GVHD prophylaxis by decreasing the dose and duration of CsA use led to increases in aGVHD and cGVHD, but reduced relapse rates compared to standard dose prophylaxis [54].

COMMON FACTORS AFFECTING RISK OF RELAPSE

Disease and Disease Status

The most common factors affecting the risk of relapse include disease, disease status, chemotherapy sensitivity, and the intrinsic disease sensitivity to GVL [55] (Table 1). Additional factors include the graft source, graft manipulation, and the conditioning regimen utilized for the AlloHSCT [55-58]. In a meta-analysis of trials where patients were randomized to receive either PBSC or BM allografts [56], PBSCs led to faster neutrophil and platelet engraftment and more grade III/IV aGVHD and extensive cGVHD, but lower relapse rates (21% versus 27% at 3 years; odds ratio [OR] = 0.71; 95% confidence interval [CI], 0.54 to 0.93; $P = .01$). The relapse protection was apparent in patients with advance (33% versus 51%) and early disease (16% versus 20%). Retrospective registry analyses indicate increased rates of extensive cGVHD with PBSCs, without clear reduction in relapse, although heterogeneity may obscure a potential benefit [55,57]. Prospective testing of PBSCs versus BM in URD grafting is underway through the BMT CTN. Relative to the impact of the conditioning regimen intensity on relapse, some comparison studies suggest higher relapse rates after RIC than after MA. However, this question needs prospective testing in comparable cohorts of patients [58].

Risk Factors for Relapse in AML

Compared with other therapies, alloHSCT results in superior DFS and OS for patients with intermediate- and poor-risk AML [59]. Unfortunately, relapse remains the major cause of treatment failure after alloHSCT in AML, particularly for patients with advanced disease.

Disease characteristics

The risk of AML relapse is best defined by disease stage at time of alloHSCT and cytogenetic profile. Patients in CR1 have less risk than those beyond CR1. Moreover, although alloHSCT can rescue

Table 1. Epidemiology and Natural History of Relapse Following Allogeneic HCT

Risk factors for relapse	Relapse incidence post allo-HCT	Outcome post relapse	Risk factors influencing outcome	Areas needing study
Acute Myeloid Leukemia				
- Transplant beyond first complete remission - Poor risk cytogenetics - FLT3-ITD mutations - Secondary AML (prior chemo/radiotherapy) - Age >60 years - Comorbidities - Precedent MDS - HLA-matching - Single CB transplantation - Gender donor/recipient combinations other than F→M - Specific KIR haplotypes - Reduced intensity and non-myeloablative conditioning - In vitro and in vivo T cell depletion	- AML in CR1: 10-40% - Advanced disease stage: >40-50% - After RIC allo-HCT: 18-50%	- Generally poor long-term survival - Limited DLI response	- Patient age - Remission duration - Use of DLI - Favorable cytogenetics - Presence of comorbidities at relapse - Disease stage upon relapse (e.g. lower tumor burden at relapse)	- Impact of novel therapies (hypomethylating agents, HDAC inhibitors etc.) - Impact of new molecular classifications - Incidence of relapse after haploidentical and cord blood transplants - Preferred timing of transplantation in light of rapid availability of haploidentical and UCB vs. URD allo-HCT - Role of maintenance therapies after allo-HCT (prophylactic DLI, hypomethylating agents etc.) - Role of minimal residual disease (MRD) detection in predicting relapse.
Myelodysplastic Syndrome				
- MDS stage (IPSS or WPSS) - Bone marrow blasts and cytogenetics	- Low-risk disease: 5-20% - High-risk disease: 10-40%	- Generally poor; long-term survival in 0-40%	- Patient age - Patient PS - Presence of comorbidities at relapse (GVHD, infections etc) - Disease stage upon relapse - Remission duration - Donor availability	***Retrospective studies:*** - Estimate relapse rates for patients undergoing HSCT after hypomethylating agent treatment (transplant at best response or after failure) - Impact of new MDS classifications and outcomes in transplantation - Incidence of relapse after haploidentical and cord blood transplants; - Preferred timing of transplantation in light of rapid availability of haploidentical and UCB vs. URD HSCT ***Prospective studies:*** - Hypomethylating agents, angiogenesis inhibitors and other medications as maintenance therapy after HSCT for high-risk of relapse patients. - Role of MRD detection in predicting relapse and defining need for further interventions post HSCT
Chronic Myelogenous Leukemia				
- Age - Disease stage - Time interval from diagnosis to transplant - Donor type	- Unclear if relapse rate is higher with older age - 20% (CP) to 65% (BP) - >1-2 years worse results	Disease stage is the major determinant of long-term survival: CP: 30-60% AP: 10-40% BC: 0-10%	- Patient PS - Presence of comorbidities at relapse (GVHD, infections etc) - Disease stage upon relapse - Remission -duration - Donor availability - Sensitivity to TKIs	- Influence of BCR-ABL kinase mutations on HSCT outcomes - Impact of new TKI in predicting peri-HCT outcomes - Will patients who failed TKI pre-HCT respond following a post-HCT relapse? - Relapse rates/overall results after transplants after alternative donor, haploidentical and cord blood transplants
Acute Lymphoblastic Leukemia				
- WBC - Ph+; t(4;11) - Time to CR1 - Duration of CR1	25-50% CR1 40-60% CR2	Short survival; Limited DLI response	Early relapse worse; no other data	- MRD assay pre HCT to predict;intervene to prevent relapse - Detailed epid study to predict relapse; Pre-HCT risk factors Young; mid adult; Older adult

Aggressive Non-Hodgkin Lymphoma				
- Chemoresistant & < complete remission at transplant - >3 lines prior chemotherapy - T-cell phenotype <u>better</u> (PTCL, AITL, ALCL) - Mantle-cell lymphoma <u>better</u> - Increasing Age - Prior Auto-SCT - NMA conditioning - Early Progression after 1^0 therapy (<12 months) - Use of non-TBI conditioning - Bone marrow involvement at transplant - Elevated LDH at Transplant	9-30% sensitive 18-75% resistant ≤ 20% relapse ≤ 20% (higher if TCD) * Relative risk of progression ~3.0	Short survival & poor response to DLI for chemo-resistant disease	Very high relapse rates for salvage allo-HCT after failed auto-SCT (40-50% at 3 yrs) without clear evidence of a plateau	- The presence of a graft-versus-lymphoma effect in aggressive lymphoma is controversial and further prospective efforts to identify GVL are needed (except for mantle-cell and T-cell lymphoma) - Standardization of patient population definitions including IPI score and molecular pathology - Study of allo-HCT in rituximab-refractory disease where auto-SCT may not be effective - Impact of targeted or disease-specific conditioning regimens - Maintenance strategies
Indolent Non-Hodgkin Lymphoma				
- Chemoresistant disease - Transformed histology - NMA conditioning - Use of non-TBI conditioning - Bone marrow involvement at transplant - Rituximab within 6 months - KPS ≤80% - "Tandem" AutoSCT → AlloSCT (**selected for more aggressive disease[120]**)	40% - <15% - Significant only on univariate analysis - Hazard Ratio for relapse 5.47 (95% CI 1.5-21)	- Disease course tends to be similar to underlying histology - Palliative responses to conventional therapies and response to DLI have been reported	- Incomplete or falling donor chimerism not associated with increase relapse risk in all series	- Timing of allo-HCT - Standardized definitions of patient population & risk scores at allo-HCT (e.g. FLIPI) - Impact of targeted or disease-specific conditioning regimens - Role in rituximab-refractory disease
Hodgkin Lymphoma				
- Extranodal disease - KPS <90% - <CR at transplantation - Bulky disease - <u>After RIC</u>: Low-dose TBI conditioning Refractory disease >3 lines prior therapy Donor ♀: recipient ♂ - <u>Pediatric</u>: Poor performance status Refractory disease RIC (vs. myeloablative)*after 9 months following allo-HCT	<u>Relative risk of relapse (95% CI)</u>: 3.1 (1.3-7.2) 2.5 (0.9-7.1) 70% 70% 70% 3.2 (1.2-8.4) 2.1 (1.0-4.4) 4.4 (1.0-19.0)	- Palliative responses to post-relapse chemotherapy & radiotherapy - Rare durable responses to DLI reported	- Lower risk of relapse with haploidentical sibling donor (Hazard Ratio for relapse 0.25, 95% CI 0.2-0.8) or URD (HR 0.43, 95% CI 0.2-0.9) - Alemtuzumab conditioning did not impact relapse risk	- Further evidence of GVL - Use of alternative donors (UCB or haploidentical) validated in multicenter studies - Impact of targeted or disease-specific conditioning regimens
Chronic lymphocytic leukemia				
- Chemorefractory disease - Response >CR/PR - Bulky disease - T cell depletion - Late donor chimerism - Absence of cGVHD	2-48% TCD 68%	Little data, DLI responses 15-50%		- Detailed prospective epidemiology study of CLL disease and transplant specific factors that impact relapse - Evaluation of pre and post transplant MRD in predicting relapse - Evaluation of CLL biology and lineage chimerism and relapse

(*Continued*)

Table 1. (*Continued*)

Risk factors for relapse	Relapse incidence post allo-HCT	Outcome post relapse	Risk factors influencing outcome	Areas needing study
Multiple Myeloma - Poor patient performance status - Gender donor/recipient combinations other than F→M - Allo-HCT > 1 year from diagnosis - Durie stage 3 at diagnosis - Chemoresistant disease - Elevated B2 microglobulin - Deletion chromosome 13, deletion 17p - RIC regimens - T-cell depleted grafts - Campath or ATG use - Lack of complete response	- 50% at 5 years	- Poor, DLI has efficacy - OS post relapse 2-4 years	- Better outcome with newer drugs	Retrospective: - Impact of novel agent therapy and response status at time of HCT - Myeloablative vs. RIC conditioning regimens - Tandem auto-allo vs. single allo - Outcome of patients following relapse: efficacy of DLI and efficacy of novel agents Prospective: - Evaluation of MRD following allo-HCT - Maintenance therapy with novel agents - Role of immunomodulatory drugs with or with out prophylactic DLI
GVL - URD not < Sib - UCB similar but little data - Presence of GVHD: but I/II>0=III/IV				- Disease specific/phenotype specific analysis of relapse with GVH - Compare disease relapse after HCT using novel GVHD prophylaxis regimens to standard calcineurin inhibitor and methotrexate regimens - Assess the need of in vivo T-cell depletion antibodies (ATG or alemtuzumab) in addition to GVHD prophylaxis in high-resolution HLA match unrelated donor HCT - Correlation of cGVHD features and relapse - Impact of tumor biology on relapse in cGVHD - Prospective cohort study with sufficient detail of information on the disease relapse, transplant and cGVHD characteristics
GVHD Prophylaxis - Ex vivo T-cell depletion - In vivo T-cell depletion by antibodies – inconclusive - Higher dose and duration of calcineurin inhibitor (CSA) - MMF vs. MTX in addition to calcineurin inhibitor – no effect - MTX vs. no in addition to tacrolimus/sirolimus – no effect - tacrolimus vs. CSA – no effect				- Study GVHD prophylaxis regimens that do not require chronic immunossupression, such as ex vivo T-cell depletion or post transplant cyclophosphamide as platform for disease specific cellular therapy to reduce relapse. - Compare disease relapse after HCT using novel GVHD prophylaxis regimens to standard calcineurin inhibitor and methotrexate regimens. - Assess the need of in vivo T-cell depletion antibodies (ATG or alemtuzumab) in addition to GVHD prophylaxis in high resolution HLA match unrelated donor HCT.

CB indicates cord blood; HSCT, hematopoietic stem cell transplantation; RIC, reduced-intensity conditioning; MDS, myelodysplastic syndromes; KIR, killer cell immunoglobulin-like receptor; GVHD, graft-versus-host disease; UCB, umbilical cord blood, URD, unrelated donor; DLI, donor leukocyte infusion.

some patients with primary refractory AML, the relapse rate remains high at approximately 51% (95% CI, 38%-65%) [60]. Estimates of relapse incidence and survival for alloHSCT for AML in CR1 can be derived from prospective studies that allow for a "biologic assignment" of donor/no donor comparison, at least for sibling donor grafting. Koreth et al. [59] analyzed prospective biologic assignment in clinical trials of alloHSCT versus consolidation with conventional chemotherapy or autologous HSCT or both for AML in CR1 (24 international trials with 6007 patients). For alloHSCT the hazard ratio (HR) of relapse or death for AML in CR1 was 0.80 (95% CI, 0.74-0.86). Although the value of alloHSCT in cytogenetic subsets of AML has been reported, molecularly defined subsets have not been well studied. FLT3-ITD mutations increase risk, whereas NPM1 mutation without FLT3-ITD or a normal karyotype confer better prognosis [61-63]. Outcome of alloHSCT in FLT3/ITD-positive AML showed a strong reduction of relapse after alloHSCT with hazard ratios nearing 0.5 [63-65].

Patient characteristics

The median age at diagnosis of AML is approximately 65 years. Advanced age and preceding MDS are predictors of increased post-HSCT relapse [66-68]. Outcome may be worse in older (>60 years) patients, reflecting both underlying disease biology and accompanying comorbidities. The increased relapse risk with advancing age also reflects the higher proportion of patients with adverse cytogenetics and/or overexpression of MDR-1 [69]. However, a recent CIBMTR analysis showed no increased relapse risk because of age alone [70]. Other patient-related factors, such as number of prior chemotherapy regimens [68] and patient race, may add further risk [71-73]. Baker et al. [72] found that after alloHSCT, Hispanics had higher risks of treatment failure (death or relapse; RR = 1.30; 95% CI, 1.08-1.54) and overall mortality (RR = 1.23; 95% CI, 1.03-1.47).

Donor characteristics

Despite improvements in supportive care and HLA matching, outcome following URD alloHSCT for AML is still inferior to that after matched sibling HCT [74,75]. UCB has been studied as an alternative and the antileukemic effect of single UCB transplant appeared comparable to URD adult donor alloHSCT [22,76]. In addition, double UCB transplantation may lead to a reduced relapse risk in acute leukemia versus single-unit UCBT [77,78].

After controlling for GVHD as a time-dependent covariate, a female donor into a male recipient of alloHSCT reduces relapse compared to other donor/recipient sex combinations [79]. Non-HLA-genetic factors may also limit relapse after alloHSCT. In a study of 448 transplants in AML patients, Cooley et al. [18] showed that URD donors with KIR B haplotypes confer significant survival benefit to patients undergoing T cell-replete alloHSCT, because of a decreased relapse rate and the lower TRM.

Conditioning regimens

Most reports of RIC alloHSCT for AML are small and heterogeneous for disease status and demographics. In the largest studies of RIC alloHSCT for AML, the relapse rate ranged from 18% to 50% [80]. Lower relapse rates are achieved during CR1 compared with more advanced disease [81]. Sequential pre-HSCT consolidation chemotherapy might limit leukemia relapse rates [82,83]. The European Group for Blood and Marrow Transplantation (EBMT) analyses suggest higher relapse rates with RIC regimens, but similar DFS between myeloablative (MA) and RIC regimens [84]. Shimoni et al. [85] studied this balance between dose intensity, disease relapse, and TRM in 112 consecutive patients with AML/MDS. TRM was higher after the MA Bu-Cy regimen, but relapse rates were lower.

The inclusion of in vivo T cell depletion with either ATG or alemtuzumab in an RIC regimen may also increase the incidence of relapse [41,83]. Prospective trials are planned, but no clear guidelines exist to choose the proper conditioning intensity for patients in remission. RIC regimens are thought to be inadequate for patients with active leukemia.

Risk Factors for Relapse in MDS

Disease characteristics

After alloHSCT, MDS reported relapse rates range from 20% to 60%, depending upon the intensity of conditioning and disease status [70,86-89]. (Table 1) MDS stage remains the strongest predictor of relapse. Lower risk disease, defined by the International Prognostic Scoring System (IPSS) yields recurrence rates of 5% to 20%, with long-term disease control in 30% to 70%. An "inverse" selection bias may send fewer early MDS patients to alloHSCT because of available hypomethylating agents or lenalidomide [90-92]. Recent transplant series include more patients with older and advanced MDS. Poor prognosis cytogenetic abnormalities, especially those involving chromosome 7, and BM blast percentage are the strongest predictors of post-HSCT disease control [87-89].

Data on alloHSCT for therapy-related (a.k.a. secondary) MDS are uncertain, yet relapse is a major cause of failure. The EBMT reported data of 461 alloHSCT patients with therapy-related MDS or AML (median age = 40 years) [70]. The cumulative incidence of TRM and relapse at 3 years was 37% and 31%, respectively. Relapse was more common with active MDS, abnormal cytogenetics, older age, and therapy-related

MDS. In a recent report of 551 MDS patients (age 40-65+ years) undergoing RIC alloHSCT [87], TRM was similar in older cohorts, and at 3 years there was no age-related difference in relapse (29% versus 33%), LFS (36% versus 23%), and OS (39% versus 29%). Advanced disease was a significant risk factor for OS, LFS, TRM, and relapse. Therapy-related MDS can be controlled with alloHSCT, and a recent CIBMTR report described only 31% incidence of relapse at 3 years for 857 patients with therapy-related AML and MDS [93]. MDS is of intermediate sensitivity to GVL effect, but the impact of regimen intensity on transplant outcome is uncertain [94-97].

Donor characteristics

Younger donors or better HLA matched URD can result in modestly reduced TRM, but no augmented GVL was associated with less well-matched URD [79,98]. Patients without matched related or URD may receive haploidentical or UCB HSCT. The experience with haploidentical donor HSCT in MDS is limited; no data clarifies the GVL potency and relapse risk with these usually T cell-depleted HSCT. In the context of AML transplanted in CR, relapse using UCB is similar to or less than URD or related donor HSCT [99,100].

Transplant characteristics

cGVHD can lower relapse incidence and improved DFS and OS. In 1 study of 148 patients, lower risk of relapse in de novo MDS patients followed extensive cGVHD and low or intermediate-1 risk IPSS [101], but other studies differed [70,87]. For patients with MDS and AML, GVHD may not limit relapse because of the competing risk of GVHD-induced mortality [86].

Mixed chimerism, particularly after RIC transplantation, does not necessarily imply a poor prognosis, but its persistence may augment relapse risks [102]. Persisting evidence of recipient hematopoiesis may be early manifestations of relapse, especially after MA HSCT when mixed chimerism is unexpected.

Outcome after relapse

Rapidly evolving, refractory relapses of MDS after alloHSCT are often associated with short survival, whereas later or indolent recurrences are more likely to receive therapy and to be considered for a second HSCT [103]. Older age, comorbidities (including infections) and ongoing GVHD are important considerations dictating patients' tolerance of further therapy. Long-term survival is reported from 0% to 40% [86,103].

Future research

There is a need for retrospectives analyses on alloHSCT for MDS addressing several topics including: (1) timing of alloHSCT at best response to hypomethylating agent or after failure, as clear estimates of relapse rates are unknown; (2) determination of the impact of new MDS classifications in predicting HSCT outcomes; and (3) determination of the incidence of relapse after haploidentical and cord blood transplants, particularly with their rapid availability [104]. Prospective studies are needed in the following areas: (1) hypomethylating agents and other medications as maintenance therapy after alloHSCT; (2) role of minimal residual disease (MRD) detection in predicting relapse and defining need for further post-alloHSCT interventions.

Risk Factors for Relapse in CML

Most alloHSCT for CML are now performed only for tyrosine kinase inhibitor (TKI) resistance or intolerance except in countries where TKI availability is markedly limited by cost. The initial signs of CML relapse following alloHSCT are determined by a rise in BCR-ABL transcript level. BCR-ABL transcript levels may fluctuate during the first 6 to 12 months after alloHSCT and may not indicate inevitable leukemia progression unless transcripts steadily rise over time. Relapse from 20% to 65%, depend mostly on disease stage at HSCT [17]. Late relapses do occur, and the cumulative incidence at 15 years can be up to 17%, even for patients in remission at 5 years [105,106].

Disease characteristics

CML stage at the time of alloHSCT is the strongest predictor of relapse. Gratwohl et al. [107] and the EBMT proposed a CML HCST scoring system in the 1990s based upon risk factors of age, disease stage, time from diagnosis to HSCT, donor type, and donor-recipient sex (female donors being worse). This can predict TRM and DFS (but not relapse with survival at 5 years of 72%, 70%, 62%, 48%, 40%, 18%, and 22% for patients with scores 0, 1, 2, 3, 4, 5, and 6, respectively. An update including HSCT from 1990 to 2004 (n = 13,416) showed half of low-risk patients alive at 20 years, and a low risk score (0 or 1 risk factors) yielded 2-year survival of 80%. GVHD rates remain high and risks of relapse are unchanged [108]. BCR-ABL kinase mutations-mediating TKI resistance may not affect HSCT outcomes if adjusted for disease stage, but recent data is limited [109].

Prior treatment with interferon or imatinib does not worsen outcomes after alloHSCT [110,111]. Patients with chronic phase CML and a suboptimal or transient response to imatinib may have a higher mortality, but relapse rates are similar to historic controls [111]. Treatment with other TKIs does not increase TRM, but data are insufficient to evaluate relapse rates [110].

Transplant characteristics

PBSC grafts may reduce TRM in advanced patients, but no consistent impact on relapse has been observed in either sibling or URD grafts. As mentioned, compared to related donors, URD HSCT do not yield superior protection against relapse [17]. CML is very sensitive to the GVL effect and RIC HSCT can yield long-term disease control for chronic phase patients. Fludarabine plus melphalan conditioning can be effective in advanced or older patients beyond chronic phase, although TRM rates are high [111-114].

Outcome after relapse

Patients relapsing into chronic phase, cytogenetic, or molecular relapses have the best prognosis using either imatinib and/or DLI. Survival for patients relapsing into accelerated phase is only 10% to 40% and in blast phase is very poor. Withdrawal of immunosuppression may reinduce remission in a few of patients relapsing with chronic phase or subclinical CML.

DLI may induce remission in up to 75% of patients relapsing in chronic phase, but not in advanced disease. GVHD (in 50%) or BM aplasia (<5%) are complications of DLI. Smaller cell infusions with lower T cell doses or possibly CD8 depletion may limit GVHD. It is unclear if patients who failed TKI pre-HSCT will respond to TKI following a post-HSCT relapse, even without documented BCR-ABL mutations [115-117].

Future research

Study of BCR-ABL mutations, and the impact of new TKI in predicting peri-HSCT outcomes is still needed. Relapse rates after transplants using alternative donor, haploidentical, and CB transplants remain to be better defined.

Risk Factors for Relapse in ALL

Disease characteristics

Factors predicting relapse for initial therapy of ALL also predict risks of relapse following alloHSCT. High WBC count at diagnosis, adverse cytogenetics such as Ph+ or t(4;11) as well as a mature B phenotype and short initial remission are all associated with higher incidence of post-HSCT relapse [118-130]. In CR1, alloHSCT yields 20% to 40% relapses [123-129]. Early reports suggest limited relapse risks in adult CR1 patients undergoing RIC HSCT [131-139]. Although no studies have validated the utility of postallograft consolidation or maintenance therapy, imatinib or other TKIs have promise in reducing relapse risks in Ph+ ALL [140-145].

For HSCT during CR2 or in later remission, relapse risks are higher, ranging from 40% to 60% in published series, but with lesser prognostic impact of adverse high-risk features. For standard risk ALL, particularly in children where transplants in CR2 for those with on-therapy initial relapse are indicated, promising survival without recurrence is reported [118,130,131,144,146,147]. Relapse incidences of 30% to 50% are reported though these risks are higher in adults or those with high risk features [118,121,130,132,141,145].

Transplant characteristics

Protection against relapse using alternative, URD or UCB donors have been similar or worse than HLA-matched HSCT [120,121,130-132,148-151]. No consistent better protection against relapse follows partial matched or URD donors; the observed GVL is not enhanced by the greater HLA disparity [2]. HSCT during active relapse for ALL is most often unsuccessful with >70% recurrence, although 10% to 20% of patients may survive (CIBMTR data, 2009).

Future research

Newer approaches including DLI, intensified conditioning, peritransplant targeted therapy, or TKI have not meaningfully increased survival of ALL patients with relapse after alloHSCT. Identifying high-risk patients for early allografting remains the most promising approach to reduce relapse hazards.

Risk Factors for Relapse in Multiple Myeloma

AlloHSCT provides durable disease control in myeloma, but TRM and relapse remains the most important reasons for failure [152]. Most patients relapse after alloHSCT at a median of 56 months [153]. Similar studies of RIC HSCT showed 42.3% progression at 3 years [154]. Two recent studies, which included tandem autologous + RIC alloHSCT, had a median time to relapse of 5 years [155,156].

Disease characteristics

The following characteristics have all been associated with inferior outcome for myeloma patients undergoing AlloHSCT: transplant beyond 1 year from diagnosis; >8 cycles of chemotherapy; beta-2 microglobulin (B2M) >2.5 mg/dL; female patients transplanted from male donors; and Durie stage 3 disease. Advanced and chemoresistant disease also leads to increased relapse risk [157,158]. Among patients undergoing tandem autologous + RIC alloHSCT, B2M >3.5 and time to first autologous HSCT >10 months were associated with increased relapse risk [156]. In a recent series of RIC alloHSCT, the presence of del13(q14) or del17(p13) led to increased risk of relapse [159]. In a prospective EBMT study comparing tandem auto-allo to tandem autologous HSCT, the auto-allo HSCT led to lower relapse rates, among patients with del13 [155].

Transplant characteristics

PBSC has been associated with a higher risk of cGVHD without reduction in myeloma relapse [160]. No specific conditioning regimens have enhanced prevention of relapse of myeloma, but with conventional MA alloHSCT, progression at 5 years was significantly lower for melphalan/total body irradiation (TBI) (36.7%) compared with cyclophosphamide/TBI (80.8%) [163]. RIC regimens, often following an autograft may augment the risk of relapse, but with less TRM [156,164]. Smaller studies suggest that use of prophylactic DLI can limit the increased relapse risk following T cell-depleted grafts. No consistent data suggest less relapse accompanying GVHD [43,155,156,158,161-164].

The depth of response from alloHSCT has an impact on the risk of relapse. Molecular techniques for measuring MRD suggest lower relapse rates in those with PCR-negative disease. PCR assessment of MRD after alloHSCT showed half achieving a molecular CR versus 16% of autografts resulting in less relapse and longer PFS (35 versus 110 months) [165].

Outcome following relapse after alloHSCT for myeloma

Only limited data are available on outcome after relapse following alloHSCT. In 63 patients refractory or relapsed after RIC alloHSCT, DLI yielded a median survival of 23.6 months following relapse. Novel agents (e.g., lenalidomide and bortezomib) may benefit some patients relapsing after alloHSCT [156,166-169]. Following treatment with these novel agents or DLI, the median OS was 3.7 years from relapse among the 51 patients who had relapsed after RIC alloHSCT. Patients with cGHVD prior to relapse and HSCT within 10 months of diagnosis had better outcomes following relapse. For 23 patients treated with bortezomib, the median PFS was 6 months with 21 of 23 patients alive at 6 months after relapse [167]. Another series using bortezomib reported 65% survival at 18 months [168].

Future research

The treatment of myeloma has undergone a paradigm shift in the recent years with the incorporation of new drugs such as immunomodulatory drugs and proteasome inhibitors. Studies need to be designed to examine the question of using these drugs in the context of maintenance post-SCT to decrease risk of relapse as well as their use in conjunction with salvage approaches such as DLI.

Risk Factors for Relapse in Lymphomas

AlloHSCT for lymphoma is often performed for advanced disease or for progression after autologous HSCT [170-174]. RIC regimens allow alloHSCT for older or higher risk lymphoma patients, yet relapse remains a common problem [174-176]. Survival after relapse reflects the underlying disease histology, similar to that reported after autologous HSCT [177,178]; however, survival is poor for aggressive histology or pre-HSCT chemorefractory non-Hodgkin lymphoma (NHL) [172,173]. Extended survival has been reported following DLI alone or with additional conventional therapy for chemosensitive histologies, especially indolent lymphoma [179,180]. Histologic distinctions and chemosensitivity are the most important determinants of relapse risk and survival after relapse [181-183]. A risk score based on observed relapses after RIC conditioning has confirmed the observation that the risk is low (approximately 20%) for indolent and mantle cell lymphoma and for those in remission, but high (50%-60%) for Hodgkin lymphoma (HL) and aggressive NHL not in CR [184] The graft-versus-lymphoma effect has not been well quantified after alloHSCT [12].

Hodgkin lymphoma

Early experience with MA conditioning and alloHSCT demonstrated prohibitive TRM, limiting its application until development of RIC [171]. Unfortunately, relapse remains common after alloHSCT for HL, in excess of 60% in most series [174,181], and is most common in those with extranodal disease, Karnofsky performance status <90%, and those not in CR.

Nearly half of HL patients undergoing alloHSCT from matched related donors with a RIC regimen experienced relapse; alemtuzumab did not affect the relapse rate [185]. Survival was worse for refractory disease, although 8 of 14 patients responded to DLI; 4 with a durable CR. The EBMT compared MA to RIC regimens in 168 with HL; relapse occurred in 57% and was more common after RIC [15]. Bulky and refractory disease at alloHSCT was associated with increased relapse risk. Importantly, cGVHD was associated with a lower relapse rate, suggesting a GVL effect.

In 285 RIC alloHSCT, relapse occurred in 147 patients and was significantly more common with refractory disease, >3 prior therapies and female donor:male recipients [186]. Sixty-four with persistent or progressive HL received DLI, and 13 of 41 evaluable patients achieved a CR [186]. Fifty-eight patients undergoing RIC alloHSCT had a median PFS <5 months, although OS was >2 years, indicating that some responded to further therapy (including 6 of 14 patients with DLI) [182]. A UK report described 38 RIC patients with 15 of 21 relapsing patients received DLI and half responded [187]. A pediatric series was similar except that durable response to DLI was infrequent [188]. Importantly, the relapse rate after NMA conditioning was lower with haploidentical donor [189]. The CIBMTR reported alloHSCT from

URD as feasible, but associated with significant relapse, 1-year PFS of 30% and OS of 56% [190].

Indolent lymphomas

MA alloHSCT from an MRD can cure some patients with follicular and low-grade lymphoma. The relapse risk is lower (15%-20%) [191-194] than other lymphoma histologies [172,174,181,184,195], even with RIC conditioning [175,196-198]. Transformed indolent lymphoma, as expected, has a higher risk of relapse [176] Rituximab given within 6 months of alloHSCT may lower relapse risk [199]. Relapse may reestablish indolent disease with reported responsiveness to DLI or to withdrawal of immunosuppression [181,200] or rituximab [201]. Relapse in follicular lymphoma is associated with chemoresistant disease, RIC conditioning, non-TBI MA conditioning, BM involvement, KPS ≤80%, and tandem auto→ alloHCT (the latter appears to reflect selection of patients for tandem transplantation with clinically aggressive disease) [197].

Aggressive lymphomas

AlloHSCT for aggressive lymphoma (e.g., diffuse large B-cell lymphoma) is often used for progression following auto-HSCT or chemorefractory disease [173,174,195,197,202-205]. Relapse is particularly common (up to 75%) for those not in CR, with chemorefractory disease and after salvage alloHSCT [176]. Survival following relapse of aggressive lymphoma after alloHSCT is poor with infrequent responses to DLI [175,195,197,203,204,206]. Relapse is more common after more than 3 lines of prior chemotherapy, increasing age, early disease progression after initial therapy, non-TBI conditioning, and marrow involvement or elevated LDH at transplant. In contrast, relapse following alloHSCT for peripheral T cell lymphoma and mantle cell lymphoma are significantly lower (20% or less), and DLI may be of value [172,205,207-214].

Future research

A uniform definition of lymphoma risk is needed in transplant studies, including resistant disease, patient (IPI and FLIPI), and disease risk scores (germinal center B cell phenotype); standard reporting of relapse incidence and treatment are also needed. Outcomes after alloHSCT plus clear indications for DLI would be valuable. These data could define the best lymphoma populations for alloHSCT.

Risk Factors for Relapse in Chronic lymphocytic leukemia (CLL)

CLL is a more common indication for alloHSCT [215]. Disease response after allogeneic transplantation for CLL is delayed after either MA or RIC conditioning and can take 3 or more months to achieve maximum response [216,217]. Relapse after MA HSCT for CLL is reported at 5% to 32% [11,217-219]; relapse rates after RIC alloHSCT are reported to be 5% to 48%, which is approximately 10% higher than after MA conditioning [217-221]. Nearly all recent reports of alloHSCT for CLL use RIC. Late CLL relapses can also occur in about 5% of patients [217,222].

Disease characteristics

Chemorefractory disease and disease status (CR or PR versus advanced) are risk factors for relapse [223]. In 82 patients after NMA HSCT the only significant factor for prediction of relapse was lymphadenopathy ≥5 cm (71% versus 27%; $P = .0004$) [218].

AlloHSCT is effective both in good risk and poor risk CLL. In 44 high-risk CLL patients with 17p deletion (all heavily pretreated) who received RIC, the 4-year cumulative incidence of progression was 34%. More than 3 lines of chemotherapy and T cell depletion with alemtuzumab led to higher risks of relapse [219]. Mixed T cell chimerism at day 90 and chemorefractory disease, but not ZAP-70 positivity, were associated with higher risk of disease progression [224].

Transplant characteristics

Complete donor chimerism and achievement of MRD negativity by multicolor flow cytometry or real-time quantitative PCR may predict extended DFS [216,225,226]. cGVHD may limit CLL relapse [11], but relapse rates are similar using either matched related or URD [215,217,218,221].

Outcome after relapse

Data on outcome of CLL patients who relapse after alloHSCT are few. Some respond to DLI [215,218]; some responses occur to withdrawal of immunosuppression, rituximab, or DLI. Better responses associate with 100% chimerism of donor T cells [224].

Future research

Analyses of larger data sets through multicenter collaboration or registries are needed to clarify the limited data of alloHSCT for CLL. Details of disease status, prior treatments, biologic markers, transplant regimen, and posttransplant events are particularly important.

STATISTICAL METHODS FOR ANALYZING RELAPSE AFTER HSCT

In cancer studies, researchers often need to analyze competing risks data, where each subject is at risk of failure from multiple (K) different causes. For

competing risks data, we observe the first failure and type of failure for each subject. In HSCT studies, disease relapse and TRM are 2 common competing events. In the medical literature, commonly *1 − Kaplan-Meier estimate* is used to compute the relapse rate treating the competing event of TRM as censored at the time of occurrence. This overestimates the incidence of relapse in the presence of the competing risk of TRM [227,228]. The cumulative incidence function (CIF) is the probability of a specific event occurring at or before a given time point *t*. It has been shown that CIF is a proper summary curve for analyzing competing risks data. For competing risks data, one often wishes to study the covariate effects on the CIF of a particular failure event.

Estimating and modeling the cause-specific hazard function has been considered a standard approach for competing risks data. The Cox proportional hazards model is the most commonly used regression model for all causes. Because the CIF reflects all competing cause-specific hazard functions, this approach gives a complex nonlinear modeling relationship for the cumulative incidence curves. It is hard to summarize the covariate effect and to identify the time-varying effect on the CIF for a particular type of failure. New regression approaches have been developed to model the CIF directly. Recently, Klein and Zhang [229], Martinussen and Scheike [230], Pintilie [231], Klein and Moeschberger [232], and Zhang et al. [233] reviewed some basic statistical methods for analyzing competing risks data.

Univariate Analysis

It is important to report the cumulative incidence rate for both competing events: relapse and TRM. The sum of cumulative incidence of relapse and TRM is the cumulative incidence rate of treatment failure, which equals 1 minus the probability of DFS. Often, we need to compare the relapse rates between treatment groups. In practice, the log-rank test has been commonly used and reported along with the cumulative incidence curves by treatment groups. The log-rank test compares the cause-specific hazards of relapse, whereas the cumulative incidence function of relapse is determined by cause-specific hazards of both relapse and TRM. Thus, in some studies the log-rank test may lead to a different conclusion compared to the reported cumulative incidences. Recently, Gray [234] developed a test, which directly compares the cumulative incidence curves. This should be used to compare the CIF of relapse between groups.

Currently, only a few statistical packages are available to implement CIF for competing risks data, and even fewer packages can be used to compute Gray's test for comparing the cumulative incidence functions. SAS macros have been developed to compute the cumulative incidence functions by various authors. Recently, SAS v9.1 has included a macro ("cumincid.sas") to compute the CIF. Some add-on *R* packages can be used to analyzing competing risks data. *R* is open source software that is freely available at http://www.r-project.org. The *R*-cmprsk [235] package can be used to compute and plot the cumulative incidence functions and perform Gray's test to directly compare the CIF. Scrucca et al. [236] provided a detailed guide for analyzing competing risks data using the cmprsk package though an HSCT example.

In HSCT studies, we may observe that the treatment effect of relapse changes over time. The researchers and patients often want to know when the treatments have different relapse rates and which treatments have higher relapse rates over time. We can plot the difference of the 2 cumulative incidence relapse curves along with the 95% simultaneous confidence band. The time when the zero line lies outside of 95% confidence band indicates when 2 cumulative incidence functions are different. A simulation method can be used to construct the 95% confidence band [237,238].

Multivariate Analysis

In many HSCT studies, clinicians often need to assess the effect of covariates on the relapse rate. This has been done most commonly by fitting a Cox model, which models the cause-specific hazards of relapse. Recently, new statistical methods have been developed to directly model the CIF. The first approach models the subdistribution hazard function, which can be used to directly interpret the covariate effect on the CIF. Fine and Gray [239] proposed a Cox type proportional subdistribution hazards model that has been implemented in *R*-cmprsk package. The second approach models the CIF using a pseudovalue technique [240]. Klein et al. [241] developed a SAS macro and an *R* add-on function to compute pseudovalues for censored competing risks data. The third and final approach is based on binomial regression models using the inverse probability of censoring weighting techniques. Scheike et al. [242] proposed a fully nonparametric regression model and class general semiparametric regression models. A *R*-timereg package has been developed for the binomial regression modeling by Scheike et al. [243] provided a detailed guide for using the *R*-timereg package. Zhang et al. [233] described an overview of modeling cumulative incidence function for competing risks data.

To study the GVT effect, clinicians often need to assess the GVHD effect on relapse. To analyze the GVHD effect, we need to understand that GVHD and death without GVHD are 2 competing risk events and at the time of transplant, it is unknown whether and when a patient will develop GVHD. We should treat GVHD as a time-dependent covariate. The

Cox model, which allows for time-dependent covariates, can be used to model cause-specific hazards of relapse. The SAS PHREG procedure implements this time-dependent Cox modeling. In HSCT studies, researchers may wish to model cumulative incidence function directly with a time-dependent covariate. It has been pointed out that including a time-dependent covariate to directly model cumulative incidence functions could lead to serious bias [244]. New statistical methods to directly model the cumulative incidence function with time-dependent covariates are yet to be developed.

CONCLUSION

Disease relapse remains a major cause of treatment failure in a significant proportion of patients undergoing alloHSCT without much improvement over the last 3 decades. Although some factors (e.g., disease status at alloHSCT or GVHD effects) are common, other disease-specific factors may be unique to the risk of relapse after alloHSCT. The impact of RIC regimens on relapse and survival still need to be assessed using contemporary supportive care and comparable patient populations. The outcome of patients relapsing after an alloHSCT generally remains poor even though interventions including DLI can benefit some patients. Trials examining targeted therapies along with improved safety of alloHSCT may result in improved outcomes, yet selection bias necessitates prospective assessment to gauge the real contribution of any new therapies. Ongoing cGVHD or other residual post-alloHSCT morbidities may limit the applicability of new therapies. Developing strategies to promptly identify patients as alloHSCT candidates, while malignancy is in more treatable stage, could decrease relapses rates after alloHSCT. Better understanding and monitoring of MRD post-transplant could lead to novel preemptive treatments of relapse. Analyses of larger cohorts through multicenter collaborations or registries remain essential to probe questions not amenable to single center or prospective studies. Studies need to provide data with detail on disease status, prior treatments, biologic markers, and posttransplant events. Stringent statistical methods to study relapse remain an important area of research. The opportunities for improvement in prevention and management of post-alloHSCT relapse are apparent, but clinical discipline in their careful study remains important.

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