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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 Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation

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Relapse is a major cause of treatment failure after allogeneic hematopoietic stem cell transplantation (alloHSCT). Treatment options for relapse have been inadequate, and the majority of patients ultimately die of their disease. There is no standard approach to treating relapse after alloHSCT. Withdrawal of immune suppression and donor lymphocyte infusions are commonly used for all diseases; although these interventions are remarkably effective for relapsed chronic myelogenous leukemia, they have limited efficacy in other hematologic malignancies. Conventional and novel chemotherapy, monoclonal antibody therapy, targeted therapies, and second transplants have been utilized in a variety of relapsed diseases, but reports on these therapies are generally anecdotal and retrospective. As such, there is an immediate need for well-designed, disease-specific trials for treatment of relapse after alloHSCT. This report summarizes current treatment options under investigation for relapse after alloHSCT in a disease-specific manner. In addition, recommendations are provided for specific areas of research necessary in the treatment of relapse after alloHSCT.

KEY WORDS: Allogeneic hematopoietic stem cell transplantation, Treatment, Donor lymphocyte infusion

INTRODUCTION

Relapsed disease is a major cause of treatment failure after allogeneic hematopoietic stem cell transplantation (alloHSCT). Treatment options for patients who relapse have been inadequate, and the majority of these patients ultimately die of their disease. Although donor lymphocyte/leukocyte infusions (DLIs) have been dramatically effective for patients with relapsed chronic myelogenous leukemia (CML), they have limited activity for patients who relapse with acute leukemia. The role of graft-versus-leukemia (GVL), or more generically, graft-versus-tumor (GVT) induction with DLI is less well defined for patients who relapse with diseases other than CML and acute leukemia, but it is clear that, at least in some cases, sustained remissions are induced for patients with chronic lymphocytic leukemia (CLL), multiple myeloma (MM), Hodgkin lymphoma (HL), and non-Hodgkin lymphoma (NHL). Importantly, there is very limited information on therapeutic interventions other than DLI to treat relapse after alloHSCT.

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This report explores disease-specific treatment options for patients who relapse after alloHSCT. There is no standard approach for relapse of a specific disease because treatment options are dependent on many factors including disease activity, timing of relapse, clinical complications, graft-versus-host disease (GVHD), the use of immunosuppression, prior therapies, donor availability, susceptibility to GVT induction, alternative options, and many other issues. However, many issues are relevant across all diseases. Timing, dose, and scheduling of DLIs are not well defined except for CML. Novel approaches to enhance GVT induction by either improving T cell function or specificity are being studied for several diseases. Second transplants remain a viable option for a small subset of patients who relapse, and there is a rapidly growing list of biological therapies that have activity in relapse when GVT induction is not appropriate or effective. Understanding the biology of relapse [1] and defining the role for currently available treatment options is critical to develop and rapidly test new and potentially curative therapies for relapse after alloHSCT.

CML

Summary of Current Status

Although alloHSCT was previously the therapy of choice for patients with CML in chronic phase (CP), the advent of tyrosine kinase inhibitors (TKIs) now limits this approach to patients that are resistant to or intolerant of these drugs. Patients suffering from accelerated phase (AP) or blast crisis (BC) CML may preferentially be transplanted after entering a second CP of the disease following chemotherapy and/or TKI therapy. Although the relapse rate after alloHSCT is low for CP patients, the relapse rate for patients transplanted in AP or BC is high, and treatment requires a different strategy. The choice of treatment of relapse after transplantation depends not only on the disease state at the time of relapse, but is also influenced by the initial treatment, because most patients transplanted in CP are resistant to first generation TKIs. Relapse after transplantation can be divided into molecular relapse or persistence (as defined by the detection by polymerase chain reaction (PCR) of BCR/ABL mRNA transcripts in the absence of cytogenetic abnormalities), cytogenetic relapse, or hematologic relapse of CP, AP, or BC.

CML is particularly sensitive to control by allogeneic donor T cells, the GVL effect. This was initially demonstrated in patients who remitted when immunosuppression was stopped and GVHD flared, by the observation of high relapse rates if the alloHSCT utilized T cell-depleted allografts, and subsequently confirmed by sensitivity of relapsed CML to DLI [2-5]. At present, only limited data support the concept of a disease-specific GVL reaction [6,7]. It is likely that much of the effect reflects graft-versus-hematopoiesis or a less specific GVHD reaction toward minor histocompatibility antigens (mHag) such as HA-1 or H-Y [8-10].

The majority of patients with CP CML who have molecular, cytogenetic, or hematologic relapses enter sustained remissions after treatment with DLIs. Complete remission (CR) rates of 70% to 90% in CP CML have been reported even with relatively low doses of DLI. The interval between DLI and response appears to be dependent on T cell dose. Similarly, the development of GVHD after DLI is dependent on the T cell dose and the interval between alloHSCT and DLI. Higher doses of DLI and shorter interval between alloHSCT and DLI are associated with increased risk of GVHD [11-13]. Because the progression rate of relapsed CML CP is slow, DLIs may be started at low doses of 0.3-1 $\times$ 10^7 $CD3^+$ cells/kg leading to clinical response as late as 1 year following treatment [14].

In contrast, CML in AP and BC are less susceptible to treatment with DLI only. Although remission rates of 20% to 40% [15] have been reported, because of the aggressive character of the disease, control of the malignancy by additional pretreatment with chemotherapy with or without TKIs may be necessary to allow sufficient time and circumstances for a therapeutic immune response to occur. Alternatively, patients may be treated with combined DLIs and TKIs. However, the role of TKIs in the successful treatment of patients who have been previously resistant to TKIs (eg, with T315I mutations) awaits the development of more specific drugs.

Finally, there is a small cohort of patients with extramedullary relapses. These may occur after the primary transplant or may even occur after remission induction with DLI. These relapses tend to be resistant to further immunologic interventions [16,17].

Treatment Options for Relapsed CML after alloHSCT

Withdrawal of immune suppression

Because CML is highly susceptible to T cell-mediated recognition by donor T cells, tapering immune suppression administered after transplantation for prevention or treatment of GVHD may lead to activation of alloreactive T cells capable of suppressing or eradicating the malignancy [18]. Discontinuation of immune suppression may also be necessary to allow other subsequent immunological interventions including DLI and vaccination. If the relapse occurs while a patient is receiving immunosuppressive therapy, the drugs can be discontinued in order to induce a GVHD/GVL flare. There is some risk that significant GVHD will follow this maneuver. If the patient

relapses after immunosuppressants have been stopped, a different strategy is required.

DLI combined with TKIs

It is not clear whether addition of TKIs to this treatment will improve or impair the immune response of DLIs [19]. However, prior therapy with imatinib does not seem to affect outcomes [20]. Patients that were treated initially with alloHSCT for advanced disease may be treated with TKIs after transplantation to prevent development of relapse. If despite this treatment these patients relapse after transplantation, further treatment with the same TKI does not appear to be rational, unless it can be demonstrated that the resistant clone has been eliminated by the transplantation. In such cases, administration of alpha interferon may augment the immunologic response, and if necessary, control the disease [21,22]. Whether or not second-generation TKIs should be added to DLIs is unclear [23,24]. In case of progression to AC or BC, administration of second-generation TKIs, potentially in combination with conventional chemotherapy, may be necessary to control the disease, thus allowing sufficient time for the DLI to exhibit its therapeutic effect, which may take several months.

DLI preceded by chemotherapy

Although relapsed-advanced CML is susceptible to DLIs in a minority of cases without addition of chemotherapy, it may be necessary to first control the disease with chemotherapy, despite the vulnerability of the hematopoietic system after transplantation. Systemic chemotherapy or treatment with monoclonal antibodies (mAbs) coupled to chemotherapy (eg gemtuzumab ozogamicin) can be used to control the disease and permit time to allow DLIs to exert their therapeutic effects. Chemotherapy pretreatment may not only control the disease, but may also provide a "danger signal" to the immune system amplifying the immune response. Furthermore, it is possible that the lymphopenic phase following chemotherapy may amplify the immune response because of homeostatic proliferation of the immune cells infused. Treatment of systemic BC may therefore preferentially be comprised of chemotherapy rapidly followed by DLI with or without TKIs depending on prior therapy, possibly in combination with alpha interferon [14]. Although the combination of DLI and chemotherapy may increase the likelihood of development of GVHD [25], this risk may be preferred over the likelihood of an insufficient response. Indeed, one could categorize this approach as a form of nonmyeloablative (NMA) transplantation. Administration of alpha interferon may further augment the initiation of the immune response [22].

Major Unanswered Basic Issues in the Treatment of Relapsed CML after alloHSCT

Defining the appropriate target antigens

Although DLI for relapsed CML may be highly effective, it can be accompanied by severe GVHD [4,26]. If immune suppression is necessary as treatment of GVHD, it may severely impair the GVL reactivity. Separation of GVL reactivity from GVHD is therefore essential to improve outcomes. The clinical response to DLI is likely to be dependent on the target structures recognized by the donor derived T cells. Because autologous HSCT and transplantation using stem cells from syngeneic twins have not been found to be associated with a clinically proven GVL effect, infusion of T cells recognizing allo-antigens on recipient leukemic cells is probably essential for the development of GVL reactivity. T cells recognizing mHag, defined as polymorphic peptides derived from intracellular proteins and presented in the context of HLA molecules, are probably responsible for both GVHD and GVL reactivity [8]. It has been hypothesized that T cells recognizing mHag selectively expressed on hematopoietic cells from the patient will cause GVL reactivity with no or limited GVHD [27]. Alternatively, T cell responses directed against tumor-associated, overexpressed self antigens like WT-1, proteinase-3, or PRAME may also contribute to the antileukemic effect. BCR/ABL specific T cell responses have been reported to be generated in vitro, but clear high avidity in vivo responses have not been demonstrated [28-30]. Characterization of the immune responses of patients responding to DLIs with CRs in the absence of GVHD may lead to better design of T cell populations to be used for adoptive transfer.

Interference of TKIs with immune responses

Several reports have indicated that T cell reactivity may be impaired in the presence of TKIs [31,32]. TKI exposure may take CML precursor cells out of active cell cycle making them less susceptible to T cell mediated cytotoxicity. Furthermore, in vitro, TKIs have been demonstrated to be capable of directly inhibiting T cell function or inducing apoptosis of activated T cells. Therefore, although TKI treatment of molecular, cytogenetic, or hematologic relapse of CML after transplantation may appear attractive to control the disease, T cell-mediated cure may be impaired by simultaneous treatment with T cells and TKIs [19].

Incongruent clinical responses

Extramedullary relapses in the presence of clinical CRs of CML in bone marrow (BM) have been observed following DLIs [16,17]. This may be because of the inability of T cells to recognize the target structures

on the malignant cells, local suppression of T cell recognition by inhibitory signals as provided for instance by regulatory T cells (Tregs), or inability of relevant T cells to home to the tumor site. Impaired expression of human leukocyte antigens (HLA) on hematologic tumor cells has been reported, but the frequency is unknown [33]. However, the recognition of mHag expressed only on subsets of CML cells, not including the transforming tumor stem cell, may be a cause of tumor escape. Detailed analysis of biopsies from extramedullary tumors and the T cell responses in these patients are necessary to unravel the biology of this type of tumor escape. Local radiotherapy may not only suppress the tumor, but also provide a danger signal directing T cells to the tumor site.

In vivo induction of immune responses by vaccination

Boosting the immune response specifically directed against CML may be an attractive strategy to amplify relevant anti tumor responses following transplantation and/or DLI [28-30,34]. Vaccination studies using tumor specific antigens (BCR/ABL peptide), tumor-associated, overexpressed antigens (WT1, proteinase 3, or PRAME), as well as peptides specific for mHag such as HA1, are being explored to boost the immune response. Especially in minimal residual disease (MRD) circumstances when antigen presentation by the tumor cells is limited, amplification of the (memory) immune response allowing immune surveillance may be relevant. Careful functional characterization of the immune response induced in vivo is necessary to reveal whether the T cells recognize antigens endogenously processed by the tumor, rather than just low avidity peptide-specific reactivity that does not contribute to antitumor reactivity. At present, phase I/II studies are being undertaken to evaluate the toxicity and possible efficacy of this approach.

Major Unanswered Clinical Issues on the Treatment of Relapsed CML after alloHSCT

Cure or control

alloHSCT has been advocated as a curative treatment of CML, but cure can only be achieved if the malignant stem cell can be destroyed. The immune response generated in GVHD/GVL is likely to be polyclonal, targeting multiple target antigens including antigens expressed on CML stem cells as well as on nontarget cells. Thus, when large numbers of T cells are infused, acute and chronic GVHD (aGVHD, cGVHD) may lead to both early and late complications that impair quality of life. A potential strategy to reduce the risk of GVHD is to administer low-dose DLI late after an initial T cell-depleted alloHSCT. T cell depletion may lead to a more restricted GVL without GVHD, with a higher likelihood of relapse, but which then may be successfully treated with repeated doses of DLI. Hence, the ability to treat relapse is directly relevant to the choice of initial therapy for CML. In contrast, the ultimate goal of TKI therapy is permanent suppression of the P210 fusion peptide, not necessarily cure of the disease. This appears to result in excellent long-term outcomes with preserved quality of life. These approaches have not been studied head to head, so at present it is unclear which approach is preferable.

DLI with or without TKI

Prevention of relapse after transplantation using first or subsequent generation TKIs may appear to be an attractive approach. However, administration of TKIs may also impair the therapeutic effect of DLIs. Therefore, if AP or BC are not likely to develop, the overall high success rate of DLI alone or in combination with alpha interferon after transplantation may favor postponing coadministration of TKIs [25]. In a patient with a high risk of relapsing with AP or BC, TKIs in the posttransplant period may be a reasonable strategy, although a randomized study investigating the use of TKIs after alloHSCT would be useful. Arguments can be found both in favor and against simultaneous treatment of DLIs and TKIs [31,32,35,36].

Manipulation of the graft or DLI

Manipulation of the graft and/or DLI is the most obvious approach to separate GVL from GVHD. Complete T cell depletion of the graft to prevent GVHD eliminates the initial GVL effect, but the elimination of immune suppressive therapy after alloHSCT allows the postponed administration of lymphocytes or lymphocyte subsets. Postponed administration of DLI reduces the risk and severity of GVHD, and may result in better quality of life after treatment. Treatment with only $CD4^+$ T cells may result in conversion into full donor chimerism with limited risk of GVHD, although long-term follow-up is needed [37]. Coadministration of Tregs may reduce GVHD, but whether it will impair GVL needs to be determined. Treatment with T cell products only recognizing recipient hematopoietic cells is being developed.

Current Research Initiatives on the Treatment of Relapsed CML after alloHSCT

The infrequency of alloHSCT for CML limits the ability to perform large-scale clinical studies. Therefore, careful monitoring of studies with limited numbers of patients will more likely give insight into new strategies to more optimally treat patients with allogeneic transplantation and adoptive T cell therapy. A few of the proposed major initiatives and questions on this subject are described in the subsequent sections.

Modification of DLI

Separation of DLIs into cellular subsets may maintain or increase the clinical efficacy against CML and decrease the likelihood of developing GVHD. Although it is not clear whether CML stem cells express class II HLA during their cell cycle, most CML progenitor cells highly express HLA class II molecules, whereas under steady-state conditions most nonhematopoietic tissues are HLA class II negative. Administration of purified $CD4^+$ cells may therefore exhibit GVL reactivity with limited risk of GVHD [37]. It is also possible to activate T cells ex vivo to enhance the GVL response [38].

Targeting mHags or leukemia-associated antigens by adoptive transfer

In vitro selection, activation, and expansion of T cells recognizing mHag or leukemia-associated antigens (LAA) may allow effective treatment of leukemia after transplantation. Removal of T cells from the graft and replacing them with antigen-specific T cells or treatment with these purified cells instead of DLIs may allow administration of high doses of tumor-reactive T cells with a more limited risk of GVL. In vitro protocols allowing the isolation of antigen-specific T cells under good manufacturing practice (GMP) conditions urgently need to be developed for these purposes. Further analysis of immune responses from patients successfully treated with DLI in the absence of GVHD will result in a better definition of mHags and LAA that can be used to isolate tumor reactive T cells for clinical use [27].

Vaccination of patient or donor

Vaccination of the patient after transplantation and/or DLI with mHags or LAA may boost the immune response. Peptide vaccination has been shown to be capable of boosting existing immune responses in vivo. Because shortly after transplantation the naïve T cell repertoire is severely impaired, vaccination of the patient with single antigens may have only limited effect. Vaccination of the donor prior to harvesting of the immune cells used for treatment may significantly amplify the response and facilitate the isolation of tumor reactive T cells from donor cells. Importantly, vaccination of donors with mHags or tumor specific antigens is expected to be harmless to the donor. Another alternative is vaccination of the patient after transplantation with a cellular leukemia vaccine designed to stimulate a specific GVL response to multiple antigens [39]. The effectiveness of DLI may be improved by the in vivo coadministration of recipient-derived normal or CML-originated dendritic cells, thereby exposing the T cells in the patient to a large repertoire of mHags. Additional loading of these dendritic cells by LAA of choice may further improve the efficacy of the T cell responses initiated.

Multimodality therapy

Combining cellular immunotherapy and/or vaccination strategies with TKIs after transplantation may improve or impair the effectiveness. Randomized studies exploring the administration of TKIs are necessary to analyze whether the use of these reagents will decrease the likelihood of elimination of CML stem cells, and prevent cure of the patient. Alternatively, intermittent treatment with TKIs may be explored to more effectively combine short-term control of the disease and long-term cure.

ACUTE MYELOGENOUS LEUKEMIA

Summary of Current Status

The principal cause of failure, and ultimately of death of the patient, after transplant for acute myeloid (a.k.a. myelogenous) leukemia (AML) is relapse. Disease burden at time of transplant is the principal predictor of recurrence. The definition of relapse after transplant is itself likely to change [40]. The conventional definition (BM showing >5% blasts on morphologic exam) is most commonly used. However patients with <5% blasts have been considered to be in relapse based on recurrence of their initial cytogenetic or molecular (eg NPM1, WT1, FLT3) abnormality, or the presence of phenotypically abnormal blasts as identified by multicolor flow cytometry. The specificity of these types of "relapse" for subsequent morphologic relapse is probably high but remains to be documented more fully. Given the relation between disease burden and outcome, these newer definitions of recurrence are likely to have better prognoses than morphologic relapses [41-43].

Disease tempo is likely to affect outcome of treatment of morphologic relapse. Slowly evolving relapses are more likely to have time for donor procurement and for interventions other than chemotherapy to be considered, whereas a rapidly evolving leukocytosis at recurrence is likely to be treated with chemotherapy (or not treated at all).

Long-term disease control occurs in 0% to 50% of patients with AML who relapse after transplant. Much of this variability is because of type and tempo of relapse together with factors such as: (1) duration of remission after transplant; (2) disease status at transplant (remission patients performing better than those transplanted in relapse); (3) cytogenetics and/or presence of NPM1 and/or FLT3 mutations; and (4) and donor type (unrelated donors taking longer to provide DLI, for example). Recipient age and presence of comorbidities, including infections, are important considerations shaping the ability to tolerate further therapy, as is the presence of active GVHD at relapse.

Treatment Options for Relapsed AML after alloHSCT

Withdrawal of immune suppression

Despite anecdotal reports of success [44], withdrawal of immunosuppression (WIS) is very unlikely (<5%) to result in clinically significant benefit, at least in morphologic relapse. Disease kinetics is a major predictor of response given the time required for withdrawal to work. Responses with this approach are most likely to occur in patients relapsing with a low blast percentage, or with cytogenetic or molecular-only recurrence. Presence of GVHD at relapse is a major complicating variable, because any further GVHD induced by stopping immunosuppressants is unlikely to benefit a patient who was not "protected" against relapse by GVHD in the first place [45].

DLI

AML is of intermediate sensitivity to the GVL effect, and as such, responses to DLI vary from 0% to 60%, with higher response rates reported for low tumor burden, with the use of chemotherapy prior to DLI, and in the context of T cell-depleted transplants (notably with alemtuzumab) [6]. Most responses do not translate into long-term survival, because of GVHD, pancytopenia, infections, and disease relapse. Donor availability (logistics are intrinsically more complicated with an unrelated donor) and presence of GVHD at the time of relapse are major impediments [15,46-50].

Similar to what is observed when the recurrence is treated with a second transplant (discussed later), achievement of a CR after the infusion of lymphocytes is a prerequisite for long-term survival. Survival is also improved when relapses occur after longer remissions (>6 months) [49,51]. Development of GVHD has not been consistently associated with longer disease-free survival (DFS) or overall survival (OS) after DLI, a likely reflection of the competing risk of death because of the complication versus increased GVL effect. Most series primarily include related donor DLI, but unrelated donors are increasingly being used as well. Analysis of unrelated donor DLI data is subject to 2 major biases. First, delays intrinsic to the procurement process would indicate that patients so treated are those whose disease is indolent or responsive enough to allow the treatment to occur in the several weeks necessary to perform the infusion. Second, the delay may impose time for disease progression and for other complications to occur, leading to worse outcomes. In 1 retrospective analysis of 23 patients, the CR rate was 42%, and 1-year DFS was 23%. The incidences of aGVHD and extensive cGVHD rates were 35% and 40%, respectively, and 8% of the patients developed BM aplasia [15].

DLI preceded by chemotherapy

Use of chemotherapy appears to improve the results of DLI [49,51]. Choice of chemotherapy regimen varies widely, and it is impossible to make specific agent recommendations based on published literature. Response rates vary from 10% to 60%, with higher response rates than those reported for DLI alone.

The European Group for Blood and Marrow Transplant (EBMT) reported a retrospective analysis of 399 patients with AML in first hematologic relapse after transplant, and compared patients that received DLI (n = 171) to patients that did not receive DLI (n = 228). At a median follow-up of 27 and 40 months, respectively for DLI and non-DLI patients, actuarial 2-year survival was 21% (±3%) versus 9% (±2%). Improved survival was associated with younger age (<37 years), longer duration of remission after alloHSCT (>5 months), and use of DLI for salvage. In the DLI subgroup, having less blasts in the BM (<35%), female sex, presence of favorable cytogenetics, and CR at the time of DLI were covariates associated with improved survival [51]. The benefit of chemotherapy prior to DLI is suggested here by the 2-year survival >50% for patients that received DLI in CR.

Special clinical situations using DLI for relapsed AML

DLI after alternative donor transplants. DLI is not an option after unrelated cord blood transplantation because the donor is not available. There is, however, preliminary experience with DLI after alloHSCT from haploidentical related donors. In 1 series, 20 patients received granulocyte-colony stimulating factor (G-CSF)-primed DLI to treat relapse occurring at a median of 177 days after alloHSCT. There were 8 survivors, and the incidence of severe GVHD was apparently reduced by using GVHD prophylaxis after DLI [52]. Rizzieri et al. [53] investigated early DLI given after T cell-depleted NMA alloHSCT in 17 patients that received an HLA-mismatched related donor transplant. Infusions were given at a median of 50 days after alloHSCT, with a median $CD3^+$ cell dose/kg of 1×10^5. Severe aGVHD occurred in 14% of patients receiving this cell dose. Long-term survival, however, was achieved in only a few patients because of disease relapse.

DLI in children with relapsed leukemia. A retrospective analysis was conducted in 45 children with relapsed leukemia, 21 of who had either myelodysplastic syndrome (MDS) or AML, who were treated with DLI with and without chemotherapy. Factors associated with increased likelihood of achieving CR included the use of pre-DLI chemotherapy and initial posttransplant remission of at least 6 months. The

outcomes for these 45 children were compared to 1229 patients from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry with similar characteristics who did not receive DLIs. After adjusting for the time from relapse to DLI, there was no difference in survival between patients who received DLI and those who did not [54]. These findings suggest that any survival benefit from DLI in children with relapsed AML is small. The use of DLI in children outside of clinical trials should be restricted to late relapses and be preceded by cytoreduction.

DLI graft characteristics. Controversies in the DLI setting include the use of G-CSF mobilized DLI [55] to prevent BM aplasia, and the definition of an "ideal" cell composition. $CD4^+$ T cell enrichment has been reported to decrease GVHD without compromising GVL [56,57]. The issue of cell dose is also unresolved, and most of the prospective data has been obtained in CML, a disease where a dose-response relationship may exist. There is wide variation in the literature, with mononuclear cell doses ranging from 0.1 to 10×10^8/kg, making a clear-cut recommendation impossible. Dose escalation is appealing for indolent diseases, but may be of little practical value with fully relapsed AML [11,58].

Chemotherapy

Attempts to assess outcomes in patients with AML treated with conventional chemotherapy alone for relapse after alloHSCT are hampered by the inability to ascertain the patient characteristics that directed the use of such therapy. Furthermore, reports on the use of chemotherapy for relapse after alloHSCT at times do not separate patients with AML, acute lymphocytic leukemia (ALL), CML, or "high-grade" MDS, and multivariate analyses do not consistently indicate that results are not influenced by diagnosis. Nonetheless, a sampling of the literature makes it clear that results of conventional chemotherapy for relapse after alloHSCT are for the most part remarkably poor. A retrospective analysis from the Fred Hutchinson Cancer Research Center (FHCRC) using data collected from 1977 to 1984 indicated that 55 of 95 patients with relapsed AML after alloHSCT received chemotherapy. Thirty-two percent of the 34 patients given cytarabine (with and without adriamycin) achieved CR with a median DFS of 9.7 months [59,60]. The remission rate was highly influenced by time to relapse after alloHSCT, such that the authors recommended that reinduction be attempted only in patients relapsing at more than 1 year after alloHSCT. A multivariate analysis including 220 FHCRC patients relapsing after alloHSCT for AML from 1995 to 2004, of whom approximately 75% received chemotherapy with and without WIS therapy, confirmed the importance of time from alloHSCT to relapse. Specifically 2-year survival estimates for patients relapsing less than 100 days, 100-200 days, and greater than 200 days from alloHSCT were 3%, 9%, and 19%, respectively. Further demonstration of the direct relation between the time from transplant to relapse and the effectiveness of subsequent chemotherapy come from papers by Levine et al. [49] and Choi et al. [61], both of which explored the use of DLI after chemotherapy for relapse following alloHSCT. The former reported a 1-year survival probability of 10% (95% confidence interval [CI] = 3%-31%) if relapse occurred within 6 months of transplant versus 44% (95% CI = 29%-68%) if relapse occurred later. These type of data led Mielcarek et al. [59] and Levine et al. [49] much as it did Mortimer et al. [60] 15 to 20 years earlier to suggest that standard chemotherapy, with and without DLI, be used only in patients who relapse 3 to 6 months after alloHSCT, with other patients being offered participation in clinical trials or palliative care if such trials were not available.

The ability to identify AML patients at high risk of relapse after alloHSCT together with the frequent failure of therapies given only at relapse suggests that such high-risk patients be treated with prophylactic intent after alloHSCT. A major problem has been that the candidate therapies have appeared either too toxic or liable to abrogate a GVL effect if used at such time. However, the introduction of less toxic drugs has obviated this problem.

Azacitidine, which in addition to its anti-AML activity may increase the immunogenicity of AML blasts, provides the most instructive current example. de Lima and colleagues [62] at the M.D. Anderson Cancer Center conducted a phase 1 trial of azacitidne as posttransplant maintenance therapy in 42 patients who underwent reduced-intensity alloHSCT for relapsed/refractory AML. They found that starting 40 days, after alloHSCT azacitidine could be given at 32 mg/m^2/day for 5 consecutive days every 4 weeks for at least 4 cycles without an untoward incidence of GVHD (11% grade III, no grade IV) or other toxicities, although dose escalation to 40 mg/m^2 daily was limited by thrombocytopenia. The authors have begun a trial randomizing high-risk patients to azacitidine or no maintenance therapy post-alloHSCT, although the low risk associated with azacitidine suggests that its use as antirelapse prophylaxis could potentially be extended to patients at lower risk of relapse. The M.D. Anderson group has also treated patients with AML and MDS relapsing after alloHSCT with low-dose azacitidine. Preliminary experience indicates a 20% long-term disease control rate for patients with "indolent" relapses, without the need for immunosuppression withdrawal. This drug has also been investigated with DLIs, or as a way to reduce disease burden prior to alloHSCT, in the hope of improving transplant outcomes [63-65].

The experience with azacitidine serves as an example that other "less intense" drugs could be investigated either at relapse following alloHSCT, or preferably, in the prophylactic setting. A problem has been the frequent reluctance of physicians, cooperative groups, and pharmaceutical companies to even include patients who have relapsed after alloHSCT in clinical trials. Although there is understandable concern of toxicity (and of interference with GVL in the prophylactic situation), the benefit to risk considerations would seem to favor inclusion of at least some subsets of patients with relapsed disease, if not patients at high risk of relapse. Perhaps setting a precedent for such use, a clinical trial of the aurora kinase A inhibitor C14005 (Millenium Pharmaceuticals, Cambridge, MA) for relapsed AML includes patients in relapse after alloHSCT as does a trial of FLT3 kinase inhibitor AC220 (Ambit Pharmaceuticals, San Diego, CA). Patients with FLT3 internal tandem duplications are at high risk of relapse following conventional chemotherapy, and hence, are likely to be disproportionately included among patients given alloHSCT in first CR. In this context, the activity of sorafenib, which can inhibit not only FLT3, but also raf kinase and other receptor tyrosine kinases, in 4 such patients in relapse after alloHSCT is noteworthy as it resulted in 2 CRs [66]. However, the brief duration of these responses again argues for prophylactic administration. Such a study using AC220 was being planned at the time of this publication. As the number of specific anti-AML therapies increase, more patients should become candidates for similar approaches. Among patients who lack a specific drug target, randomized designs might be employed to suggest which nonspecific therapies are most worthy of pursuing in larger trials [67].

Second allogeneic transplant

The likelihood of benefit from a second transplant for relapsed AML is increased by achievement of CR (or a lower disease bulk) prior to the second transplant and a longer time from the first to relapse (often somewhat arbitrarily set at >6 months). Younger age is beneficial, as is the general health status of the recipient, although this is less documented in large registry-based retrospective analyses. There are no prospective, multicenter trials in this setting, but available data indicates that only a minority of relapsing patients are treated with a second alloHSCT [43,45,68].

The presence of GVHD at relapse is a frequent deterrent to any further cell therapy, including second alloHSCT. The use of GVHD prophylaxis/treatment during second transplant may minimize the impact of GVHD (which may also be modulated by the chemotherapy itself), although this remains the topic of debate among investigators.

Donor availability is a major issue after transplants from volunteer unrelated donors or cord blood (CB). Second transplants from the same donor are not an option for CB, for example. Speed of procurement, on the other hand, may be a major advantage for CB or haploidentical transplants over volunteer unrelated donors for those patients without HLA-matched family donors, shortening the time to alloHSCT. Accordingly, as with DLIs, the majority of second transplants are performed for patients with a related donor. It is unclear if a second transplant from a different versus the original donor leads to improved outcomes. Most reported studies are underpowered to answer this question.

Available evidence suggests that the use of alternative donors for second alloHSCT is associated with a relatively high treatment-related mortality (TRM). A retrospective analysis by the CIBMTR looked at 279 patients with acute and chronic leukemias relapsing after HLA-identical sibling alloHSCT who received a second transplant [69]. The 5-year cumulative incidences of TRM and relapse were 30% (range: 24%-36%) and 42% (range: 36%-48%), respectively, whereas 5-year survival probability was 28% (23%-34%). Risks of treatment failure and mortality were lower in patients younger than age 20 years and in patients with a CR duration of at least 6 months after first alloHSCT. Longer remission after the first transplant (>6 months) and achievement of CR prior to second transplantation led to reduced recurrence risk, whereas use of reduced-intensity conditioning (RIC) regimen was associated with a higher risk of relapse.

There are several controversial issues surrounding the use of second transplants to treat AML recurrence. Treatment of refractory relapses occurring early post-alloHSCT outside of clinical trials is difficult to recommend given current results. Whether the source of stem cells, BM versus peripheral blood (PB), affects outcomes is largely unknown. PB often has been used because of a perceived higher GVL effect with this source of hematopoietic stem cells; however, there is also concern of increased GVHD with its use. The choice of preparative regimen is often decided on the basis of institutional preferences, prior therapy, and investigator experience. The use of NMA and RIC regimens have gained popularity in this setting given high TRM with myeloablative (MA) conditioning when used for the second transplant, especially when the first transplant used MA chemotherapy and/or radiation therapy. The use of RIC regimens may be associated with higher relapse rates; however, and the decision guiding the choice of preparative regimen has to take into account duration of CR after the first alloHSCT (longer duration may allow the use of higher intensity regimen), age, performance status, and other factors usually employed to select patients for ablative chemoradiation conditioning. The uncertainty extends to the GVHD prophylaxis regimen. Suboptimal GVHD

prophylaxis in an attempt to maximize GVL is often hampered by prohibitive TRM/GVHD rates, and it is unknown if any given regimen is better than any other.

Natural killer (NK) cells

NK cell function is regulated by interactions between killer immunoglobulin-like receptors (KIRs) present on the NK cells and major histocompatibility complex (MHC) molecules present on the target cells. Following highly encouraging findings from the Perugia group demonstrating a strong protective effect of donor NK cells on AML relapse in the T cell-depleted haploidentical transplant setting [70], several groups have explored the role of antileukemic effects of NK cells in other alloHSCT settings. Reduced AML relapse rates have recently been correlated with donor NK cell properties in T cell-replete transplants using related donors [71], unrelated donors [72], and NMA conditioning [73]. At present, consensus has not yet been achieved on how to reliably predict NK alloreactivity, as several hypotheses have been advanced. The original Perugia hypothesis, known as the KIR ligand incompatibility model, suggested that NK alloreactivity could be predicted by comparison of donor and recipient HLA class I genotypes. Subsequently, it became recognized that NK cell alloreactivity is determined by the net effect of activating and inhibitory signals transmitted between target cells and NK cells. In alloHSCT, donor NK cells attack recipient cells that fail to sufficiently engage the inhibitory KIRs. In this model, NK alloreactivity can be predicted by comparing donor KIR genotypes (which are inherited independently of HLA genes) and recipient HLA class I genotypes. However, even with improvements in prediction of NK alloreactivity, numerous practical questions regarding NK cell mediated antileukemic activity remain, including the effects of the transplanted cell dose and chimerism. An even more crucial issue for studies of NK cells for treatment of relapsed AML is the present limited ability to generate the large numbers of ex vivo clinical grade NK cells needed for clinical trials [74]. Thus, although promising as a potential antileukemia therapy, advances in NK cell purification and production will be essential for future clinical study.

Cytokines

The role of cytokines in treatment of relapse is uncertain. Use of interferon-α, interleukin (IL)-2, myeloid colony stimulating factors (eg, granulocyte macrophage colony-stimulating factor [GM-CSF], G-CSF), and combinations of these cytokines can be found in the literature, generally as case reports or small trials [3]. Responses have been described, but long-term disease control is unusual with cytokines alone.

Treatment of extramedullary leukemia

Extramedullary (EM) relapse of AML following alloHSCT can occur simultaneously with medullary recurrence or as an isolated site of relapse. It has been suggested that EM relapses are more commonly diagnosed after DLI. Most studies of EM recurrence were published more than 10 years ago, and the relevance of these studies to current practice is not clear. In a review of 78 consecutive transplants for AML, EM relapses developed in 8 of 78 (10%) patients, evenly split between isolated EM relapse and concurrent medullary relapse [75]. None of the patients had a prior history of EM leukemia. Risk factors for EM relapse were higher risk disease at time of transplant and absence of GVHD. An analysis by the University of Michigan (Levine, unpublished data) identified EM leukemia relapse in 26 of 257 (10%) consecutive transplants for AML performed at their institution between January 2001 and May 2008. All but 2 of these relapses were isolated to EM sites. The median age was 48 years (range: 0.6-69 years). Univariate analysis identified several statistically significant risk factors for EM relapse (Table 1). Two well-known risk factors for relapse, high-risk cytogenetics, and high-risk disease at time of transplant, were associated with an increased risk of EM relapse. Patients with AML FAB morphologic classification of M4 or M5, both of which are associated with EM disease, were more likely to experience EM relapse than other subtypes of AML. Interestingly, children (aged $\leq$18 years) were more likely to experience EM relapse than adult patients. A history of EM disease prior to transplant was not statistically associated with post-alloHSCT EM relapse, although small numbers may account for this finding. More than half of the 28 patients who had EM disease prior to alloHSCT relapsed, 9 (32%) with EM relapse and 4 (14%) with isolated BM relapse. EM relapses occurred in a wide variety of sites including visceral organs such as the lungs, skin, lymph nodes, and spinal fluid, but the soft tissues were the most commonly involved site. Treatment for EM relapse typically included chemotherapy and/or radiotherapy alone (n = 13) or in combination with DLI (n = 8). Despite these measures, postrelapse remission was achieved in only 6 (23%) patients. However, with a median of 13 months of follow-up (range: 9-70 months), these remissions were durable without subsequent relapse.

Conclusions on the Treatment of Relapsed AML after alloHSCT

Current therapeutic modalities benefit a small minority of patients who experience relapse of their AML following alloHSCT. These are younger patients with longer DFS, and with good performance status. In this subgroup, chemotherapy and DLI, with or without a second alloHSCT are "standard options." However,

Table 1. Variables Associated with Extra-medullary Relapse (University of Michigan Data)

Variable	Hazard Ratio	*P*-Value	Variable	Hazard Ratio	*P*-Value
EM disease prior to TXP	1.150	.63	Related Donor	1.139	.52
Time from DX to TXP More than 6 Months	0.897	.59	HLA Mismatched	1.606	.08
High risk cytogenetics	1.574	.03	Sex Mismatch	0.930	.74
M4/M5 FAB classification	1.564	.03	PBSC Stem Cell Source	0.878	.59
High-risk disease at TXP	1.962	.001	TBI-based conditioning	0.644	.26
Age over 18 years	0.608	.04	Busulfan-based conditioning	1.597	.26
Full-intensity conditioning	0.832	.50			

EM indicates extramedullary disease; DX, diagnosis; PBSC, peripheral blood stem cell; TBI, total body irradiation; TXP, transplant.

given the highly selected nature of the group, it seems reasonable to argue that all relapses after alloHSCT are potentially eligible for clinical trials and should be treated as such. Multicenter, prospective clinical studies are needed, and a list of obstacles and of potential approaches is listed in Tables 2 and 3.

ALL

Summary of Current Status

Relapsed ALL has a poor prognosis. Although curative salvage treatment is possible in a minority of children [76], the outlook for adults is particularly dismal with only 7% of relapsed patients surviving at 5 years. This is regardless of age or prior therapy, as well as duration of a prior first remission [77]. Relapse after an allogeneic transplant is almost always incurable.

In practice, a cure following relapse after an alloHSCT is almost always associated with a second allogeneic transplant in childhood ALL. There are some select survivors following a second allogeneic transplant; a leukemia-free survival (LFS) of 21% at 2 years for patients transplanted in CR was reported in an EBMT study [78]. Similarly, a Japanese study reported a 19% LFS at 2 years; however, it was only 9% at 4 years [79]. There are only isolated reports of such survivors in adults with relapsed ALL after alloHSCT. TRM rates are extremely high, and enrollment bias is likely. Age <16 years and duration from first transplant to relapse of >6 months are associated with better outcome. The impact of donor selection, graft source, and conditioning regimen on outcome of second transplant has not been fully elucidated [69,80].

Table 2. Key Obstacles for Development of Large, Randomized, Prospective Clinical Studies of Relapsed AML after Allogeneic HSCT

- Lack of large, multicenter prospective phase I and II studies to define experimental arms in a randomized study.
- Lack of large databases dealing specifically with relapse information.
- Lack of a broad discussion and consensus that should ideally involve drug companies and the FDA on the need to enroll patients in phase I, II, or III clinical trials for the treatment of AML relapsing after allogeneic HSCT.

AML indicates acute myelogenous leukemia; HSCT, hematopoietic stem cell transplantation.

Using currently available therapeutic modalities, the few patients that may ultimately be cured are those whose relapse occurs prior to the onset of GVL or in the absence of GVHD posttransplant. Second alloHSCT should involve careful consideration of the appropriate donor. It may be the same donor. However, if the patient developed GVHD, one might argue that there was not an effective GVL response and consider an alternative donor. If there was no prior GVHD, a different donor may be considered, including an unrelated donor. Alternatively, one could consider a haploidentical donor (with T cell depletion) in an attempt to use GVL that is not primarily mediated by T cells (rather by other modalities, such as NK alloreactivity, although this is not thought to be so potent in ALL). Ciceri et al. [81] reported some success with haploidentical transplants for ALL beyond first CR.

Another group that may possibly be cured is Philadelphia (Ph) chromosome- or BCR/ABL-positive ALL patients who are not resistant to a TKI. Responses,

Table 3. Critical Questions to Address for Patients with Relapsed AML after alloHSCT

Potential to answer with a large database:

- Outcome of AML relapse after all forms of allogeneic HSCT, including haploidentical and CB transplants.
- Result of DLI or second transplants after haploidentical and CB HSCT.
- Better definition of a patient population more likely to benefit from "aggressive" versus palliative care.

Potential to answer with prospective multicenter clinical trials and the use of a sample repository

- Role of MRD detection in predicting relapse and defining need for further interventions post-HSCT.
- Investigation of hypomethylation agents or "targeted" therapies to prevent or treat relapse
- Better definition of MRD-defined relapse or persistent disease after HSCT—treatment of molecular or flow cytometry-detected relapse (without evidence of overt hematologic recurrence).
- Use of ex vivo expanded NK cells to treat relapse.
- Cord blood: ex vivo expansion of T cells.
- Ex vivo expansion of donor T cells through costimulation.
- Leukemia-specific DLI using antigen-specific cytotoxic T lymphocytes.
- Use of new technologies to inactivate alloreactive donor T cells.
- Use of new technologies to increase immune recognition (CARs, etc).
- DLI cell composition manipulation to decrease GVHD and increase GVL.
- Cell of origin of relapse: recipient's versus donor's.
- Genetic profiling of relapsed AML.

AML indicates acute myelogenous leukemia; CB, cord blood; alloHSCT, allogeneic hematopoietic stem cell transplantation; DLI, donor lymphocyte infusion; MRD, minimal residual disease; GVL, graft-versus-leukemia; GVHD, graft-versus-host disease; CARs, chimeric antigen receptors.

including CRs, can occur and may be durable for months or even years. Conventional chemotherapy can prolong survival in selected patients, with long transplant-to-relapse intervals and isolated EM relapses representing prognostic factors for successful remission induction [82]. This section will briefly consider cellular manipulations as well as novel chemotherapeutic agents and targeted therapies for relapsed ALL and will emphasize potential future directions.

Treatment Options for Relapsed ALL after alloHSCT

DLIs

The GVL effect in ALL, contrary to common perception, is probably 1 of the most potent strategies with curative potential. This GVL effect in humans was actually first described in patients undergoing an allogeneic transplantation for ALL, as described in the classic paper by Weiden et al. [83] in 1979. A number of nonrandomized studies have supported the existence of a potent allogeneic GVL effect in ALL [84-86]. In an Eastern Oncology Group/Medical Research Council study in adults with ALL in first CR,, GVL activity was unequivocally established. Of 239 Ph-negative patients at standard risk who had a sibling donor, the relapse rate was 24% compared to 49% in 333 standard-risk patients who did not have a donor (P <.00005) [87]. Among Ph-negative high-risk patients, the relapse rate was 37% for the 204 patients with a donor versus 63% for 261 patients without a donor (P <.00005). Notably, increasing the intensity of GVHD prophylaxis is associated with a higher risk of relapse after alloHSCT in adults and children with ALL [88,89].

Given the potent GVL effect in ALL, DLI is an attractive therapeutic option for treating relapse after an allogeneic transplant. In practice, unlike CML, they are almost never effective in ALL in the state of florid relapse. There are multiple factors that may limit the effectiveness of DLI against ALL. Clinically, the rapid proliferative rate of ALL is such that often the kinetics of disease progression may outpace the duration required to achieve a maximum GVL effect. Furthermore, unlike myeloid cells, B-lineage lymphoblasts have very low expression of T cell costimulatory molecules (eg, B7.1, B7.2), and thus present antigens poorly and may induce T cell anergy [90].

CRs have occasionally been induced by DLI and/or WIS for patients with ALL, although the reported response rates of large series are quite poor, ranging from 0% to 20% [4,15,48,91-99]. Although remissions can be achieved, many are induced by the additional use of chemotherapy, and are usually short lived, with few long-term survivors [100]. As has been observed in CML, the response rates of ALL to DLI are higher in the setting of MRD (eg, molecular or cytogenetic relapse) [101]. DLIs can induce remissions in approximately one-third of children with ALL prior to overt relapse [102,103]. Because of the low likelihood of achieving a durable CR, DLIs are not considered standard for patients with ALL relapsing after alloHSCT [104].

Second allogeneic transplant

As previously described, a second allogeneic transplant is 1 of the few treatment options that provides the possibility for long-term survival following relapse of ALL after an alloHSCT. However, TRM rates associated with second allogeneic transplantation are extremely high. The utilization of NMA and RIC regimens may reduce TRM associated with second transplants and allow achievement of GVL-induced eradication of residual ALL. Unfortunately, there are very few data reporting RIC alloHSCT in ALL. The EBMT published the outcome of 97 patients with ALL who received RIC alloHSCT [105]. However, there was a great deal of heterogeneity among the patients with varying RIC regimens. Clearly, some RIC regimens were similar to what others would consider as a standard MA conditioning regimen. A retrospective analysis of 27 patients who received RIC alloHSCT, using data from 4 prospective multicenter trials, attempted to demonstrate whether there was a difference in relapse rates between patients who either did (n = 17) or did not (n = 10) have GVHD [106]. Although relapse was lower among patients with GVHD, the analysis was retrospective and the numbers were small. A similar report from Japan [107] reported on RIC alloHSCT in 33 ALL patients and also attempted to correlate the relapse rate to the incidence of aGVHD and cGVHD; again a nonsignificant difference was observed. Clearly, RIC alloHSCT is feasible and can effect cures in patients with ALL [108-110]. Important to this review, a minority of the patients in the published series of RIC alloHSCT represent second transplants to manage ALL who have relapsed after a prior allogeneic transplant, although some successes have been reported [109].

Conventional chemotherapy and targeted therapies

In patients with adequate performance status, responses may be achieved with standard ALL therapies, or with newer agents such as clofarabine [111,112] or nelarabine [113,114], or even with some of the less toxic new formulations of existing drugs such as liposomal vincristine [115]. The focus of new approaches will be on maintaining leukemia responses. Paradoxically, imatinib and second generation TKIs have been capable of inducing molecular CR after alloHSCT and achieving prolonged DFS with or without DLI [116-119].

Adoptive cell therapies

The successes and limitations of DLIs in the management of posttransplant ALL relapse have led to investigations of other forms of adoptive cellular therapies after alloHSCT. For example, ex vivo expanded cytotoxic T-lymphocyte clones (CTLs) that recognize leukemia-associated antigen targets (eg, WT1) and mHag may be active against relapsed ALL after alloHSCT [6]. Notably, leukemia-associated antigen-specific CTLs have been detected in normal stem cell donors, raising the possibility that these might be utilized to manage posttransplant relapse [120]. Strategies have also been developed to enhance lymphocyte effector functions, and posttransplant clinical trials of a number of such approaches are being conducted [121,122]. Antigen-driven oligoclonal peripheral T cell expansion has been shown to develop during recovery from profound T cell depletion [123]. Thus, the immune repertoire might be effectively skewed toward tumor-associated antigens by utilizing adoptive therapies in the early posttransplant period, as has been observed in the autologous transplant setting following lymphocyte-depleting chemotherapy [124]. Chimeric antigen receptors (CARs) have been designed to enable immune effectors to bind to and induce cellular cytotoxicity against ALL blasts that express CD19 [125,126]. Clinical trials of allogeneic T cells and NK cells engineered with CD19-directed CARs are currently being evaluated in clinical trials for children and adults with posttransplant relapsed ALL.

mAbs

Because mAbs were first generated against human differentiation antigens there has been the expectation that they would be used in the treatment of hematologic malignancies [127]. Multiple mAb-based reagents that target ALL-associated surface antigens have been developed for investigation in humans.

Unconjugated mAbs. Unconjugated mAbs may require functional immune effector mechanisms, which are commonly deficient in the setting of posttransplant relapse, and it is unlikely that unconjugated mAbs will have adequate single-agent efficacy in most cases of ALL. However, rare cases of CRs of individuals with ALL have been reported with mAbs targeting CD52 (alemtuzumab) and CD20 (rituximab) [128-131]. mAbs against CD20 and CD22 have been safely combined with standard chemotherapy in the therapy of ALL and response rates appear favorable in comparison to historical experience with chemotherapy alone [132,133]. mAbs against CD20 and CD22 have been safely combined with standard chemotherapy in the therapy of ALL, and response rates appear favorable in comparison to historic experience with chemotherapy alone [132,133].

The use of mAbs that target tumor-associated antigens might be useful in the treatment of relapse after alloHSCT provided there are adequate effectors capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) [134]. Anti-CD19 mAbs enhanced posttransplant donor-derived mononuclear cell mediated lysis of CD19+ lymphoblasts in a preclinical model [135].

Conjugated mAbs. The cytotoxicity of mAbs can be dramatically increased by linkage to toxic moieties such as chemotherapeutic agents, bacterial and plant toxins, and radionuclides. Importantly, these agents do not require functional immunity for activity, and thus can be effective even in profoundly immunocompromised hosts such as after transplantation. The anti-CD33 mAb linked to calicheamicin (gemtuzumab ozogamicin), approved for use in AML but subsequently withdrawn by the manufacturer in the United States for toxicity issues, has successfully induced CR in cases of ALL with CD33 expression [136]. Studies of recombinant anti-CD22 *Pseudomonas*-based immunotoxins in ALL have recently been conducted, and activity and tolerability has been observed post-alloHSCT [137]. The agent is synergistic with standard chemotherapy has been demonstrated, and a Phase II trials with this combination are planned. Radioisotope-conjugated mAb constructs that target leukemia-associated or hematopoietic antigens (eg, CD20, CD25, CD45) have been developed. These are often associated with severe myelosuppression and thus have been utilized as MA conditioning prior to alloHSCT [138]. Targeted immunotoxins, such as denileukin diftitox, which targets the IL-2 receptor, have been studied in some lymphoid malignancies [139] and may potentially also be effective in some subtypes of ALL.

Bispecific mAbs. A recombinant anti-CD19/anti-CD3ε bi-specific antibody (MT103, blinatumomab) has recently been shown to be active in hematologic malignancies [140]. Large prospective clinical trials are now planned. Importantly, these agents recruit and thus require functional T cells for activity and thus may have increased activity following immune reconstitution after alloHSCT.

Cancer vaccines

A variety of leukemia-associated antigens including tumor-specific translocation fusion products, lineage-specific antigens, genes expressed aberrantly or in higher than normal levels, histocompatibility antigens, and viral-associated antigens have been utilized in novel cancer vaccines. Studies of peptide vaccines have predominantly been conducted in the setting of myelogenous leukemias [141]. The largest study of peptide vaccination published to date represents a Phase I trial of a WT1 peptide administered with Montanide for patients with WT1-expressing hematologic malignancies

and solid tumors. Responses were observed in hematologic malignancies including reduction in leukemic blasts (2/10) and WT1 transcript levels (7/10). This approach is particularly appealing in the posttransplant setting as toxicity is expected to be minimal. Molldrem and colleagues [142] reported a case of successful PR1 vaccination for AML and posttransplant relapse. Dendritic cells and artificial antigen presenting cells can be utilized in cancer vaccines to improve the immune response to tumor-associated antigens [143]. To obviate the need to define target antigens and to avoid restriction to specific HLA alleles, autologous and allogeneic tumor cell preparations can be employed as an immunogenic source. ALL blasts can be used directly as an antigenic source (eg, apoptotic bodies or tumor lysates) or they can be modified to improve antigen presentation. Investigators at the Dana-Farber Cancer Institute have demonstrated that B-precursor ALL blasts can be rendered capable of presenting antigens by incubation with CD40 ligand and IL-4. However, a clinical trial highlighted 2 important obstacles to vaccine therapy in ALL: the propensity for rapid disease progression, and profound immune deficiency [144]. The application of such approaches to the posttransplant setting, and the development of novel adjuvants such as IL-7 and toll-like receptor agonists, offer promise. It is predicted that continued advances in tumor immunology and immunotherapy will facilitate the application of these approaches to the treatment of relapsed ALL after alloHSCT.

Conclusions and Major Research Initiatives on the Treatment of Relapsed ALL after alloHSCT

Relapsed ALL following an allogeneic transplant has a dismal prognosis, especially in adults. There is a limited role for DLI, except possibly as prevention of relapse in the setting of MRD. For those achieving a second CR, rare cures may be observed following a second allogeneic transplant, and this approach should be considered for younger individuals who relapse at least 6 to 12 months posttransplant. Clinical trials are needed to assess whether prolongation of response might be achieved using cellular manipulations, attenuated chemotherapeutic agents, and targeted approaches such as mAb-based therapies. The challenge in this area remains daunting. Prospective studies of novel therapies should be performed to ascertain whether early intervention prior to florid relapse might improve the outcome for ALL that recurs after alloHSCT.

NHL

Summary of Current Status

The term NHL encompasses a heterogeneous group of diseases that range from indolent to highly aggressive. Increasing evidence using NMA and RIC regimens and Tcell-replete grafts demonstrates significant graft-versus-lymphoma activity capable of long-term disease control for some histologic subsets of NHL. The prognosis of patients with NHL relapsing after allogeneic transplantation remains poorly defined. The tolerability and efficacy of available treatments often depend on tumor histology, conditioning intensity, whether or not T cell depletion was used, and the presence or absence of active GVHD. One goal of salvage therapy would be to achieve remission, potentially allowing GVT activity to establish disease control. In the absence of GVHD, this may be augmented by DLI. Chemotherapy treatments may be better tolerated after alloHSCT following the establishment of robust hematopoiesis from the graft. mAb therapy may provide tumor reduction and potentially augment GVT activity through enhanced antigen presentation. Last, second transplants from alternative donors following MA or RIC may be possible; however, significant TRM and generally poor disease control are frequently observed.

Factors Influencing the Outcome of Relapse after alloHSCT

A large number of factors influence the outcome of relapse post-alloHSCT and will be briefly discussed here.

NHL histology

The clinical behavior of the underlying NHL has a critical impact on the outcome of relapse post alloHSCT [145]. Patients with aggressive NHL (T cell or DLBCL or other high grade histologies) often relapse with rapid growth kinetics and are chemotherapy refractory to many agents. This leads to fewer effective treatment options and treatment is often palliative. DLI is frequently ineffective because of the tumor out growing any attempted immune-mediated GVT effects. In contrast, patients with indolent histologies (follicular, small lymphocytic, and others) may relapse with slow-growing disease and be amenable to treatment options such as DLIs, mAbs, WIS, single-agent, or multiagent chemotherapy. These histologies appear to be more frequently responsive to GVT effects. Whether this is because of intrinsic sensitivity or because of their slower tempo remains a matter of debate. Mantle cell NHL, which clinically often appears aggressive also appears to be quite sensitive to GVT effects and in general responds like the other indolent NHL's.

Impact of prior therapy

Patients with chemorefractory disease at the time of alloHSCT who subsequently relapse also have fewer

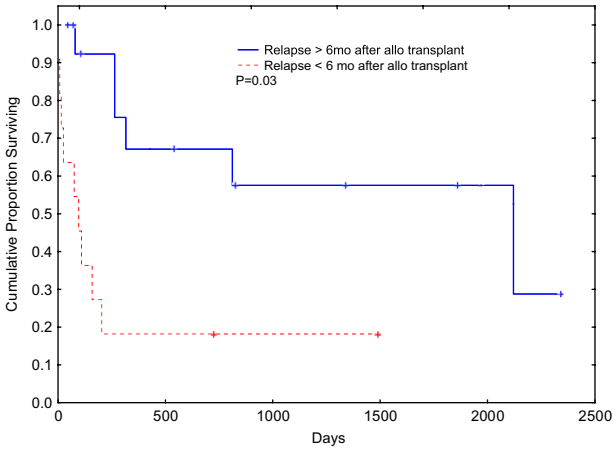

Figure 1. Survival of lymphoma patients relapsing after allogeneic transplant, by time to relapse.

good salvage options. This needs to be considered when designing subsequent treatments.

Timing of relapse

Patients who relapse early posttransplant or grow through aggressive conditioning regimens have a poor outcome (Figure 1). Treatment is often limited to palliative disease control. By contrast, those with late recurrences frequently can achieve further durable remissions. Patients who relapse early following NMA and RIC regimens have a greater number of treatment options including antibody treatments, chemotherapy, DLI, or consideration of second transplants from the same or alternate donors. In this setting, consideration of second transplant with higher risk MA conditioning may be given.

Transplant conditioning intensity

The intensity of transplant conditioning also effects the outcome and potential treatment options in patients relapsing following alloHSCT. Relapse, especially early following MA conditioning, is often associated with rapid disease progression with relatively few treatment options. DLI or nonhematopoietic toxic agents such as mAbs may be considered. However, aggressive chemotherapeutic combinations are usually poorly tolerated. Second transplants following MA conditioning have prohibitively high TRM and second transplants using RIC and HCT have been associated with poor disease control. Patients who relapse following RIC or NMA alloHSCT frequently have a greater number of options as discussed before, including consideration of second alloHSCT.

T cell-replete versus T cell-depleted allografts

Manipulation of the allogeneic graft through in vitro or in vivo T cell depletion can clearly decrease the risk of significant GVHD. However, this has been associated with a delayed onset of GVL effects and a greater risk of early relapse. Using RIC regimens, T cells are essential to induce GVT effects [146]. In patients without GVHD, DLI can be considered with variable results, often dictated by disease histology and the effects of prior therapy. Second transplants may also be considered using T cell-replete grafts. Patients receiving T cell-replete grafts have higher rates of GVHD, but with a lower incidence of relapse. Patients relapsing in the face of ongoing GVHD are generally not candidates for DLI.

Treatment Options for Relapsed NHL after alloHSCT

The management of relapse following alloHSCT is complicated by many of the factors mentioned before. The ability to treat and the effectiveness of the salvage therapy is largely dependent on tumor histology, chemotherapy sensitivity, patient comorbidities, and the presence or absence of GVHD.

WIS

Tapering or abrupt WIS is often the first attempted treatment for patients who have persistent or progressive disease early post-alloHSCT. This can only be done in the absence of significant GVHD, and for patients still on immunosuppressive drugs. To our knowledge, the first observation of clinical benefit of GVL effects in lymphoma was reported in a patient with Burkitt's lymphoma who relapsed after allogeneic transplant and obtained a durable remission upon withdrawal of cyclosporine [147]. Clinical benefits of GVL effects have since been demonstrated in practically every subtype of lymphoma (reviewed by Grigg and Ritchie) [148], but the frequency of responses and their duration have been addressed in only a few studies, summarized in Table 3. An early study described a strategy of discontinuing immunosuppression followed by DLI (if no response) in patients with relapsed or persistent disease following allogeneic transplantation [149]. Four of 9 patients (both indolent and aggressive histologies) responded to immunosuppression withdrawal alone. For patients with this option it should be considered. Risks include induction of severe GVHD requiring therapy. The bulk of evidence suggests that this is most effective in indolent and mantle cell NHL. Although patients with aggressive histologies may respond to immunosuppression withdrawal, the rapid progression of disease in this situation does not often allow GVT effects to regain control of the disease. Thus, additional treatments such as chemotherapy or radiotherapy are often added.

DLIs

Patients who are off immunosuppression and who do not have GVHD may be candidates for DLI. This has been associated with antilymphoma responses in

nearly all histologic subtypes of NHL (Table 3). Most reports are from cases presented in the context of larger clinical trial results of transplantation. Antilymphoma activity from DLI alone is more common in the indolent histologies, but is also used following salvage chemotherapy or radiotherapy and has been reported to induce long remissions in some patients with aggressive NHL histologies. Again, the risks of DLI appear to be related to the induction of GVHD and resulting complications of immunosuppressive therapy. Of note, many of the CRs to immunologic manipulations appear durable, demonstrating the ongoing benefit of GVT activity. Relatively few data exist regarding the relationship between dose of DLI and response in lymphoma.

mAbs

Patients with B cell NHL who relapse following alloHSCT are frequently treated with the anti-CD20 mAb, rituximab [150]. This treatment has minimal hematologic toxicity and is usually well tolerated. There is some in vitro data that tumor cell killing via antibody mediated pathways may induce GVT activity. In these experiments, tumor cell lines that are opsonized by antibody appear to have augmented presentation of antigens to allogeneic T cells [151]. Rituximab use in allogeneic transplantation may have beneficial effects on cGVHD as well as disease relapse (reviewed by Ratanatharathorn et al., 2009) [152]. Thus, for patients with CD20 expressing B cell lymphomas who relapse following alloHSCT, treatment with rituximab is common. Details of the frequency of success are, however, largely unknown.

Chemotherapy

For patients who are medically able to receive treatment and who have either rapidly progressive or bulky relapsed disease, additional treatments are usually required to control their disease. Au et al. [153] reported on the use of intensive chemotherapy followed by infusion of hematopoietic stem cells from the original donor to treat 5 patients who had relapsed post alloHSCT. All patients initially responded (4 CR), although only 1 was a long-term survivor. A case study reported the use of irinotecan and immunosuppression withdrawal to successfully treat aggressive NHL post alloHSCT [154]. There have been no systematic studies on the success of this approach, and examples are provided in the discussion of specific histologic subtypes of NHL.

Radiation therapy

Radiation therapy may provide control of persistent or localized relapsed disease post-alloHSCT. Anecdotal reports of prolonged remissions with or without DLI have been reported in the context of alloHSCT trials. Behre and colleagues [155] described the activity of involved field radiation therapy followed by DLI in 2 patients (diffuse large B cell lymphoma [DLBCL] and marginal zone NHL) with local relapse. Systematic evaluation of this approach has not been reported.

Other immune manipulations

Other approaches aimed at augmenting the graft-versus-lymphoma after alloHSCT have been attempted. Bashey et al. [156] used the blocking anti-CTLA-4 monoclonal antibody, ipilimumab, in a dose finding study in 29 patients with relapsed malignancy following alloHSCT. CTLA-4 blockade may increase T cell activity. Three patients with lymphoid malignancies had objective responses (HL and mantle cell NHL). A case report of the use of low dose thalidomide to induce remission in a patient with relapsed DLBCL following an MA transplant suggests that further study of these types of approaches are warranted [157]. Additional reports have suggested that treatment with IL-2 or interferon alpha post-alloHSCT relapse may induce GVHD and subsequent tumor control [158,159].

Second transplant

The use of a second alloHSCT as a salvage for a first failed transplant has not been widely studied in NHL. The use of an MA alloHSCT following prior high-dose chemotherapy and an autologous transplant has generally been poorly tolerated with a high TRM [160]. A report from the EBMT registry in 114 lymphoma patients who underwent MA alloHSCT after prior autologous transplantation demonstrated a 5 year OS of only 24% and progression-free survival (PFS) of only 5% [161]. The disease progression rate was 45% at 1 year and 70% at 5 years. Better results seem to have been observed with NMA conditioning regimens through the reduction in TRM. However, there have been no prospective studies of second alloHSCT following a failed allograft. As discussed for other diseases in other sections of this report, options include the use of a different donor to stimulate more GVT activity, including the use of mismatched, haploidentical, unrelated adult donors or cord blood cell products.

Outcomes in Specific Lymphoma Histologies (Table 4)

Indolent (follicular) NHL

Patients with the indolent histologies of NHL have generally been grouped together in most transplant studies because of the large number of histologies and the low incidence of each subtype. The largest studied histology is follicular NHL and serves as the major example of this group of NHLs. A report from the M.D. Anderson Cancer Center included 2 relapsed

patients treated with rituximab with and without DLI [162]. Both achieved CR. The Seattle transplant consortium also reported the outcome of 2 patients with relapsed follicular NHL [163]. One received rituximab and DLI and achieved a second long lasting CR (2+ years); another with progression early posttransplant achieved a long lasting CR (4+ years) following WIS. The risk of relapse appears to be greater following T cell-depleted grafts that can be offset by planned T cell add-back or DLI [164]. Morris et al. [165] reported responses in 6 of 10 patients receiving DLI for relapse following transplantation with an alemtuzumab-containing reduced-intensity regimen, and Ingram et al. [166]/reported CR in 4 of 6 patients receiving DLI for relapse following a more intensive BEAM (BCNU, etoposide, cytarabine, melphalan)-alemtuzumab regimen.

Thus, a reasonable strategy for patients with indolent NHL who relapse or have persistent disease in the absence of GVHD is to consider WIS, mAb therapy, and DLI. For patients not responding to this approach, or those who have GVHD, treatment may include antibody therapy, chemoradiotherapy with the goal of obtaining a CR, and reestablishment of GVT control. Second allogeneic transplants may be considered, but have not been widely studied.

Aggressive (diffuse large B cell) NHL

Treatment of relapse of aggressive NHL following alloHSCT is frequently difficult because of the rapidly progressive nature of the disease. In addition, many patients are chemotherapy resistant, and the majority will have failed high-dose regimens and autologous HSCT prior to being considered for alloHSCT. Disease status (partial or CR), chemotherapy sensitivity, disease burden, and patient comorbidities are all important factors having an impact on the risk of relapse in most studies. Rezvani et al. [163] from the Seattle transplant consortium reported on 6 patients relapsing after a very low-dose NMAe regimen (fludarabine [Flu] and 200 cGy total body irradiation). Two of 6 patients achieved long-term CR (34+ and 54+ months) following either a second transplant or irradiation, rituximab, and tapering of immune suppression. DLI was ineffective in 2 of the others. A report from Thomson et al. [167] in patients receiving an RIC regimen containing alemtuzumab, Flu, and melphalan included information on 5 relapsing patients with primary DLBCL. Only 1 was a long-term survivor (76+ months) following surgery, irradiation, rituximab, and DLI. Sirvent at al. [168] recently reported on the use of allogeneic transplantation for patients with aggressive DLBCL in the French transplant registry. Twenty of the 26 relapsed patients died of disease, 5 remain in CR after treatment for relapse with various combinations of chemotherapy, radiotherapy, and DLI. In a series of 44 patients from the Vancouver BC transplant group treated with MA conditioning and alloHSCT, 13 patients progressed or relapsed, and all subsequently died from disease (3 received DLI).

The outcome of DLI or WIS for aggressive NHL was reported in 15 patients with evidence of disease or relapse by day +100 post-allografting by Bishop et al. [169]. Six of 11 patients treated with WIS or DLI alone had responses, and 3 of 4 patients treated with chemotherapy and DLI responded. Six patients remained in

Table 4. GVL Induction in Non-Hodgkin's Lymphoma for Patients with Relapse After AlloHSCT

Study	Conditioning for Original tx	N	Diagnosis	Preceding Chemo/radiotherapy	CR/PR	Response	Response at Latest Follow-up: Time from Last DLI - Median (Range)
Donor Lymphocyte Infusion							
Russell 2005 [231]	T-depleted 15 Non-T-depleted 2	17	MCL (4), FL (4), CLL (4), DL (5)	9	11	11	3-year PFS 52%, 3 yr OS of 58%
Bloor 2008 [232]	T-depleted 16	17	CLL 3; MCL 3; FL6; T CL5	8	13	13	3 progressed and responded to further DLI, 3 with ongoing treatment, 10 in remission MFU 26 mo after completing DLI (12-60)
Bishop 2008 [169]	RIC	5	DL	4	3		3 ongoing CR 83+, 76+, 74+
Van Besien 1997 [149]	Myeloablative	3	DL(2), PL(1)			0	
Marks 2002 [318]	T depleted	15	FL (15)	?	8		7 ongoing CR med 31 mo after DLI (16-40)
Mandigers 2003 [319]	T depleted	7	FL (5) SL (2)	4	6		4 ongoing CR 43+, 49+, 80+, 89+mo
Withdrawal of immunosuppression							
Van Besien 1997 [149]	Myeloablative	9	DL(4)LBL (2) FL (2) PL (1)	?	3		3 ongoing CR 2+, 20+, 22 mo
Bishop 2008 [169]	RIC	13	DL	0	6		3 ongoing CR 63+, 42+, 44+

CLL indicates chronic lymphocytic leukemia; CR, complete remission; DL, diffuse large cell; DLI, donor lymphocyte infusion; FL, follicular lymphoma; MCL, mantle cell lymphoma; mo, month; RIC, reduced-intensity conditioning; OS, overall survival; PFS, progression-free survival; PL, prolymphocytic leukemia; TCL, T cell lymphoma PR, partial response; SL, small lymphocytic lymphoma; yr, year.

a complete response with long follow-up. In the earlier study by van Besien [149], immunosuppression withdrawal led to responses in 2 patients with aggressive NHL with persistent disease post-allografting.

Overall these results suggest that GVT effects may be capable of promoting long-term responses in some patients with aggressive NHL, and that treatment of relapse with aggressive salvage therapy (chemotherapy ± radiotherapy) followed by DLI may achieve long-term survival in a minority of relapsed patients.

Mantle cell NHL

There are very little data on the management of relapsed mantle cell lymphoma following transplantation, partly because relapse rates may be relatively low with T cell-replete protocols [170]. Khouri et al. [171] reported induction of a complete response following DLI in 1 of 3 patients relapsing following transplantation. Recent extension of these results has demonstrated that the few patients who relapse early can be induced to complete response by immunomanipulation (rituximab ± DLI or WIS) [172,173]. The use of T cell depletion appears to increase the risk of relapse, and requires T cell add-back or DLI in many patients [165]. This suggests that mantle cell NHL is quite sensitive to the impact of GVT effects and that those patients who experience relapse or persistent disease after alloHSCT should be treated with approaches aimed at reducing immunosuppression, mAb therapy, and consideration of DLI.

T cell lymphoma

An increasing number of studies have recently been published evaluating the role of allogeneic transplantation for the treatment of aggressive T cell malignancies. Shiratori et al. [174] reported on 15 patients with adult T cell leukemia/lymphoma treated with allogeneic transplantation. Four of 6 patients with persistent or relapsed disease responded to abrupt WIS. Small series suggest graft-versus-lymphoma activity following both RIC and MA conditioning in patients with peripheral T cell NHL, with some evidence of response to immunosuppression withdrawal for a minority of patients who progress/relapse [175,176]. Kyriakou et al. [177] analyzed the outcome of alloHSCT for patients with angioimmunoblastic T cell lymphoma reported to the EBMT. Eight of 45 patients progressed or relapsed, and 2 of 2 responded to DLI with long-lasting CR. One patient who relapsed following an NMA transplant did well following a second MA allograft.

Currently, there does appear to be evidence of graft-versus-lymphoma effects in patients with T cell lymphomas. For patients who relapse following alloHSCT, treatment with immunosuppression withdrawal, DLI, with or without chemotherapy should be considered.

Unanswered Questions in the Treatment of Relapsed NHL after alloHSCT

Most of the information on the fate of patients with NHL relapsing after allogeneic transplantation is anecdotal and all of it retrospective. Prognosis of individual patients relapsing after allogeneic transplantation is not well defined, although in cases of late recurrences, and particularly for those with indolent histologies, a number of effective interventions may exist.

Most interest has been in the investigation of DLI or modified DLI infusions, but optimal dose and schedule remain to be defined. The majority of information on DLI has been obtained in T cell-depleted transplants, and these may represent a quite different biologic stratum than those undergoing T cell-replete transplants.

The observation of responses to WIS to potent GVL effects; but similarly durable responses to often modest chemotherapeutic interventions are interesting. Many patients have persistent donor chimerism at the time of disease recurrence, and it is likely that GVL effects remain operative and amplify the benefits of chemotherapy. This suggests that aggressive approaches to obtain subsequent remissions should be considered. In addition, strategies aimed at triggering enhanced GVT activity through the use of immune modulating agents appear promising.

Proposed Major Initiatives on the Treatment of Relapsed NHL after alloHSCT

The most urgent issue in lymphoma is to develop national and international collaborations for prospective studies in more homogeneous and larger patient populations. DLI and cellular interventions are of major interest but chemotherapeutic interventions also provide tantalizing clues and may be more practical. Most patients relapsing after allogeneic transplantation are excluded from studies of novel agents because of the mere fact of having undergone the allogeneic transplant or because of low blood counts. In addition, pharmaceutical companies are reluctant to include these patients as they have a high rate of ongoing complications and toxicity related to their prior therapy. These restrictions need to be carefully considered because often unsubstantiated exclusions can deprive patients of potential major benefits and the drug industry of potential novel observations [178,179].

HL

Summary of Current Status

The high TRM (range: 43%-61%) that has been associated with alloHSCT using MA conditioning to treat HL (a.k.a. Hodgkin disease) has both restricted

the number of patients undergoing allogeneic transplantation and reduced the number of patients surviving long enough to relapse [180-183]. Therefore, despite the relatively high relapse rates in surviving patients, there is very little experience reported in managing relapsed patients following ablative transplantation. The use of NMA and RIC regimens have greatly reduced the TRM associated with allografting for HL (range: 3%-25% at 1-3 years), and disease relapse is now the most common cause for treatment failure (range: 44%-81% at 2-3 years) [145,184-188]. Therefore, there is accumulating data on treatment approaches for relapsed HL; this also provides an increasing population in whom questions concerning appropriate therapeutic strategies for relapse must be addressed. To date, however, there has been no consensus regarding these issues, often with no prescriptive guidance within prospective series.

Treatment Strategies for Relapsed HL after alloHSCT

The 2 major current strategies used to treat relapsed HL have been salvage chemoradiotherapy and/or DLI. The published literature is essentially unhelpful in providing an evidence base to guide practice, as salvage chemoradiotherapy regimens are often not reported in detail and vary considerably even within single series. Response rates likely reflect disease-related features (eg, prior therapy, chemotherapy sensitivity at transplant, time to relapse, tempo of relapse), with no current suggestion that any particular regimen is likely to affect a cure.

Experience with DLI, largely restricted to unmanipulated T cells, provides increasingly persuasive support for the existence of a graft-versus-HL effect (Table 5) [189]. Response rates have been broadly consistent between series with an overall response rate of 43% and CR rates of 29% in cases where such information was provided, although interpretation of immune responsiveness is often complicated by administration of salvage chemotherapy or radiation prior to DLI. Responses have been durable in a small but significant number of patients (approximately 25%). These figures are supported by an EBMT registry-based report, which clearly has some overlap in terms of reported patients [190]. Although specific details are more restricted, the response rate was 32%, and an additional 15% was reported to have either stable disease or brief clinical responses. In the 18 patients treated with DLI alone, the response rate was 44%. With HL, there is evidence to suggest a correlation between T cell dose and both the development of GVHD and disease response [184,191,192]. It is not clear whether there is actually a dose-response or dose-toxicity relationship or more likely a minimal threshold dose that needs to be achieved. The optimal $CD3^+$ T cell dose for DLI purposes, however, remains unclear and varies among different reports, and interpretation of individual cases is further complicated by the influences of donor source, degree of HLA-mismatching, and probably also time from transplantation on post-DLI outcomes.

Unanswered Questions on the Treatment of Relapsed HL after alloHSCT

Given the relative scarcity of reported experience, it is little surprise that most questions regarding optimal management of relapse of HL post-allograft remain unanswered. Reliable predictors of durable DLI responses would clearly be helpful in planning future exploratory interventional studies. Factors such as the influence of tumor histology on outcomes, and the role and optimal type of salvage chemoradiotherapy remain unknown. The role of newer salvage agents such as gemcitabine, alone or in combination with cellular therapies, could be addressed in prospective studies. mAbs are of potential interest as salvage agents, and these might augment DLI responses. Thus, anti-CD20 mAbs could be evaluated in $CD20^+$ nodular lymphocyte predominant cases. Relatively few of these cases are likely to be transplanted because of the relative rarity of this histological subtype and the high cure rates with conventional approaches, suggesting that multinational studies would be required to assess efficacy. Other mAbs, which are currently being assessed for therapeutic activity in relapsed HL, include anti-CD25 and anti-CD30, both of which may be more effective if used as vectors for delivery of radioconjugates or cytotoxics such as calicheamicin.

Most of the durable salvage responses reported to date have followed DLI in the setting of T cell-depleted transplants, although whether this is a critical factor remains unclear. Mixed chimerism is more common following T cell-depleted transplants. In murine models the presence of mixed chimerism of recipient derived antigen-presenting cells (APCs) has been suggested to be important in supporting GVT responses following DLI, but the issue remains contentious in the setting of clinical studies in humans. Rates of GVHD are also lower following T cell depletion [193], and it is possible that patients relapsing following T cell-depleted transplants represent a biologically different population than those relapsing following T cell-replete transplants. In the latter case, relapse might reflect a failure of alloreactivity, predicating a low chance of long-term response to DLI. In contrast, relapse following T cell depletion might reflect an untested GVT effect, particularly in those without GVHD (associating with mixed chimerism). It is also possible, however, that the differences reflect

Table 5. Donor Lymphocyte Infusions for Patients with Relapsed Hodgkin Lymphoma after alloHSCT

Study	N	Preceding Chemotherapy	CR/PR	Response Rate	Response Rate (DLI Only)	Response at Latest Follow-up: Time from Last DLI - Median (Range)
UK [184]	16	3	8/1	56%	54%	5 CR 2223 days (1851-2388)[320]
Spain [186]	11	3	3/3	55%	N/A	None ongoing
UMN [188]	2	unknown	0/2	100%	unknown	None ongoing
GITMO [187]	12*	3	3†	33%*	33%	unknown
MDACC [192]	14	11	3/3	43%	33%	1 PR 264 days
DFCI [145]	13	unknown	2/0	15%	unknown	unknown
EBMT Registry	41‡	23	13[b]	32%	44%	unknown

alloHSCT indicates allogeneic hematopoietic stem cell transplanatation; DLI, donor lymphocyte infusion; CR, complete remission; PR, partial remission.
*Twelve received DLI for relapse, 3 with prior chemotherapy who were reported as not evaluable for response.
†Overall response rate, not reported separately as CR/PR rates.
‡Sixty-four patients received DLI for relapse/progression but data follow-up data are available on only 41.

patient-specific factors (eg, disease status prior to transplantation) unrelated to transplant conditioning. All of these issues could potentially be addressed in prospective studies.

The identity of the targets relevant to immunologic responses remains unknown. As with other hematologic malignancies, establishing the identity of these targets remains an imperative for development of potentially safer adoptive cellular therapeutics and/or vaccination strategies. There is now compelling evidence that Epstein-Barr Virus (EBV) may contribute to the pathogenesis of a significant number of cases of HL [194-196]. EBV-associated HL, in contrast to classic posttransplant lymphoproliferative disorders, express a less immunogenic profile of latent phase proteins including EBNA-1, LMP-1, and LMP-2a [197,198]. Initial experience with adoptive transfer of EBV-specific T cells into patients with EBV-associated HL has provided provocative inferential evidence that some tumors might be targeted by the immune system in this way [199]. Because the cellular product was generated by culture on large B cell lymphoma cells, the majority of the EBV-specific T cells had specificities other than LMP-1 and LMP-2, but the LMP-2-specific subsets were found to expand in vivo following transfer, contribute to the memory pool, and to traffic to tumor sites, providing the impetus for subsequent attempts to optimize the generation of LMP-2-specific cellular products [200]. Overall, this experience thus hints that EBV-associated antigens could be potential immunologic targets for GVT activity in those with EBV-associated HL. However, the majority of patients receiving allogeneic transplants will fall into the young adult category, presenting mainly with nodular sclerosing histology, and with relatively few EBV-associated cases [184].

The majority of experience with DLI to date has been with unmanipulated lymphocytes. Whether selection of specific subsets (eg, $CD8^+$ T cell depletion or $CD4^+$ T cell selection), or other manipulation, including nonspecific activation and expansion through costimulation [24] offers any advantage is probably a more generic issue that should be considered outside the setting of disease-specific studies. Redirection of T cell specificity with either T cell receptors or CARs, targeting either EBV-specific antigens in the small subset of appropriate cases or perhaps CD30 is a further possibility [201].

All salvage strategies are potentially toxic. Functional imaging (eg, FDG-positron emission tomography [PET]), particularly in combined modality with computed tomography (PET-CT) analyses, may both limit inappropriate therapy for equivocal residual posttransplant masses, and allow earlier intervention prior to the development of significantly increased volume on CT scans [202]. Again, it remains unclear whether this will improve overall outcomes, but it is an area that warrants further study.

Proposed Major Initiatives on the Treatment of Relapsed HL after alloHSCT

Evidence supporting a potent allogeneic graft-versus-HL effect is increasingly compelling. Many of the issues treating relapsed HL overlap with those in other disease types, and the value of trying to enhance activity of cellular therapies across disease types needs to be explored. In HL, addressing critical issues related to timing of intervention, factors predictive of response, appropriate cell dose, and long-term outcome after relapse, will require multicenter collaborations rapidly testing new interventions and adopting uniform treatment strategies. Forming international collaborative trial groups for this purpose should be a major goal to improve outcomes for patients with relapsed HL.

CLL

Summary of Current Status

Relapse, including disease progression or recurrence, is a major cause of treatment failure after alloHSCT for CLL, affecting up to 50% of patients [203-209], or more in some subgroups [206,210]. Successful treatment of CLL relapse after allotransplant has been reported, including durable

complete responses, albeit with wide variation in approach to therapy and the frequency and duration of response [165,203,205,207,211].

There are few studies that directly address prognosis after allotransplant in individuals with CLL progression or relapse. In a study of NMA transplant for CLL nearly one-third of those who failed to achieve remission remained alive at median follow-up of 29 months (range: 11-66 months) [203]. This lengthy survival in patients with suboptimal response to allotransplant is consistent with a GVL effect.

The pattern and time of relapse suggests different mechanisms of failure. Very early progression or relapse after transplant often reflects inadequate tumor control with conditioning, with unabated disease progression prior to maturation of the donor immune system and establishment of GVT. In such cases therapeutic strategies to augment GVT may be effective. In contrast, relapse shortly after remission following conditioning may reflect inadequate GVL ability to sustain the initial response. Efficacy of efforts to boost a donor antitumor immune response would be influenced by potential reversibility of the GVL deficiency. Reduced PFS has been noted in recipients of T cell-depleted allografts [206,212] and those with longer duration of mixed hematopoietic chimerism [205,207]; both clinical scenarios are potentially addressed by WIS and DLI. Persistence of MRD after transplant and withdrawal of immune suppression are also associated with poor PFS, and may indicate patients with a qualitative GVT defect that would be less likely to respond to immunomodulation [213].

Relapse of CLL can be seen many months or years after allotransplant [203]. Such late relapse may reflect loss of established GVT control, plausibly because of clonal evolution of CLL, and "immune escape." Consistent with this are observations that tumor behavior is altered in relapse after transplant, noted in CLL and other malignancies [17,214-216]. Additionally, it is worth considering whether late recurrence might represent de novo CLL of donor origin. Donor-derived CLL presenting as a late relapse has been reported, as have donors with a relatively common precursor state, monoclonal B cell lymphocytosis (MBL) [217,218]. MBL clones can be detected in up to 18% of unaffected members of "CLL families" and more than 5% of the general population over 65 years [219-223]. Thus, transfer and subsequent development of donor-derived CLL is plausible after transplantation with either related or unrelated donors. Intuitively, whether because of clonal evolution with development of "GVL resistance" or transfer of a donor clone, late relapse may be less responsive to immune manipulations, including WIS and DLI. Paradoxically, if late relapse indicates a new or transformed clone, it may be more sensitive to cytotoxic therapy than prior tumor behavior would otherwise indicate.

Treatment Options for Relapsed CLL after alloHSCT

DLI

There is significant circumstantial evidence for GVT in CLL that includes observations of lower relapse rates after allogeneic versus autologous transplantation [224], decreased relapse in patients who develop cGVHD [224,225], increased relapse in recipients of T cell-depleted allografts [226] with subsequent response to delayed DLI [224], and delayed responses after NMA transplantation [179,226]. Therefore, in the absence of significant GVHD, initial treatment for CLL progression or relapse is often with withdrawal of immune suppression and DLI, maneuvers that have been reported to induce durable complete responses [205,226,227].

Broad interpretation of the DLI literature for CLL response is limited by heterogeneity of factors that influence efficacy, such as disease status, donor chimerism, and indication for DLI (mixed chimerism with persistent disease, disease progression with full donor chimerism, etc.), and of DLI products (subset enrichment, cell dose, etc.) [4,54,104,228-230]. Widely disparate results likely reflect this heterogeneity. In some series, efficacy of DLI for relapsed lymphoid malignancy was as high as 75% in indolent tumors, including CLL [104,231,232]. Responses were far less frequent in others (Table 6). For example, Khouri et al. [205] reported on 10 patients with CLL treated with NMA allotransplant and planned WIS followed by DLI for persistent disease at day 100. Three responded to WIS without DLI. Six of 7 patients who received DLI responded; 8 of 9 responders had also received rituximab. In contrast, in a report on 64 patients treated for chemotherapy-refractory CLL with NMA alloHSCT [211], only 1 of 6 patients with CLL progression responded to DLI (5 of whom also received chemotherapy) [203].

The importance of disease status on DLI efficacy is illustrated by use of planned DLI for treatment of persistent or progressive disease after T cell-depleted allotransplant. Hoogendoorn et al. [212] reported on 12 patients with advanced CLL treated with RIC and ex vivo alemtuzumab-depleted allografts; at 6 months, those with persistent disease or mixed chimerism were given DLI. Additional DLI at escalating doses were permitted in the absence of GVHD. Although none of the 7 patients with progressive disease responded to DLI, 4 patients with DLI for persistent disease achieved durable CR. In a similar approach, Delgado et al. [204] reported on 41 patients with CLL treated with RIC allotransplant, with systemic alemtuzumab

Table 6. Reported Outcomes for DLI in CLL Progression after AlloHSCT

Reference	N (CLL/Total)	DLI Response CR/PR/PD	Adjunctive Rx CR/PR/PD	Notes
Russell 2005 [231]	4/17	3/0/0	0/–/–	4th patient likely CR; not evaluable for response because of aplasia after DLI, required 2nd SCT→DCR. All developed GVHD
Ritgen 2004 [321]	3	2/0/1	0/–/0	9 NST for CLL/Unmutated V_H 5 cGVHD → MRD^{neg} (no DLI) 3 DLI for MRD
Gribben 2005 [322]	7/7	6/0/1	0/–/0	Myeloablative, TCD-SCT CD8-Depleted DLI. [37] GVHD 50%
Marks 2002 [318]	8/81	0/1/7	–/0/0	
Sorror 2005 [211]	6	0/1/5	–/0/4	PR → GVHD → death 4 received various CLL treatments prior to DLI
Khouri 2004 [205]	7/7	4/2/1	3/2/0	No relapse at median 10 months Adjuvant rituximab in 5/7 3 WIS → GVHD → CR (no DLI)
Delgado 2006 [204]	14	5/1/8	1/0/5	2 GVHD deaths in responders

ND indicates no data; WIS, withdrawal of immune suppression; CR, complete remission; DCR, durable complete response; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; OS, overall survival; EFS, event-free survival; MRD, MRD, minimal residual disease; CLL, chronic lymphocytic leukemia.

for T cell depletion in vivo. At 6 months, patients with mixed chimerism or persistent disease were treated with escalating doses of DLI. Responses were seen in 1 of 3 patients who received DLI for persistent disease and in 3 of 11 patients with progressive disease.

Although it is difficult to draw definite conclusions from these and other studies, they clearly indicate the biologic potential of GVL effects in CLL. Further studies are needed to determine the optimal indication, timing, and dose of DLI, to identify those most likely to benefit, and to define criteria for addition of adjunctive CLL treatment. For example, MRD monitoring might be useful as a means of identifying optimal timing and patient selection. Ritgen et al. [213] have described 5 distinct patterns of MRD kinetics after allotransplant; assessing DLI responses and toxicity with respect to these patterns of MRD kinetics may permit prediction of CLL sensitivity to GVL versus "secondary graft-versus-CLL resistance," with potential implications for DLI failure.

Augmented DLI

Separation of GVL activity from GVHD, the "Holy Grail" of allotransplant research, has influenced efforts to improve outcomes after DLI for CLL. In some cases, CLL cells may inhibit a potential cell-mediated antitumor effect. Multiple immune defects have been described in untreated individuals with CLL and may contribute to GVL failure of the transplanted immune system. Imbalances in T cell subsets, diminished T cell signaling response, suppressed NK cell function, and maturation and functional defects of APCs are among the potential culprits that have been described [233]. Porter and colleagues [122] hypothesized that inadequate costimulatory signaling may contribute to ineffective GVL activity and that providing CD3 and CD28 costimulation of donor lymphocytes ex vivo would produce an activated T cell product (aDLI) capable of initiating a GVL response. A phase I dose-escalation trial demonstrated the feasibility and safety of a DLI following unmanipulated DLI in patients with relapsed disease after allogeneic transplantation, including a patient with CLL who remains in CR for more than 5 years [234].

Another approach under investigation is directing donor T cells to cell surface antigens found on malignant cells. Bi20 (FBTA05) is an engineered antibody with bi-specificity for CD20 and CD3 and trifunctional recruitment of B, T, and $Fc\gamma RI^+$ accessory cells, hypothesizing that colocalization of tumor and T cells would improve GVL responses. Buhmann and colleagues [235] tested Bi20 in combination with DLI or stem cell-mobilized donor PB mononuclear cells (mobilized DLI) in previously allotransplanted patients. This trial included 3 subjects with treatment-refractory, p53-mutated CLL. All showed a transient clinical response with improvement in B symptoms, lymphadenopathy, splenomegaly, and clearing of leukemic cells from the blood with increasing doses of Bi20, but progressed following discontinuation of Bi20-DLI. Another strategy is genetic engineering of donor T cells to express CARs to B cell antigens (eg, CD19) along with costimulatory signaling molecules. Early reports are promising in preclinical studies [236] and in treatment of B cell malignancies in the autologous setting. Clinical trials assessing the safety and efficacy of CD19-CAR-transduced donor T cell therapy for allotransplant relapse are underway. Serious inflammatory-mediated toxicities after CAR-transduced T cell transfer have been reported [237,238], which may be target- and/or construct-dependent, and/or result from immune-depleting preparative regimens used in autologous adoptive cell therapies. Concern that inflammatory responses could result in GVHD toxicity in the allogeneic setting has led Cooper and colleagues [239] to develop an approach to alloanergize CAR-transduced donor T cells.

Dendritic cell (DC) vaccines

DC vaccine approaches are being explored for CLL, with clinical trials showing promise using apoptotic whole-cell autologous DC preparations [240,241]. Effective vaccines may be a useful adjunct

to DLI [242]. Whole-cell preparations may have advantages in the allogeneic setting, allowing the potential for GVL activity against multiple cellular proteins. Alternatively, antigen-specific DC vaccines might be useful in patients with relapse and GVHD, more effectively targeting an augmented GVL response. Survivin is a "universal tumor antigen," found on many tumor types, including CLL, as well as normal hematopoietic tissue. It is an immunogenic protein, and an extensively studied vaccine candidate [243]. Peptide and DC vaccines using survivin alone or in combination with other TAA are in development [244] as are survivin-specific CTLs [245].

Chemotherapy approaches

Data are limited regarding the use of chemotherapy for CLL relapse after alloHSCT. Many individuals with CLL undergo allotransplant upon identification of Flu-refractory disease, which predicts poor response to salvage chemotherapy [246] as well as to relapse after allogeneic transplantation [205]. However, response to salvage regimens for relapsed CLL after allotransplant may be different, because *ATM* and *TP53* mutations, strongly associated with resistance to Flu, alkylating agents and rituximab-based regimens [247-250], do not predict for treatment failure after allotransplantation [203,207,251,252]. It is interesting to speculate whether clonal evolution of CLL in response to GVL explains the anecdotal experience of restored chemotherapy sensitivity after allotransplant.

The only published reports on chemotherapy salvage regimens for relapsed CLL after alloHSCT are case series describing regimens given for cytoreduction prior to of DLI therapy. Sorror and colleagues [211] reported no durable responses in 4 individuals with CLL relapse using cytoreductive chemotherapy (Flu/rituximab, CHOP, pentostatin/vincristine/prednisone), and DLI. A later report describes 5 individuals with CLL relapse who, after treatment with mAbs combined with chemotherapy, were among a group of patients who survived between 1 and 5 years after treatment [203]. Delgado and colleagues [204] reported on 6 patients with CLL relapse treated with various regimens prior to DLI. There was 1 durable complete response to CHOP, and 2 others had prolonged survival.

The effects of the specific agent or agents on engraftment, GVT and GVHD need to be factored in to choice of CLL therapy. Purine analogs, including Flu, are active in Flu-refractory disease when used in combination with alkylating agents, particularly cyclophosphamide (Cy); the combination has efficacy in bulky or alemtuzumab-refractory disease [253,254]. But these regimens are myelosuppressive and result in profound lymphocyte depletion, so it should prompt consideration of donor stem-cell support. The addition of rituximab to Flu and Cy (FCR) improves response rates and time to progression in the refractory setting, although complete responses are uncommon (overall response rate = 59%; complete response rate = 5%) [255,256]. Pentostatin may be less myelosuppressive than Flu, so may be preferred for use after allotransplant; it also has activity in combination with Cy for refractory CLL [257]. Here, too, the addition of rituximab improves efficacy, with small, Phase II studies demonstrating response rates that compare favorably with FCR [258].

Another treatment option for relapsed CLL is bendamustine. Designed to have both alkylator and purine antimetabolite properties, and only partial cross-resistance with other alkylating agents in vitro [259], bendamustine has activity against quiescent and dividing cells, with activity unaffected by p53 or ZAP-70 status [260]. However, increased hematologic toxicity might be anticipated in treating CLL relapse after allotransplant.

Immunotherapeutic agents

Some mAbs and immunomodulatory drugs have activity against high-risk CLL. These agents may work synergistically with standard salvage chemotherapy regimens, with potential strengths and pitfalls in their use after allotransplant. Alemtuzumab is an effective treatment of relapsed and refractory CLL. Few patients have received alemtuzumab for treatment of relapse after allotransplant, with no durable responses reported [204]. Profound and long-lasting B and T cell depletion, significant BM suppression, and risk of serious infection limit its use in the post-alloHSCT setting outside of the context of a clinical trial and/or second transplant.

Rituximab treatment of CLL relapse is an appealing therapeutic option, as it is a commonly used targeted agent, is familiar to transplant physicians, and has a manageable toxicity profile. In treatment of relapse after allotransplant, "single-agent" rituximab may, in fact, work synergistically with an allogeneic immune response, not only targeting residual $CD20^+$ CLL cells for ADCC-mediated cell death, but also supporting donor cell-mediated antitumor cytotoxicity through immunomodulatory effects (eg, effect of B cell depletion on homeostatic cytokine levels). Combining rituximab with DLI is a common and rational, albeit inadequately studied strategy for treating relapsed CLL, with direct CLL targeting and, potentially, reduction of the significant risk of GVHD, thereby minimizing the requirement for systemic immune suppressive therapy [261].

Immunomodulatory drugs, such as lenalidomide, may also have a role in treatment of relapse after transplantation. This small molecule has a wide range of immunomodulatory effects, including T cell activation through CD28, enhancement of NK cell cytotoxicity,

increased expression of IL-2 and interferon-γ, as well as direct pro-apoptotic effects [262]. It is clinically active in Flu-refractory CLL with overall response rates of 30% achieved in patients with 11q- or 17p-deletions [263,264]. However, the drug should be used cautiously as life-threatening tumor flare reaction and tumor lysis syndrome have been reported [265], and wide-ranging immunomodulatory effects may have unanticipated, negative consequences after allotransplant.

Investigational targeted agents

Ofatumumab is a humanized anti-CD20 mAb that binds to a different epitope than rituximab. It has increased complement-dependent cytotoxicity against B cells, redistributes CD20 into similar lipid raft regions with a lower dissociation rate, and, in Phase I/II studies, has shown impressive single-agent activity in relapsed/refractory CLL [266,267]. Clinical investigation in the treatment of allotransplant relapse, as a single agent or combined with DLI, is warranted.

CD22 is often expressed on the surface of CLL cells, even when CD20 is lost after mAb therapy. CAT-8015 (HA22) is a recombinant anti-CD22 immunotoxin, with murine antihuman CD22 fused to a truncated form of pseudomonas exotoxin, PE38. It is in clinical evaluation for CD22-positive lymphoid malignancies, including a pediatric study permitting allotransplant recipients with tumor relapse (eg, ALL, NHL). If activity is demonstrated in refractory CLL, investigation in relapse after allotransplant would be valuable [137,268].

The inhibitor of apoptosis (IAP) family of proteins are being actively investigated in cancer therapy. Antisense and small molecule therapeutics indirectly inhibit IAP function via reduced mRNA expression of the target protein. In a phase III trial for relapsed/refractory CLL, the addition of oblimersen, the antisense Bcl-2, to Flu and Cy resulted in a higher complete response rate (17% versus 7%), a longer response duration [269], but is unfortunately no longer under development. Survivin is another IAP, and may be a more effective target than other IAP [270]. In addition to antiapoptotic functions, it is a nodal protein linking multiple pathways of cellular homeostasis (with regulatory activity in cell division, nonapoptotic cell death, stress response, and tumor angiogenesis) [271]. YM155, a small molecule suppressor of survivin expression, is in clinical trials for CLL; whether it could increase CLL susceptibility to DLI is worthy of investigation. Lumiliximab is a chimeric macaque-human anti-CD23 mAb. CD23 is a low-affinity IgE receptor that is highly expressed on CLL cells. The antibody primarily functions through induction of apoptosis of CLL cells, through down-regulation of BCL-2, BCL-X_L, and XIAP, and through activation of pro-apoptotic protein BAX and release of cytochrome C [272]. Addition of the antibody to the FCR regimen appears to improve response rates in relapsed/refractory CLL [273], investigation in conjunction with DLI for relapse after alloHSCT may be fruitful.

Flavopiridol, an investigational cyclin-dependent kinase inhibitor, has shown promise against refractory CLL in Phase I/II studies. Flavopiridol induces apoptosis through a p53-independent pathway, and has been shown to decrease expression of anti-apoptotic proteins found in CLL, for example, MCL-1 [274], and XIAP [275]. In Phase II study for relapsed CLL, 53% responded, including more than half of subjects with 11q or 17p deletions, regardless of nodal size; median duration of response was 10-12 months. Serious adverse events included severe tumor lysis syndrome and IL-6-mediated cytokine release syndrome (CRS), manifestations included fever, rash, and secretory diarrhea. Although CRS was abrogated by the addition of prophylactic dexamethasone, clinical features would be difficult to distinguish from aGVHD [276,277].

Recommended Treatment Approaches for Relapsed CLL after alloHSCT

In the absence of evidence-based therapeutic options, the following approach takes into account the behavior of CLL progression, status of donor engraftment, and risk of GVHD. As a first step, it is necessary to define the behavior of the CLL in the context of donor engraftment, immune suppression, and GVHD. Figure 2 shows a conceptual framework for treatment decisions that can be used for relapsed CLL as well as other malignancies, and uses tumor behavior and allograft function to determine whether the therapeutic goal is augmentation of the donor immune response, cytoreductive tumor control, or both. As virtually all established treatments for refractory CLL will also result in lymphocyte depletion, there may be the additional effect of providing in vivo cytokine (eg, IL-7 and IL-15) support for donor lymphocyte activation and expansion. General approaches may include the following.

Early relapse

Evaluation should include assessment of BM and PB chimerism, and a complete staging evaluation to determine sites of disease. The following considerations influence specific treatment strategies.

CLL progression following an initial response to the preparative regimen indicates inadequate GVT, potentially because of persistent mixed chimerism, a weak or blunted GVT, or lack of GVT. Treatment goals are to control tumor and boost GVT, and depend on pace of progression. Absent aGVHD, for indolent progression it would be reasonable to try

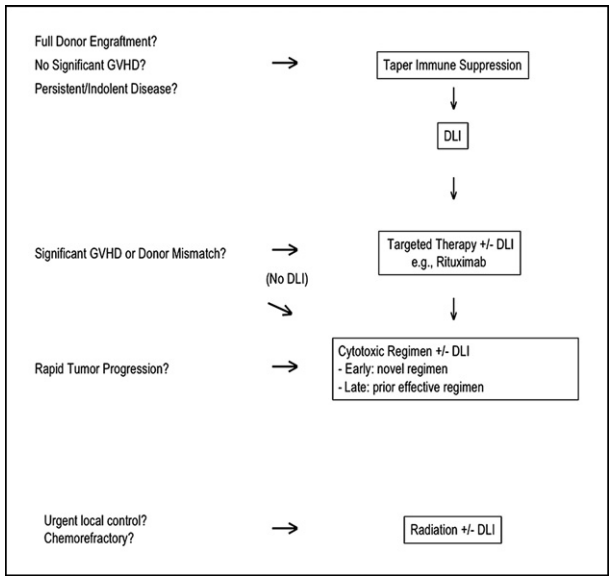

Figure 2. Conceptual framework for treatment decisions for patients with relapsed CLL after alloHSCT.

withdrawal of immune suppression and DLI, escalating to the addition of a targeted agent (eg, rituximab) or retrial of the last active chemotherapy regimen for more rapidly progressing disease.

In chemotherapy-refractory CLL, with progression through the preparative regimen, it may not be possible to determine whether there is any GVT activity likely, and poses an extremely difficult treatment challenge. If an untried regimen is available, it would be reasonable to consider a trial with mobilized DLI support.

In the case of CLL persistence upon establishment of full donor chimerism, subclinical GVT may be present. Absent clear progression, it would be reasonable to consider watchful waiting, employing WIS and/or DLI if no response is observed at subsequent restaging, with addition of rituximab if there is evidence of indolent progression.

In CLL progression following treatment of GVHD, a blunted GVT response can be suspected. There are no established treatment approaches that permit GVT in this setting, and treatment goals are to control tumor with minimal additional toxicity. Reasonable alternatives include local irradiation, rituximab, and single-agent therapy, depending on sites of disease. The safety of intensive regimens, vis-à-vis GVHD and allograft function, has not been established, nor is there data to suggest long-term efficacy. Alemtuzumab-containing salvage therapy cannot be recommended outside of a clinical trial, given risk of potentially irreversible immune suppression, particularly in the setting of active GVHD and contraindication to DLI. Consideration for investigational therapies should always be considered.

Late relapse

Evaluation should include assessment of BM and PB chimerism, a complete staging evaluation to determine sites of disease, and a biopsy of active disease to determine histology and/or chimerism, that is, to rule out transformation, posttransplant lymphoproliferative disease, donor CLL (consider in very late BM relapse and/or family history of lymphoid malignancies). The following considerations influence specific treatment strategies:

Late nodal relapse in the absence of BM involvement may reflect transformation to more aggressive tumor. Treatment goals are to control tumor and boost allograft function, and consideration of a highly active salvage regimen with stem-cell mobilized DLI support is reasonable.

Recurrence of CLL may reflect waning GVT potency, plausible causes include CLL immune escape, with outgrowth of allo-resistant clones, and/or "burn-out" of the donor immune response. Treatment goals are to reestablish disease sensitivity and/or potency of GVT effects. In an indolent recurrence, it would be reasonable to consider a trial of immune suppression withdrawal, if possible, followed by a DLI with or without rituximab. In more aggressive recurrences, it would be reasonable to consider the use of salvage chemotherapy with DLI, even if the patient has been refractory in the past. The recurrent CLL may have lost resistance, and the lymphoid depleting effects of the regimen may support subsequent reestablishment of GVT.

Very late recurrence of CLL and/or late recurrence in BM only should prompt consideration of a donor-derived CLL, particularly in sibling-donor allograft recipients with a family history of lymphoid malignancies. Given the increasing prevalence of MBL with age greater than 50 years, even absent a family history, very late BM relapse in patients whose donor was more than 50 years old could represent a transferred CLL. It would be reasonable to manage donor-derived CLL according to standard guidelines for de novo CLL, with treatment goals determined by disease stage and behavior. Donor lymphocytes or other GVT-based strategies to strengthen GVT would not have a role in treatment.

Late CLL progression in the context of cGVHD treatment may reflect blunted GVT activity. Treatment goals are to control tumor with minimal additional toxicity. Reasonable alternatives include local irradiation, and low-intensity chemotherapy, depending on sites of disease. Consideration of the addition of rituximab is warranted, as there are preliminary data to suggest that its use may help control cGVHD [278,279]. Investigational strategies to increase the tumor specificity of the donor immune response would be attractive clinical trials. As with early

progression, whereas treatment with alemtuzumab-containing regimens is theoretically attractive, with potential for controlling CLL and GVHD, the potential for irreversible immunodeficiency in this patient population is significant.

Conclusions on the Treatment of Relapsed CLL after alloHSCT

There is no single standard of care for management of CLL relapse after alloHSCT. Given the complexity and heterogeneity of patients, donors, and allograft function, treatment approaches will need to be individualized, targeting specific relapse factors. Although standard regimens may have a role in DLI treatment of CLL relapse, even in previously refractory patients, clinical trials are needed to determine the safety and efficacy of standard treatment regimens, with and without additional donor lymphocytes, as both individual patient responses and population profiles may be quite different after allotransplant. Investigation of novel approaches are needed as well, and allotransplant recipients with persistent CLL should be included in trials assessing efficacy of approved or investigational agents in which immunomodulatory effects may boost GVT responses.

MM

Summary of Current Status

Compared with other treatment modalities in multiple myeloma, alloHSCT induces the highest rate of clinical complete and molecular remission [280,281]; however, this results in long-term freedom from disease in only about 30% to 40% of the patients [280-284]. The introduction of RIC regimens has lowered the TRM [285], and allows for more patients to undergo transplantation, but the relapse rate is considerably high exceeding nearly 50% at 3 years. The incidence of relapse in patients with MM after alloHSCT is higher than in other hematologic diseases. Some investigators report a high incidence of extramedullary relapse, which does not influence efficacy of salvage therapy [286,287]. However, the majority of patients do not achieve CR (defined as negative immunofixation) after allografting. Therefore, in this section treatment options are discussed for both relapse from CR as well as for persistent and progressive disease in non-CR patients after alloHSCT.

Treatment Options for Relapsed Multiple Myeloma after alloHSCT (Table 7)

DLI

In MM, most reports using DLI are for relapse [288-294], and there are few reports about prophylactic DLI [295-297]. Response rates between 40% and 67% are reported, but in some studies additional chemotherapy or interferon-α were given [290,291]. Not all responses were durable. Nearly 30% of the patients achieved CR, and response to DLI was correlated with occurrence and severity of GVHD. The incidence of aGVHD ranges between 52% and 56% and of cGVHD between 26% and 44%.

DLI given after RIC in a dose-escalating fashion resulted in less aGVHD and cGVHD [295,297]. In a survey of 8 European transplant centers, the effect of DLI after RIC was investigated in patients with relapsed (n = 48) or persistent disease (n = 15) after alloHSCT. Nineteen percent of the patients achieved PR, and 19% achieved CR [298]. The median time to progression was 7 months for patients with PR and 28 months for patients who achieved CR.

Selected T cell infusions

To reduce the risk of GVHD after DLI, $CD8^+$ T cells can be depleted either by positive $CD4^+$ T cell enrichment or by $CD8^+$ T cell depletion. $CD8^+$ T cell depleted DLI were investigated in 14 patients in CR (n = 3) or persistent disease (n = 11) after M T cell-depleted alloHSCT as a method to induce a graft-versus-myeloma effect, which may have been compromised by the T cell depletion at time of transplant. Six of the 10 patients with measurable disease experienced CR, but these remissions were not durable in the majority of patients. aGVHD (grade II—IV) was seen in 50% of the patients [296], which was similar to reports after unmodified DLI. More recently depletion of alloreactive T cells is under investigation, but no data for this approach as DLI for relapsed myeloma patients are available [299].

Table 7. Salvage Therapies after Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Multiple Myeloma

	ORR	CR	Overall Survival
1. Donor lymphocyte infusion (DLI)	40%-67%	19%-30%	med. 23-23.6 mo
2. CD8-depleted DLI	71%	43%	2 year: 55%
3. Thalidomide	29%-83%	0%-22%	3 year: 25%
4. Lenalidomide	66%	8%-23%	med. 19.9 mo
5. Bortezomib	80%-100%	29%-30%	3 year: 50%
7. Thalidomide plus DLI	67%	22%	2 year: 100%
9. HA-1 specific T cells		1/1 CR	

ORR indicates overall response rate; CR, complete remission; n.e., not evaluable.

Combination of DLI plus novel agents

Because the immunomodulatory drugs (IMIDs) thalidomide and lenalidomide induce enhanced T cell activation and NK-cell activation [300], combination therapy could be a useful track to enhance the graft-versus-myeloma effect after alloHSCT. To enhance the antimyeloma effect of DLI after allografting, low-dose thalidomide (100 mg) in combination with DLI was investigated. The overall response rate was 67%, with 22% CR. Interestingly, no grade II = IV aGVHD was seen, and only a small minority developed limited cGVHD [301].

Novel agents

Because of the aforementioned immunologic effect of thalidomide and lenalidomide on T and NK cells, these agents might be of special interest in patients with MM after alloHSCT. Thalidomide as single agent at a median dose of 200 mg (range: 50-600 mg) has been investigated in 31 patients as salvage therapy after progression following alloHSCT. Because of toxicity the drug was been discontinued in 19% of the patients. Twenty-nine percent of the patients achieved an objective response (PR and very good partial remission [VGPR]). In 5 patients mild GVHD developed after thalidomide treatment [302].

Lenalidomide has been investigated in 24 heavily pretreated myeloma patients with relapse after alloHSCT at a dose of 15 or 25 mg. Major side effects were leukopenia (grade 3-4: 25%), and thrombocytopenia (grade 3: 17%). Nonhematologic toxicity consisted of muscle cramps (n = 9), fatigue (n = 5), and constipation (n = 2). Mild grade I-II GVHD was seen in 3 patients. Response was achieved in 66% of patients (CR = 8%, VGPR = 8%, PR = 50%, and SD = 13%). The median time to progression and survival was 9.7 and 19.9 months, respectively. Immune monitoring after lenalidomide showed significant increase of activated NK ($NKp44^+$) and T ($HLA\text{-}DR^+$) cells as well as Treg cells ($CD4^+$, $CD25^+$, $CD127^{lo}$), supporting an immunomodulating antimyeloma effect of lenalidomide [303]. A Dutch study reported on the activity of lenalidomide after allografting [304]. This study showed high activity of lenalidomide with and without dexamethasone in patients with MM after failure to alloHSCT including a CR rate of 23%. In this study, an increase of Treg cells after lenalidomide treatment was observed, but also 5 of 13 patients developed aGVHD between 2 and 13 days after start of treatment. However, patients treated with lenalidomide in combination with dexamethasone did not develop any GVHD.

Other drugs such as the proteasome-inhibitor bortezomib might have a major role after alloHSCT because it was shown in preclinical models that proteasome inhibition inhibits T cell proliferation and aGVHD by depleting alloreactive T cells and retaining the GVT effect [305-307]. Bortezomib as salvage therapy in myeloma patients who relapsed after reduced-intensity alloHSCT has been investigated in 37 patients. Major side effects were grade 1-2 peripheral neuropathy (35%), mild thrombocytopenia (24%), and fatigue (19%), whereas there was no worsening of GVHD symptoms. Seventy-three percent of the patients achieved an objective response and the estimate of OS was 65% at 18 months, which was significantly higher ($P = .002$) in patients achieving an objective response [308].

In a further study, a median of 2 cycles of bortezomib was investigated as posttransplant treatment to enhance remission status. Grade III/IV toxicity was seen for thrombocytopenia (50%), leukopenia (17%), or neuropathy (17%), which was more often seen in patients treated concomitantly with cyclosporine ($P = .06$). The median circulating $CD3^+$ T cells decreased during treatment from 550 μL to 438 μL ($P = .03$), resulting in herpes zoster infection in 3 patients (17%). The regimen was very effective inducing complete or PR in 30% and 50%, respectively [309].

Overall, the novel agents are very effective as salvage therapy and a European survey showed that even in patients refractory to DLI, salvage treatment with thalidomide or bortezomib can induce CR or PR in 83% of the cases [310]. Furthermore, it seems that these new drugs with immunomodulatory properties can induce graft-versus-myeloma effect without increasing risk of GVHD.

Second allogeneic transplant

A second allogeneic transplantation as treatment for relapsing patients has been described for myelogenous malignancies, but no data have been reported for myeloma patients.

Other investigational options-targeted therapy

Interferon-α alone induced a CR without GVHD in 4 of 5 patients after allograft, but because interferon-α was given rather early at a median of 126 days after transplantation, the contribution of interferon to achieve CR remains unclear [311]. The major issue for further improvement of immunologically based strategies post-allotransplant lies in the separation of the graft-versus-myeloma effect from the graft-versus-host reaction, which would allow a more specific tumor targeting without or with a lesser risk of GVHD. Potential candidate targets for a more specific T cell response are miHags such as HA-1. More recently, HA-1-specific T cells could be generated and induced CR in a patient with relapsed MM after alloHSCT [9]. A potential target for tumor-specific donor-T cell response is the myeloma-specific idiotypic determinant of immunoglobulin-variable region, which has been used to immunize the donor prior to alloHSCT in

order to transplant a myeloma-specific T cell response [312]. Two of 5 patients remained disease free after allografting for 7 and 8 years, respectively, whereas 1 patient died of renal failure 5 years after transplantation. In all patients immunoglobulin-specific T cell response was seen and persisted for 18 months [313]. Another potential target is cancer-testis (CT)-antigens, especially MAGEC2 or MAGEA3, which are expressed in more than 55% of myeloma cells [314]. A donor vaccination with MAGEA3 induced T cell response in the donor as well as in the recipient after alloHSCT [315]. However, frequent antibody responses against CT antigen were observed after allografting without donor vaccination [315]. This antibody response correlated with specific $CD4^+$ and $CD8^+$ T cell response. This response was neither detectable in pretransplantation samples in the patients nor in the donors, suggesting that CT antigens might represent a natural target for graft-versus-myeloma effects. KIR-ligand-donor/recipient-mismatch transplantation may be protective against relapse, suggesting a potential role of alloreactive NK-cells after allografting to treat relapse [316]. Other potential targets have been identified by analyzing humoral responses in patients who achieve CRs after DLI. One B cell antigen was B cell maturation antigen (BCMA), a transmembrane receptor of the tumor necrosis factor superfamily. In vitro analysis demonstrated serum was able to induce complement-mediated lysis and antibody-dependent cellular cytotoxicity of transfected cells as well as primary myeloma cells expressing BCMA. Perhaps either antibodies with specificity to targets such as this, or antibodies inducing stronger responses in vivo to these targets or similar targets may enhance the response to DLI [317].

Future Directions for the Treatment of Relapsed MM after alloHSCT

Although the data demonstrate the presence of a strong graft-versus-myeloma effect, many challenges remain in addressing relapse after transplant in patients with myeloma. The low complete response rate and durability of responses after DLI suggest that our current approaches are not sufficient. However, in some patients who experienced a CR after DLI, long-term survival can be achieved. Because most of the responses are associated with occurrence of GVHD, major efforts should be made to separate graft-versus-myeloma from GVHD. Efforts to enhance responses may include earlier use of DLI as well as perhaps sequential DLI to maintain remissions in patients who respond without developing GVHD. More recently available novel agents induce similar response and survival rates after alloHSCT than after relapse to an autograft or to conventional therapies. Because of the immune-modulating properties of the novel agents, combination with DLI is an attractive concept, and doses and timing of both DLI and the novel agents need to be explored. Finally, targeted cellular therapies may improve responses as well as limit toxicity.

SUMMARY

When considering treatment options for patients who relapse after alloHSCT, several issues transcend disease specificity. Other than the successes documented years ago using DLI for relapsed CML, there is remarkably limited data on the use of DLI and non-DLI therapies in other clinical situations. The lack of data regarding treatment options and outcomes results from many factors. Patients who relapse after transplant are an extremely heterogeneous group. Some may be quite ill and may still be suffering from morbidities of transplant. Some may have had, or still have, active GVHD and may or may not be on immune suppression. Furthermore, the biology and responsiveness of diseases that relapse rapidly after transplant are likely very different than diseases that relapse later after transplant. Treatment options and responses are likely to be very different in these different patient groups. This heterogeneity leads to enormous selection bias that can be compounded by reporting bias where only the best and most promising results are disseminated. Treatment options are also affected by prior therapies and the previous failed transplant. HLA-identical sibling transplants usually have access to their previous donor. Cord blood recipients never do, and DLI from an unrelated donor may be delayed and may or may not have higher risks. Therefore, there is obviously no single standard approach to treating relapse after alloHSCT.

It is unknown whether GVT induction for relapse is a generalized allogeneic effect or has disease specific targets. It is also unknown whether GVT induction can be effectively separated from GVHD. It is still unclear whether there is a relationship between cell dose and toxicity with DLI, and it is not known whether there is a dose-response effect, or rather a minimal threshold dose that must be achieved before antitumor responses occur. Whether these dose effects might be disease or disease-state specific is also unanswered.

There are clinical situations where responses to DLI consistently have been poor and maneuvers to improve GVT induction need to be tested rapidly and comprehensively. It is imperative to study and understand mechanisms leading to relapse to develop and use the proper strategy for a specific disease or specific patient. For instance, in some cases, relapse of acute leukemia or MDS after haploidentical alloHSCT has been associated with loss of recipient-specific HLA expression. In these cases, conventional DLI would not be expected to be effective, assuming HLA class I and II antigens are necessary targets for GVT

induction. In cases where relapses may be associated with ineffective T cell activation, either because of tumor suppression, lack of costimulatory molecules, or T cell-associated defects, ex vivo activation of donor T cells prior to infusion may restore GVT activity. There are also clear instances where second transplant is a reasonable and effective option, and considerations of the proper disease and patient population, conditioning regimen intensity, and donor choice for second alloHSCT need to be revisited.

Alternatives to cellular therapies to treat relapse should not be neglected. It has been difficult to use and study conventional and novel agents because the dosing regimens and toxicity profiles may be very different in posttransplant patients. Outcomes likely depend on prior therapy, disease activity, timing of relapse, GVHD, and other coincident toxicities, as well as many other factors. Furthermore, anecdotal observations suggest an interaction between ongoing GVT effects and various other therapeutic interventions. Well-designed clinical trials in specific diseases are going to be necessary to test the activity and role for these therapies, particularly in situations where cellular therapies have been ineffective. Measurements of immunologic effects in addition to disease outcomes will be needed to make progress in managing disease relapse with conventional and biologic therapies. In addition, we must overcome the general reluctance of study sponsors and investigators to include prior transplant recipients on trials studying promising new therapies; these often unsubstantiated exclusions may deprive patients of potential major benefits and slow progress in developing relapse therapies.

A number of strategies deserve careful study and might include preparation and pretreatment of the patient to either induce a minimal disease state or perhaps alter the malignant cells and environment to enhance T cell recognition and GVT activity. Alternatively, manipulation of the donor cell product through selection, activation, or targeting may enhance GVT activity. Studying the role of other cellular effectors such as NK cells and dendritic cells to enhance GVT will also be important. In many cases, a combination of these strategies may be required for maximal effect. Combining immunologic approaches with novel chemotherapy or biologic therapies in a multimodality approach may ultimately be required. Given the multitude of confounding issues, and the relatively small numbers of patients, the committee on Treatment of Relapse for this Workshop was unanimous in acknowledging the need for well-designed international cooperative trials to rapidly test and disseminate the best strategies for relapse treatment after transplant. Information gathered in the relapse setting could, at least in theory, provide crucial pathophysiologic information that may ultimately improve treatments.

Despite all the uncertainties, there is no doubt that novel biologic agents and allogeneic immunotherapy have the ability to be very potent and durable anticancer therapies. Detailed study of the current role for DLI, and exploring new applications of cellular and other biologic therapy continues to hold great promise for the very dire clinical scenario of relapsed disease after alloHSCT.

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