ASBMT American Society for Blood and Marrow Transplantation

Relapse after Allogeneic Hematopoietic Cell Therapy

Marcel R. M. van den Brink,[1] David L. Porter,[2] Sergio Giralt,[3] Sydney X. Lu,[1] Robert R. Jenq,[1] Alan Hanash,[1] Michael R. Bishop[4]

Disease relapse remains a major cause of mortality following allogeneic hematopoietic cell transplantation (HCT). Over the past decade, our understanding of the biology underlying the graft-versus-tumor/leukemia (GVT) effect has increased greatly; however, several other factors affect the occurrence and outcome of relapse, including conditioning regimen, type of allograft, and the histology, status, and sensitivity to chemotherapy of the disease being treated. The mainstay of relapse treatment is donor lymphocyte infusion (DLI), but the efficacy of DLI is quite variable depending on disease histology and state. As such, there is a significant need for novel therapies and strategies for relapse following allogeneic HCT, particularly in patients for whom DLI is not an option. The National Cancer Institute is sponsoring an international workshop to address issues and research questions relative to the biology, natural history, prevention, and treatment of relapse following allogeneic HCT.

Biol Blood Marrow Transplant 16: S138-S145 (2010) © *2010 American Society for Blood and Marrow Transplantation*

KEY WORDS: Allogeneic, Relapse, Graft versus tumor, Donor lymphocyte infusion

INTRODUCTION

In his 1975 review of bone marrow transplantation (BMT) in the *New England Journal of Medicine*, E. Donnall Thomas noted that the major barriers to the successful application of this modality were the availability of suitable donors, treatment-related toxicities, and relapse of disease [1]. The past 30 years have seen tremendous progress in addressing the need for donors for allogeneic hematopoietic cell transplantation (HCT) through the use of volunteer HLA-matched unrelated donors (MUDs), haploidentical related donors, and cord blood units (CBUs) [2]. There also have been significant improvements in supportive care measures, with better agents to treat mucositis and a marked increase in the number and efficacy of antibiotics to treat bacterial, viral, and fungal infections. Nonmyeloablative (NMA) and reduced-intensity conditioning (RIC) regimens have been introduced, which have been associated with as much as a 50% reduction in treatment-related mortality (TRM), compared with myeloablative (MA) conditioning in similar patient populations [3,4].

Despite these advances, however, there has been very little progress in reducing the incidence of relapse following allogeneic HCT and in improving the subsequent outcomes of patients who experience relapse, which remains one of the leading causes of death following allogeneic HCT (Figure 1). This limited improvement has occurred despite our improved understanding of the biology underlying the graft-versus-tumor/leukemia (GVT) effect [5] and, more importantly, the introduction of donor lymphocyte infusion (DLI) as a therapeutic option for patients experiencing disease progression or relapse after allogeneic HCT [6]. Relative to the biology underlying the GVT effect, or understanding of the major interactions among various lymphocytes (eg, T regulatory cells, natural killer [NK] cells), antigens (eg, WT1, PR1) receptors (eg, killer cell immunoglobulin-like receptors [KIR]), cytokines (eg, interleukin [IL]-2, IL-7, IL-15, transforming growth factor β-1), and the tumor environment in mediating the GVT effect has improved [7]. But, despite this greater understanding, we have been able to translate these findings into significant improvements in outcomes in only a minority of patients [8]. With regard to DLI, in the disease for which it is most effective—chronic myelogenous leukemia (CML)—allogeneic HCT is performed only in patients who are resistant to tyrosine kinase inhibitors. In the vast majority of malignant diseases for which

From the [1]Memorial Sloan-Kettering Cancer Center, New York, New York; [2]Abramson Cancer Center, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; [3]University of Texas M.D. Anderson Cancer Center, Houston, Texas; and [4]National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Financial disclosure: See Acknowledgments on pages S144.

Correspondence and reprint requests: Michael R. Bishop, MD, Experimental Transplantation and Immunology Branch, National Cancer Institute, 10 Center Drive, CRC/Room 4-3152, Bethesda, MD 20892 (email: mbishop@mail.nih.gov).

1083-8791/10/161S-0023$36.00/0
doi:10.1016/j.bbmt.2009.10.023

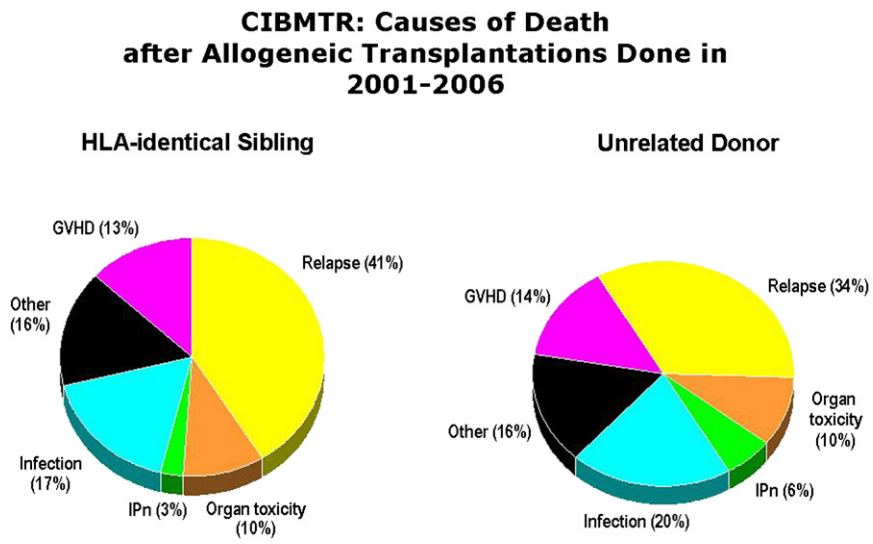

Figure 1. Causes of death following allogeneic HCT as reported to the CIBMTR.

allogeneic HCT is used, DLI is either ineffective or can provide long-term disease-free survival (DFS) for only a minority of patients [9]. These results are even more disappointing when viewed in the context of a significantly increased risk of relapse in individuals who undergo allogeneic HCT following NMA conditioning or RIC.

Most of the available medical literature on relapse following allogeneic HCT focuses on treatment, particularly on immunotherapeutic approaches, such as withdrawal of immune suppression and DLI. An important clinical question is what should be done with patients with active graft-versus-host disease (GVHD), for whom DLI is relatively contraindicated. There are relatively few reports on nonimmunologic treatments, despite the fact that sensitivity to chemotherapy is commonly cited as the most important prognostic factor associated with relapse. Other important factors affecting relapse include histology, disease state, stem cell source, graft manipulation, immunosuppression, and, as mentioned earlier, conditioning regimen. There is a paucity of data on the epidemiology, prevention, and monitoring for relapse of various diseases after allogeneic HCT. Unfortunately, the disease for which there are the most data is CML. This can serve as a model for studying relapse in other diseases, however. In this brief review, we provide an overview of the current understanding of the GVT effect and treatment approaches, and also call on the transplantation community to address the major laboratory and clinical questions related to relapse following allogeneic HCT.

T CELLS IN THE GRAFT-VERSUS-TUMOR RESPONSE

Although the conditioning regimen remains an important contributor to the antitumor potential of allogeneic HCT, recently the therapeutic effect of GVT activity has been emphasized. Extensive analysis in both human and animal studies has shown that GVT activity is mediated primarily by T cells and NK cells, although other cells also can contribute through direct or indirect mechanisms. In some cases, donor T cells can recognize a tumor-specific antigen (eg, Bcr/Abl in CML) or a minor histocompatibility antigen, such as a polymorphic antigen with restricted expression on hematopoietic cells (eg, HA-1/2); however, the major contributors to the GVT activity of donor T cells are likely alloreactive T cells recognizing alloantigens on tumor cells and normal tissue cells in the recipient. Clinical studies support this notion and have demonstrated an inverse correlation between GVHD (especially chronic GVHD [cGVHD]) and the risk of posttransplantation relapse. Thus, strategies to enhance GVT activity could result in worsening GVHD, and novel approaches to improve GVT must be evaluated for this potential complication. Here we briefly review selected approaches for enhancing GVT without exacerbating GVHD. Recent reviews of strategies to promote GVT without exacerbating GVHD are listed in Table 1 [10-15].

Posttransplantation Environment

Recent studies have resulted in a new appreciation of the posttransplantation setting as a unique environment that seems to be conducive to T cell reactivity against tumor cells as well as vaccines aimed at enhanced T cell responses. Recently, investigators studying optimal conditions for cancer immunotherapy "reinvented" MA conditioning followed by autologous HCT as an ideal setting for adoptive T cell therapies [16]. Posttransplantation infusion of T cells can produce robust T cell expansion, and vaccines and immune-modulating antibodies also appear to have

Table 1. T Cell Approaches to Enhancing GVT without Exacerbating GVHD

Strategy	Reference
Immune reconstitution	[10]
Cytolytic pathways	[11]
Trafficking	[12]
Regulatory T cells	[13]
Effector memory T cells	[14]
Adoptive cell therapy and vaccines	[15]

GVT indicates graft-versus-tumor/leukemia; GVHD, graft-versus-host disease.

augmented efficacy in the setting of diminished lymphocytes. Possible mechanisms include increased access to antigen-presenting cells (APCs; and major histocompatibility complex [MHC]/antigen), increased access to cytokines (eg, IL-2, IL-7, IL-15, IL-21), decreased suppressor cell populations, lymphopenia-induced homeostatic proliferation of naïve T cells, and radiation-induced up-regulation of trafficking/adhesion molecules and costimulatory molecules and activation of dendritic cells [17,18].

T Cell Reconstitution

Patients undergoing allogeneic HCT experience prolonged posttransplantation deficiencies in T cell numbers and function, associated with increased risk for malignant relapse, development of secondary malignancies, and suboptimal response to immunotherapeutic strategies, such as antitumor vaccination. Currently, the most promising approaches to enhancing posttransplantation T cell reconstitution include cytokines and growth factors, including growth hormone, insulin-like growth factor I, ghrelin, sex steroid ablation with leuprolide, keratinocyte growth factors, IL-7, IL-12, and IL-15. All of these agents have shown promise in animal models, and most are currently in early clinical trials [19].

T Cell Cytolysis

Cytotoxic T cells execute their function via the perforin/granzyme system and death receptor ligands (eg, FasL, tumor necrosis factor [TNF]-related apoptosis-inducing ligand [TRAIL], TNF-like weak inducer of apoptosis [TWEAK]), which trigger the target cell's own apoptotic pathways [11]. Multiple murine models have demonstrated differential use of these cytolytic pathways during GVT and target organ GVHD; for example, FasL is important for liver GVHD, whereas TNF plays a critical role in intestinal GVHD. Depending on the tumor model used, each of these pathways can be involved in GVT activity, although GVT activity by TWEAK has not been studied to date. Overexpression of TRAIL in T cells seems to be able to enhance GVT activity against certain malignancies, although TRAIL has been recently implicated in thymic GVHD (M.vdB., unpublished observations).

T Cell Trafficking

Studies in mouse models have demonstrated roles for individual selectins, integrins, and chemokines/chemokine receptors in the pathogenesis of GVHD [12]. For example, donor T cells deficient for CCR2 or β7 integrin have decreased capability to home to the liver and gastrointestinal (GI) tract, resulting in decreased GVHD, but intact GVT responses. Natalizumab is a humanized antibody to the α_4 subunit of certain integrin heterodimers, including $\alpha_4\beta_7$, which is associated with homing to the intestines. Natalizumab has been tested for use in inflammatory bowel disease and multiple sclerosis and might be useful for inhibiting migration to GVHD target tissues while still permitting activation of GVT effectors in lymphoid tissue. But, further studies with natalizumab are complicated by a controversy regarding the increased risk of progressive multifocal leukoencephalopathy observed in patients treated with this drug.

Regulatory T Cells

Various investigators have demonstrated in mouse models that regulatory T cells (Tregs) of donor or host origin can inhibit GVHD. $CD4^+CD25^+$ Tregs suppress the early expansion of alloreactive donor T cells and have been reported to limit their expression of IL-2 receptor (IL-2R) alpha-chain and their capacity to induce GVHD without abrogating GVT effector function, which is mediated primarily by the perforin lysis pathway. Thus, at least in mouse models, donor Tregs can separate GVHD from GVT activity. Several clinical studies of Treg administration in patients undergoing allogeneic HCT are currently underway.

Effector Memory T Cells

On encountering their cognate antigen in the context of appropriate costimulatory signals, naïve $CD8^+$ T cells will become activated and can develop into effector (T_{EM}) and central memory (T_{CM}) $CD8^+$ T cells. Similar differentiation patterns have been proposed for $CD4^+$ T cells. T_{CM} cells are long-lived and express CD62L and CCR7, in contrast to $CD8^+$ T_{EM} cells. Studies in mouse models have shown that selected $CD4^+$ or $CD8^+$ donor T_{EM} (as opposed to naïve) T cells cause less GVHD, but can still exert GVT activity. Several investigators are currently planning clinical trials in allogeneic HCT recipients with selected donor T_{EM} cells.

Adoptive Cell Therapy and Vaccines

Beginning with DLI, the potential of adoptive T cell therapy has been widely recognized as a way to enhance GVT activity and prevent or treat malignant

relapse. Various strategies focusing on the ex vivo expansion of donor T cells that can recognize one or more antigens on tumor cells have been developed. These cells can be modified with suicide genes (to halt the development of GVHD), modified with specific T cell receptors (TCRs) resulting in T cells with dual TCRs, chimeric antigen receptors, which use the antigen-binding portion of an antibody in combination with the TCRζ chain for activation. The cells can also be made undergo ex vivo polarization toward Th1 or Th17 or altered with various other strategies. Several of these approaches are currently in clinical trials as upfront or delayed adoptive T cell therapy in allogeneic HCT recipients.

In this review, we can touch on only a few of the many exciting strategies being developed to enhance T cell-mediated GVT. Many issues remain to be addressed, ranging from feasibility to financial costs to scientific issues. For example, the "Achilles heel" of T cells is their requirement of antigen recognition, when many tumor cells, through genetic instability and various other mechanisms, can down-regulate many potential antigens and avoid elimination by T cells. Thus, an important question for any potential tumor target antigen is whether its expression is indispensable for the survival of the tumor cells. Alternatively, the GVT activity of T cells could be directed against noncancer cells in the tumor stroma, such as tumor vasculature myeloid-derived suppressor cells. However, as our understanding of T cell biology continues to grow, new approaches to optimizing GVT effects by T cells, which remain the most important mediators of GVT, can be expected.

STRATEGIES AND OPTIONS FOR RECURRENT DISEASE FOLLOWING ALLOGENEIC HCT

Treatment options for most patients who relapse after allogeneic HCT are limited, and prognosis is generally poor, with the exception of CML. In general, the greatest potential for successful treatment of relapse is manipulation or enhancement of donor cells as GVT induction. Thus, the most common intervention for relapse is DLI. In some cases, supportive and palliative care may be the most appropriate option. Disease-specific chemotherapy or radiation can be considered in some settings, but this carries poor long-term survival [20]. In some cases, cytokines to activate T, NK, or dendritic cells have resulted in sustained remission after relapse. A second HCT may be curative, but is associated with extensive morbidity and mortality. Ultimately, newer strategies are needed to maximize efficacy and limit toxicity when treating relapse after allogeneic HCT.

Withdrawal of Immunosuppression

To maximize the GVT activity, withdrawal of immunosuppression is often the first intervention for relapse. Although numerous anecdotal successes have been reported, this approach by itself is rarely effective in patients with diseases other than CML.

Second Allogeneic HCT

Historically, the role of second allogeneic HCT has been limited by unacceptable relapse rates and high mortality. TRM is between 25% and 45% after MA second transplantation and varies from 0 to 30% after NMA second transplantation, depending on previous therapies, age, and time from first transplantation. Relapse rates are disease-dependent, but few studies report a relapse rate < 40%. However, most studies include only a small number of patients and are underpowered to make definitive conclusions. Interestingly, despite this high risk, survival rates after a second MA transplantation for acute leukemia are reportedly between 25% and 40% (although clearly this represents highly selected patients). Available data do not support a benefit with a second donor and generally demonstrate improved outcomes for younger patients and a longer time (> 6-12 months) from transplantation to relapse. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) show a 5-year survival rate of 51% in patients under age 20 years who relapsed more than 6 months after transplantation (95% confidence interval [CI] = 38%-62%) and only 3% (95% CI = 0.02%-12%) in older patients who relapsed within 6 months after transplantation (Figure 2) [21]. The European Group for Blood and Marrow Transplantation (EBMT) reported the best outcomes for patients with late relapse (> 292 days) in remission at time of second transplantation, with 53% survival at 3 years [22]. Statistically significant predictors of better survival were relapse more than 292 days after transplantation (hazard ratio [HR] = 0.5; 95% CI = 0.35-0.74; $P = .0001$), complete remission (CR) at second HCT (HR = 0.67; 95% CI = 0.46-0.97; $P = .0001$), and use of total body irradiation (TBI) with second HCT (HR = 0.5; 95% CI = 0.35-0.74; $P = .001$).

The use of RIC for a second allogeneic HCT is expected to minimize TRM, but relapse rates are high. Nevertheless, long-term survival rates of 20% to 60% have been reported. Outcome depends on many factors, including the intensity of the first and second conditioning regimens, time to relapse, underlying disease, and disease status at transplantation. Whether or not an RIC regimen improves outcome compared with conventional conditioning for a second allogeneic HCT is unknown.

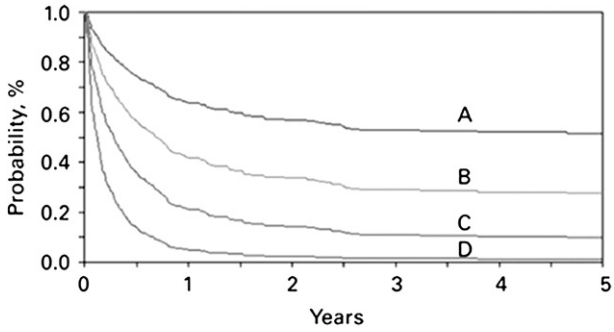

Figure 2. Second allogeneic HCT as reported to the CIBMTR [21]. Probability of overall survival after second transplantation. A, Age ≤20 years; duration of remission > 6 months. B, Age > 20 years; duration of remission > 6 months. C, Age ≤20 years; duration of remission 6 months. D, Age > 20 years; duration of remission ≤6 months.

Disease-Specific Treatments

Relapsed CML

DLI for relapsed CML is dramatically effective and induces molecular CR in up to 80% of patients who relapse in the chronic phase (CP) [23]. These remissions are sustained in the majority of patients, although late relapses raise the concern that GVT effects might have a limited life span or that the primitive leukemic stem cell may not be eradicated.

Imatinib may be an effective alternative to DLI for relapsed CML without the risk of GVHD in patients who have not been previously treated or developed resistance to this drug. Limited data suggest that up to 70% of patients achieve a molecular CR. It appears that continued therapy is necessary to prevent progression [24]. Whether second-generation tyrosine kinase inhibitors (TKIs), such as dasatinib or nilotinib, will be more effective than imatinib for relapsed CML is not known. In the modern era, most patients proceed to HCT only after developing imatinib resistance, but may remain sensitive to newer agents. It is not known, but it seems unlikely, that patients who proceed to HCT because of resistance to multiple TKIs would benefit from this therapy.

Although combined TKI and cellular therapy has not been prospectively studied, the combination of imatinib or another TKI with DLI has the advantage of affording a rapid reduction in leukemia burden and disease control until an effective immune response can develop. Moreover, it is possible that lower T cell doses can be used, thus reducing the risk of GVHD. Unfortunately, DLI is less effective for patients with accelerated and blast-phase CML; only 12% to 28% of these patients achieve remission, and many responses are transient.

When DLI and TKI therapy are not options or are ineffective, interferon-a may be a useful alternative [25]. Vaccine strategies also hold particular promise for relapse of indolent diseases like CML [26].

Acute Leukemias

For relapsed acute leukemias, both conventional chemotherapy and newer biological agents result in significant remission rates, but poor long-term survival. The use of novel agents (eg, dasatinib or a newer TKI) in patients with Ph^+ acute lymphoblastic leukemia (ALL) or 5-azacytidine for relapsed acute myelogenous leukemia (AML) may have particular benefit. Sorafenib, a multikinase inhibitor, has demonstrated preliminary activity in a small number of patients with relapsed $FLT3^+$ AML [27].

For patients with relapsed ALL, outcomes are particularly poor after DLI, with response rates of 0% to 20% and overall survival rates of < 15% [9]. Outcomes after DLI for relapsed AML are more variable. Response occurs in 15% to 30% of patients, but remissions generally are of short duration, and long-term survival is only approximately 20%. The EBMT studied outcomes in almost 400 patients with relapsed AML [28]. In the 171 patients who received DLI, those patients who achieved remission by other means demonstrated improved outcomes. In a good-risk population of patients in remission with a favorable karyotype, the 2-year overall survival (OS) was 56%. In contrast, patients who received DLI during active disease or aplasia had an OS of 9% to 20% (overall 15%), depending on other risk factors. Nevertheless, patients treated with DLI appear to have better outcomes than those who never receive DLI (OS of 21% vs 9% at 2 years). Furthermore, patients who relapse later after allogeneic HCT and receive DLI have improved outcomes compared with those who relapse early [29].

Immunotherapy often fails because rapid leukemia cell growth may outpace the cytotoxicity of donor leukocytes. CR is more common in patients with acute leukemia who receive given chemotherapy before DLI (c-DLI). One study reported CR in 47% of patients [29]. Although OS at 2 years was 19%, patients who recovered from c-DLI in CR had 1- and 2-year survival rates of 51% and 41%, respectively, compared with a 1-year survival of 5% in nonresponders. Survival at 1 year for patients with relapse occurring less than 6 months after transplantation was 10%, compared with 44% for patients who relapsed more than 6 months after transplantation ($P < .001$).

DLI for Myeloma, Hodgkin Disease, Non-Hodgkin Lymphoma, and Chronic Lymphocytic Leukemia

Response rates and remission duration following DLI in other diseases are less well defined. It is clear that a "graft-versus-myeloma" effect from DLI can induce remission in some patients who relapse after allogeneic HCT, but relapse rates are high and long-term outcomes are poor [30]. The use of newer biological

therapies, such as lenalidomide and bortezomib, will expand treatment options, not only for patients with relapsed myeloma, but also for those with chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL). Data on outcomes after DLI for relapsed NHL, CLL, and Hodgkin disease (HD) are relatively limited; however, experience demonstrates that a meaningful graft-versus-lymphoma reaction can be generated after DLI for NHL and HD [9,31,32]. Graft-versus-lymphoma activity and responses to DLI seems to be most active in patients with indolent lymphoma, mantle cell lymphoma (MCL), and CLL. Newer antibodies designed either to directly target tumor cells or to recruit T cells directly to sites of disease also hold promise for relapsed patients [33].

Relapse after RIC Transplantation

As noted earlier, RIC is associated with higher relapse rates compared with MA conditioning before allogeneic HCT. Whereas mortality is quite high in patients who relapse after RIC HCT, patients who receive therapy seem to have better outcomes than those who do not [34]. Response rates to DLI after RIC allogeneic HCT are similar to those after conventional allogeneic HCT.

New Approaches to Treating Relapse

Despite the achievements with DLI, high response rates are largely limited to CML and are tempered by significant GVHD and other toxicities. Innovative and novel immunotherapeutic approaches are currently under investigation (Table 2). Among other approaches, nonspecific ex vivo activation and expansion through costimulation of donor T cells have been used safely, with intriguing GVT responses [35]. It also may be possible to generate leukemia-specific cytotoxic T cells to use in adoptive immunotherapy [36]. Targeting cytotoxic T cells to tumor cells through gene modification with chimeric antigen receptors or bifunctional antibodies are other exciting, essentially unexplored therapies [33,37]. Vaccine strategies with tumor-specific antigens or modified tumor cells are other promising approaches to generating tumor-specific immunity [26,38]. These strategies will likely be most effective in the setting of minimal disease. Combining DLI with antibody therapy that may direct effector cells directly to tumor cells may overcome possible resistance mechanisms to GVT induction without excessive toxicity.

Because DLI seems to be the most effective for patients with minimal disease, the role of prophylactic DLI for patients in remission needs to be better defined. If donor T cells become tolerant or possibly rapidly senescent after HCT as a mechanism leading to relapse, then the use of repetitive DLI once a patient achieves remission may be useful [39]. In addition, the role of other cell populations (eg, NK and dendritic cells [DCs]) in GVT induction for relapse needs to be explored in more detail. Ultimately, understanding the biology of relapse and mechanisms involved in GVT induction will permit more effective and patient-specific approaches for relapsed disease.

Table 2. Newer Approaches to Cellular Therapies to Treat Relapse

- Combined chemotherapy and biological therapy with DLI (eg, imatinib, 5-azacytadine, gemtuzumab, bispecific antibodies)
- Ex vivo activation and expansion of donor T cells through costimulation
- Generation and infusion of tumor-specific T cells
- Generation and infusion of minor histocompatibility antigen-specific T cells
- Low-dose DLI followed by dose escalation
- Infusion of selected T cell subsets (ie, after $CD8^+$ cell depletion or $CD4^+$ cell selection)
- Inactivation of alloreactive T cells (ie, through transduction of suicide genes into donor T cells, photochemical inactivation, chemotherapy inactivation, or irradiation)
- Infusion of T regulatory cells
- Generation and infusion of Th2-type T cells
- Generation of other cellular effectors, such as NK and dendritic cells
- Manipulation of antigen-presenting cells to maximize GVT or minimize GVHD
- Administration of tumor-specific vaccines (eg, antigen-specific, modified tumor cells) combined with cellular effectors
- Recruitment of T cells to tumor through use of modified T cells expressing chimeric antigen receptors or using bispecific antibodies

DLI indicates donor lymphocyte infusion; GVHD, graft-versus-host disease.

Alternatives to cellular therapies for treating relapse must be considered as well. The use and study of conventional and novel agents has been hindered by the widely differing dosing regimens and toxicity profiles in HCT recipients. Outcome depends on previous therapy, disease activity, time of relapse, GVHD and other coincident toxicities, and many other factors. Typical dosing regimens and treatment schemes may vary widely. Evaluation of immunologic effects in addition to disease outcomes is needed to make progress in managing disease relapse. Well-designed clinical trials in specific diseases will be needed to explore the activity of and role for these therapies, particularly in situations in which cellular therapies have been ineffective. Given the very high-risk nature of these patients, it will be critical to engage not just the transplantation community, but also pharmaceutical manufacturers and regulatory agencies to rapidly address the unique issues posed by this patient population.

FIRST INTERNATIONAL WORKSHOP ON THE BIOLOGY, PREVENTION, AND TREATMENT OF RELAPSE AFTER ALLOGENEIC HCT

To address the problem of relapse following allogeneic HCT, the National Cancer Institute convened a workshop in Bethesda, Maryland, on November 2

and 3, 2009. Planning began in 2008, with the primary objectives of (1) reviewing the current "state of the science" relative to the biology, natural history, prevention, and treatment of relapse following allogeneic HCT; (2) identifying the most important questions and problems related to the biology, prevention, and treatment of relapse following allogeneic HCT over the next 5 years; (3) providing specific recommendations as to what studies and resources are needed to answer these questions and providing for the deficits relative to the research related to relapse following allogeneic HCT; and (4) providing a forum for interested researchers to interact and form networks of interest. An international group of more than 60 basic and clinical researchers was assembled and assigned to specific committees addressing the biology, strategies, and therapies for prevention, disease-specific monitoring methods and strategies, and disease-specific treatment of relapse following allogeneic HCT. Each committee generated a list of research priorities, and presented a summary of their recommendations for open discussion at the workshop. The final recommendations will be published sequentially in *Biology of Blood and Marrow Transplantation*. At the end of the 2-day workshop, an executive summary report from all of the working committees was developed for subsequent publication. A summary of the workshop recommendations will be presented at the 2010 Tandem Transplant Meetings Educational Sessions.

ACKNOWLEDGMENTS

Financial disclosure: This work was supported in part by the Center for Cancer Research, National Cancer Institute, Intramural Research Program.

REFERENCES

1. Thomas ED, Storb R, Clift RA, et al. Bone marrow transplantation. *N Engl J Med*. 1975;292:832-843. 895-902.
2. Copelan EA. Hematopoietic stem cell transplantation. *N Engl J Med*. 2006;354:1813-1826.
3. Diaconescu R, Flowers CR, Storer B, et al. Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. *Blood*. 2004;104:1550-1558.
4. Aoudjhane M, Labopin M, Gorin NC, et al. Acute Leukemia Working Party (ALWP) of the European Group for Blood and Marrow Transplantation. Comparative outcome of reduced-intensity and myeloablative conditioning regimens in HLA-identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European Group for Blood and Marrow Transplantation (EBMT). *Leukemia*. 2005; 19:2304-2312.
5. Kolb HJ. Graft-versus-leukemia effects of transplantation and donor lymphocytes. *Blood*. 2008;112:4371-4383.
6. Porter DL, Roth MS, McGarigle C, et al. Induction of graft-versus-host disease as immunotherapy for relapsed chronic myeloid leukemia. *N Engl J Med*. 1994;330:100-106.
7. Welniak LA, Blazar BR, Murphy WJ. Immunobiology of allogeneic hematopoietic stem cell transplantation. *Annu Rev Immunol*. 2007;25:139-170.
8. Ruggeri L, Capanni M, Urbani E, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. *Science*. 2002;295:2097-2100.
9. Tomblyn M, Lazarus HM. Donor lymphocyte infusions. The long and winding road: how should it be traveled? *Bone Marrow Transplant*. 2008;42:569-579.
10. van den Brink MR, Alpdogan O, Boyd RL. Strategies to enhance T-cell reconstitution in immunocompromised patients. *Nat Rev Immunol*. 2004;4:856-867.
11. van den Brink MRM, Burakoff SJ. Cytolytic pathways in haematopoietic stem-cell transplantation. *Nat Rev Immunol*. 2002;2: 273-281.
12. Wysocki CA, Panoskaltsis-Mortari A, Blazar BR, et al. Leukocyte migration and graft-versus-host disease. *Blood*. 2005;105: 4191-4199.
13. Riley JL, June CH, Blazar BR. Human T regulatory cell therapy: take a billion or so and call me in the morning. *Immunity*. 2009; 30:656-665.
14. Anderson BE, Zheng H, Taylor PA, et al. Memory T cells in GVHD and GVL. *Biol Blood Marrow Transplant*. 2008;14:19-20.
15. June CH. Adoptive T cell therapy for cancer in the clinic. *J Clin Invest*. 2007;117:1466-1476.
16. Dudley ME, Yang JC, Sherry R, et al. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. *J Clin Oncol*. 2008;26:5233-5339.
17. Eyrich M, Burger G, Marquardt K, et al. Sequential expression of adhesion and costimulatory molecules in graft-versus-host disease target organs after murine bone marrow transplantation across minor histocompatibility antigen barriers. *Biol Blood Marrow Transplant*. 2005;11:371-382.
18. Zhang Y, Louboutin JP, Zhu J, et al. Preterminal host dendritic cells in irradiated mice prime CD8+ T cell-mediated acute graft-versus-host disease. *J Clin Invest*. 2002;109:1335-1344.
19. Holland AM, van den Brink MR. Rejuvenation of the aging T cell compartment. *Curr Opin Immunol*. 2009;21:454-459.
20. Shaw BE, Russell NH. Treatment options for the management of acute leukemia relapsing following an allogeneic transplant. *Bone Marrow Transplant*. 2008;41:495-503.
21. Eapen M, Giralt SA, Horowitz MM, et al. Second transplant for acute and chronic leukemia relapsing after first HLA-identical sibling transplant. *Bone Marrow Transplant*. 2004;34:721-727.
22. Bosi A, Laszlo D, Labopin M, et al. Second allogeneic bone marrow transplantation in acute leukemia: results of a survey by the European Cooperative Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2001;19:3675-3684.
23. Collins R, Shpilberg O, Drobyski W, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. *J Clin Oncol*. 1997;15:433-444.
24. Hess G, Bunjes D, Siegert W, et al. Sustained complete molecular remissions after treatment with imatinib-mesylate in patients with failure after allogeneic stem cell transplantation for chronic myelogenous leukemia: results of a prospective phase II open-label multicenter study. *J Clin Oncol*. 2005;23: 7583-7593.
25. Higano CS, Chielens D, Raskind W, et al. Use of alpha-2a-interferon to treat cytogenetic relapse of chronic myeloid leukemia after marrow transplantation. *Blood*. 1997;90:2549-2554.
26. Rezvani K, Yong AS, Mielke S, et al. Leukemia-associated antigen-specific T-cell responses following combined PR1 and WT1 peptide vaccination in patients with myeloid malignancies. *Blood*. 2008;111:236-242.
27. Metzelder S, Wang Y, Wollmer E, et al. Compassionate use of sorafenib in FLT3-ITD-positive acute myeloid leukemia:

sustained regression before and after allogeneic stem cell transplantation. *Blood*. 2009;113:6567-6571.
28. Schmid C, Labopin M, Nagler A, et al. Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. *J Clin Oncol*. 2007;25:4938-4945.
29. Levine J, Braun T, Penza S, et al. Prospective trial of chemotherapy and donor leukocyte infusions for relapse of advanced myeloid malignancies after allogeneic stem cell transplantation. *J Clin Oncol*. 2002;20:405-412.
30. Tricot G, Vesole D, Jagannath S, et al. Graft-versus-myeloma effect: proof of principle. *Blood*. 1996;87:1196-1198.
31. Peggs KS, Hunter A, Chopra R, et al. Clinical evidence of a graft-versus-Hodgkin's lymphoma effect after reduced-intensity allogeneic transplantation. *Lancet*. 2005;365:1934-1941.
32. Bloor AJ, Thomson K, Chowdhry N, et al. High response rate to donor lymphocyte infusion after allogeneic stem cell transplantation for indolent non-Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2008;14:50-58.
33. Buhmann R, Simoes B, Stanglmaier M, et al. Immunotherapy of recurrent B-cell malignancies after allo-SCT with Bi20 (FBTA05), a trifunctional anti-CD3 x anti-CD20 antibody and donor lymphocyte infusion. *Bone Marrow Transplant*. 2009;43:383-397.
34. Bethge WA, Storer BE, Maris MB, et al. Relapse or progression after hematopoietic cell transplantation using nonmyeloablative conditioning: effect of interventions on outcome. *Exp Hematol*. 2003;31:974-980.
35. Porter DL, Levine BL, Bunin N, et al. A phase 1 trial of donor lymphocyte infusions expanded and activated ex vivo via CD3/CD28 costimulation. *Blood*. 2006;107:1325-1331.
36. Falkenburg JH, Wafelman AR, Joosten P, et al. Complete remission of accelerated phase chronic myeloid leukemia by treatment with leukemia-reactive cytotoxic T lymphocytes. *Blood*. 1999;94:1201-1208.
37. Milone M, Fish J, Carpentito C, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. *Mol Ther*. 2009;17:1453-1464.
38. Ho V, Vanneman M, Kim H, et al. Biologic activity of irradiated, autologous, GM-CSF-secreting leukemia cell vaccines early after allogeneic stem cell transplantation. *Proc Natl Acad Sci U S A*. 2009;106:15825-15830.
39. Beatty G, Smith J, Reshef R, et al. Functional unresponsiveness and replicative senescence of myeloid leukemia antigen-specific $CD8^+$ T cells after allogeneic stem cell transplantation. *Clin Cancer Res*. 2009;15:4944-4953.