Leukemia Relapse After Allogeneic Bone Marrow Transplantation: A Review

By Sergio A. Giralt and Richard E. Champlin

ALLOGENEIC BONE MARROW transplantation (BMT) is an effective treatment for hematologic malignancies. More than 5,000 transplants are performed yearly worldwide. The increasing use of human leukocyte antigen (HLA) nonidentical donors, and HLA-matched unrelated donors will assure the continued growth in the use of this therapeutic modality.

Relapse of the underlying disease remains the most frequent cause of treatment failure. Although survival after allogeneic BMT has improved over the last decade, this has been primarily because of improvements in supportive care, whereas the risk of relapse has stayed relatively constant. For patients receiving unmodified marrow transplants for early leukemias, relapse rates vary among recent reports and range from <10% to 40%, depending on patient selection, treatment regimen, and length of follow-up. Patients with more advanced disease have a higher relapse rate approaching 50% to 70%, with T-cell depletion (TCD) and absence of GVHD being important prognostic factors for relapse. The presence of specific cytogenetic abnormalities also predicts for relapse after allogeneic BMT in patients with chronic myelogenous leukemia (CML) or acute leukemia.

In this article we review the possible causes for relapse after allogeneic BMT, its natural history, and the results of treatment.

Mechanisms of Cure of Allogeneic BMT

High-dose cytoreductive therapy. Marrow transplantation was originally proposed as a means to administer high doses of chemotherapy and irradiation with the goal of eradicating the leukemia. This treatment would produce near ablation of hematopoiesis requiring allogeneic bone marrow to restore normal marrow function.

Most centers have used cyclophosphamide in combination with total-body irradiation (CY-TBI) or a combination of busulfan and cyclophosphamide (BUCY) as preparative regimens for BMT. The relative benefits of one preparative regimen over another is still under investigation. In a recent randomized trial, CY-TBI was found to be less toxic and more effective than BUCY as a preparative regimen for acute myelogenous leukemia (AML) with a 2-year actuarial disease-free survival (DFS) of 72% versus 47% for the BUCY arm (P < .01). For patients with CML transplanted during chronic phase, there were no significant differences seen with regard to overall survival, DFS and relapse between patients receiving CYTBI or BUCY, with both treatment groups having approximately 80% DFS at 2 years.

Intensification of the TBI dose to 15.75 Gy from 12 Gy decreased the 3-year relapse rate from 35% to 12% in patients with acute leukemia, but with no difference in overall DFS at 3 years (58%) because of a 32% transplant related mortality rate in the high-dose TBI-treated group.

Addition or substitution of other chemotherapeutic agents to the preparative regimen have also failed to show improvements in DFS. Recent studies using etoposide as part of the preparative regimen are promising. High-dose etoposide in combination with fractionated TBI was shown to be as effective as BUCY in the treatment of patients with advanced leukemia in a randomized trial.

Graft-versus-leukemia. Both animal models and human experience indicate that the leukemic cells are usually not totally eliminated by the preparative regimen. In most patients, an additional immune-mediated graft-versus-leukemia (GVL) effect is important to prevent relapse. The evidence for the existence of GVL in humans was indirect and was derived from the following observations. The GVL effect has been associated with the presence of graft-versus-host disease (GVHD). Relapse rates for acute lymphoblastic leukemia (ALL), AML, and CML are significantly higher in patients who do not develop acute or chronic GVHD. Rare cases have been reported in which occurrence of GVHD was associated with remissions in patients relapsing after allogeneic BMT. Syngeneic transplantation has a threefold higher risk of relapse both in AML in first complete remission (CR) and in CML when compared with allogeneic transplants from an HLA-identical sibling transplantation. In CML in particular, the relapse rate

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Submitted April 15, 1994; accepted August 3, 1994.

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0006-4971/94/8411-0043$3.00/0
after syngeneic transplant during chronic phase is 40% as reported by the International Bone Marrow Transplant Registry and 50% in the Seattle experience, which is higher than that seen for unmanipulated allogeneic BMT.\textsuperscript{35,33} The risk of relapse is also increased in patients receiving TCD transplants.\textsuperscript{5,24,37} Patients with CML who receive TCD allografts and develop GVHD have a risk of relapse that is four times higher than patients receiving unmanipulated marrows who never developed this complication, suggesting that these two events may be separable in humans and that GVL involves an allogeneic target and T cells are the effectors.\textsuperscript{6}

Kolb et al\textsuperscript{39} described reinduction of remission in three patients with CML who had hematologic and cytogenetic relapses after allogeneic BMT. These patients received infusion of donor buffy-coat cells and achieved a complete cytogenetic and hematologic remission. Providing proof that donor cells could mediate a strong antileukemic effect capable of inducing hematologic and complete cytogenetic remissions in patients with CML who relapsed after allogeneic BMT. These data have been confirmed and expanded by other groups.\textsuperscript{39-49}

Although various cell populations have been implicated, the pathophysioligic mechanisms mediating GVL are not known. In animal models, it is possible to generate donor-derived cells with isolated antileukemic activity without normal host tissue reactivity (GVL without GVHD).\textsuperscript{50-52} In humans, it has been reported that donor-derived cytotoxic T lymphocytes with antileukemic activity, but without normal host tissue reactivity, can be isolated in vitro, but cells with dual reactivity also exist.\textsuperscript{53-55} Both major histocompatibility complex (MHC)-restricted CD4\textsuperscript{+} and CD8\textsuperscript{+} cytotoxic clones with antileukemic activity have been reported, suggesting that antigens presented in the context of MHC class I and class II loci are involved.\textsuperscript{55} Other cell populations have also been implicated, such as lymphokine-activated killer cells and natural killer (NK) cells.\textsuperscript{56}

Minor histocompatibility antigens expressed on the leukemic cells could be the target antigens, but this is unknown.\textsuperscript{57} Peptides related to translocation breakpoints or abnormally phosphorylated or glycosylated proteins have also been suggested as target antigens.\textsuperscript{58}

Cytokines are involved in the pathogenesis of GVHD and probably play a role in the GVL phenomenon.\textsuperscript{59} Both CD4\textsuperscript{+} and CD8\textsuperscript{+} cells secrete interleukin-2 (IL-2), IL-3, granulocyte-macrophage colony-stimulating factor, interferon \( \alpha \) (IFN \( \alpha \)), tumor necrosis factor, and other cytokines when activated.\textsuperscript{59,60} The role cytokines play in the GVL effect is not known, but could involve a direct antileukemic effect, recruitment of accessory cells, and potentiation of the putative cellular mechanisms responsible for the antileukemic effect.\textsuperscript{52-55}

\textbf{Origin of relapse.} After successful allogeneic BMT, hematopoiesis and immunity are reconstituted from donor-derived cells. Leukemia relapse generally occurs in recipient-derived cells, indicating that clonogenic malignant cells survived the high-dose chemoradiotherapy and avoided the GVL effect. Rarely, leukemia occurs in donor-derived cells.\textsuperscript{66-68} Most of these cases have occurred late after BMT and have been associated with TBI. The mechanisms postulated for leukemic transformation of donor cells include radiation-facilitated viral leukemogenesis, persistance of the leukemic stimulus with de novo leukemic transformation, or transfer of oncogenic genetic material from host-derived leukemia cells to normal donor hematopoietic cells.\textsuperscript{69,70}

\textbf{Mechanisms of resistance.} Leukemic cells vary in their sensitivity to chemotherapy and radiation. Resistance to radiotherapy is thought to be caused by a number of mechanisms, including intrinsic resistance of the leukemic progenitor cell, kinetic resistance, enhanced DNA repair, and leukemic cell burden.\textsuperscript{71} Uckun et al\textsuperscript{72,73} recently reported that intrinsic radiation resistance as measured by surviving fractions at 200 cGy (S\textsubscript{v}) and 37\% dose slope (D\textsubscript{v}) was significantly higher in 28 patients with CD3\textsuperscript{+} T-cell ALL/non-Hodgkin’s lymphoma (NHL) than in 14 patients with CD3\textsuperscript{+} T-cell ALL/NHL. They also observed a higher likelihood of relapse and a poorer leukemia-free survival after autologous transplant in CD3\textsuperscript{+} patients (7\% v 63\% for CD3\textsuperscript{-} patients). The mechanism of radioresistance in CD3\textsuperscript{+} cells is unknown.

Preparative regimens for BMT generally involve alkylation agents such as cyclophosphamide and busulfan. Relevant mechanisms of resistance to these agents include genetic instability, glutathione synthesis, enhanced DNA repair, kinetic resistance, and others.\textsuperscript{74} Elevated levels of aldehyde dehydrogenase have been shown in human hematopoietic progenitor cells.\textsuperscript{75} Aldehyde dehydrogenase inactivates the cytotoxic metabolites of cyclophosphamide and other oxazaphosphorines, and thus, may mediate resistance to these agents.\textsuperscript{76}

Patients with acute or chronic GVHD may still relapse. This indicates that GVHD does not necessarily result in GVL or that leukemic clones can overcome the GVL effect. The mechanism behind this is unknown.

\textbf{Natural history and treatment.} The natural history of leukemia relapse after allogeneic BMT depends on the type of leukemia, interval from transplant to recurrence, the patient’s performance status, and treatment. In two large series, adults with acute leukemia who relapsed after allogeneic BMT had a median survival of 3 to 4 months if no treatment was administered.\textsuperscript{77,78}

The prognosis for patients with CML relapsing after an allogeneic BMT depends primarily on the disease phase at the time of recurrence. Patients with isolated cytogenetic relapses have a median survival of greater than 6 years compared with 3 years for patients relapsing into a clinical chronic phase (hematologic relapse).\textsuperscript{79} Multivariate analysis showed that female sex, isolated cytogenetic relapse, long interval between transplant and relapse, and IFN\( \alpha \) therapy at the time of relapse were independent favorable prognostic factors for survival.\textsuperscript{79} Transient cytogenetic relapse with spontaneous remission has been reported by many investigators, with patients receiving TCD allografts having a higher likelihood of hematologic progression.\textsuperscript{80-83}

\textbf{Cyclosporine withdrawal.} Abrupt cyclosporine withdrawal has been reported to induce hematologic and cytogenetic remissions in patients with CML, AML, and ALL. All patients reported have developed GVHD.\textsuperscript{80-83} The published experience is limited to case reports, and a more thorough
evaluation of this phenomenon is needed. In the meantime, this experience suggests that cyclosporine withdrawal can induce long-term remissions, and it is reasonable to discontinue immunosuppressive therapy in patients who relapse after allogeneic BMT.30,31

**Chemotherapy.** Frassoni et al77 reviewed 117 cases of leukemia relapse after allogeneic BMT. 41 patients with AML and 76 with ALL were reported. Forty percent of the patients achieved a CR after reinduction with conventional chemotherapy, with median survival durations of 8 months for AML and 14 months for ALL. Patients who did not respond to reinduction had a significantly worse outcome, with a median survival of 3 months.

Mortimer et al78 reported 95 patients with AML and 94 with ALL who relapsed after allogeneic BMT. Thirty percent achieved a CR, with a median survival duration of 6 months. Relapse occurring less than 1 year after transplant was the most important adverse prognostic factor for achieving a CR. Median survival was longer in patients with ALL than AML (14 months vs 8 months), but the CR rates were similar.

The optimal salvage treatment for patients who relapse after allogeneic BMT has not been established. For patients with AML, who relapse more than 1 year after BMT, combination therapy with an anthracycline and cytosine arabinoside has been most frequently used.77,78 Therapy with corticosteroids, vinca alkaloids, anthracycline and asparaginase are often effective reinduction for ALL.77,78,84,86 Children relapsing with ALL after a prolonged disease-free interval after transplantation have achieved prolonged remissions with standard chemotherapy, but most other patients will eventually relapse and should be considered for investigational strategies aimed at prolonging remissions.85,86

Patients with CML who relapse into blast crisis or accelerated phase after allogeneic BMT rarely respond to chemotherapy or IFNa; their median survival duration is less than 6 months.79 These patients should be offered investigational approaches or palliative care.

**Radiotherapy.** Extramedullary relapses after allogeneic BMT occur in 20% of patients who undergo BMT for AML and 6% to 30% of patients with ALL.78,87 Most occur in the presence of marrow relapse. Patients with symptomatic extramedullary disease who are not candidates for or who have failed to respond to chemotherapy may receive localized radiation therapy for palliation as should patients with central nervous system (CNS) or testicular relapses.88,89

Treatment of patients with isolated extramedullary relapse is more controversial. Involved-field radiotherapy has been reported to achieve long-term disease control in a few selected patients.78 However, in patients treated with standard-dose chemotherapy, isolated extramedullary relapses (testicular or CNS) usually precede systemic relapses. Because local treatment will not prevent systemic recurrence, combined modality therapy is recommended.88,89

**Second allogeneic BMT.** Second transplants have been effective in selected patients who relapse after allogeneic BMT. Outcomes have depended primarily on the interval from the first transplant to relapse; the longer the interval, the more favorable the outcome. Moreover, patients with advanced disease, poor performance status, or who have had extensive prior therapy have done poorly.90,91

The published literature supports the use of second transplants after at least 6 months from the first infusion in pediatric patients and after 1 year for adults.92-99 The rate of treatment-related mortality in such patients is between 30% and 40%. Relapse remains the single most important cause of treatment failure. The leukemia-free survival at 4 years is approximately 20% to 30% in most published series (Table 1).30-99 Patients with early relapse or those who experienced serious toxic effects or GVHD during the first transplant are poor candidates for repeat high-dose chemotherapy and should be offered alternative approaches.

The optimal preparative regimen for second transplants is unknown. Busulfan-based combinations have been used extensively for patients initially treated with TBI. Most second transplants have involved the same donor. Because patients undergoing a second transplant generally remain chimeric and retain donor-derived immunity, the preparative regimen is not required to be immunosuppressive.90 For patients with more than one possible donor, there are no data that support the use of an alternative HLA-compatible donor as a means to achieve a greater GVL effect. Because syngeneic transplants are associated with a greater risk of relapse, patients relapsing after a syngeneic BMT can be considered for an allogeneic transplant if a histocompatible donor is available; however, it is unknown, whether this approach will prove to be more effective than a second syngeneic BMT.

Some investigators are studying allogeneic peripheral blood progenitor cells as the source of cells for a second transplant. The large lymphocyte doses administered through the peripheral blood stem cell preparation may confer a greater antileukemic effect. This approach is feasible, but its efficacy is unknown.100,101

**Granulocyte colony-stimulating factor (G-CSF).** G-CSF induced complete cytogenetic and hematologic remissions in three of seven patients who had experienced relapse of acute or chronic leukemia less than 1 year from transplant.102 Fluorescence in situ hybridization of the bone marrow cells did not detect differentiation of the leukemic clone and was most consistent with preferential stimulation of donor cell populations. The three responding patients remained in remission for 20, 12, and 12 months. The treatment was well tolerated and one patient developed mild chronic GVHD.

Follow-up studies have shown that patients with circulating blasts or extramedullary relapses are unlikely to respond to G-CSF and that some of these patients may have had acceleration of their disease during treatment.103 This novel approach to therapy requires further evaluation. Whether other cytokines or hematopoietic growth factors can produce the same effect is unknown. Assessment of the in vitro sensitivity of both normal marrow and leukemic cells may be useful in predicting response.104

**Cytokine Therapy**

**IFN.** Treatment with IFNa has been effective in selected patients with recurrent CML after allogeneic BMT. IFNa has direct activity against leukemic cells and may enhance a GVL effect by upregulating MHC antigen expression and stimulating T-lymphocyte and NK cell activity.105-107
The results of IFNα therapy for CML relapse after allogeneic BMT are summarized in Table 2. In general, 30% to 40% of patients obtain a hematologic remission; up to 20% of patients achieve a complete cytogenetic remission. 40% of patients obtain a hematologic remission; up to 20% enhancement the antileukemic and cytotoxic activity of T lymphocytes and NK cells. 110 IL-2 has been studied for relapse prevention after both autologous and TCD allogeneic BMT and can be given subcutaneously or as a continuous infusion. 111–115

In a pilot trial, we have explored the combination of IFNα and low-dose IL-2 for patients with acute or chronic leukemia relapsing after allogeneic BMT. One of five patients with acute leukemia who received buffy-coat cells, accounting for an increase in nonrelapse-related mortality. It is possible that the use of long-
term methotrexate as GVHD prophylaxis contributed to the higher incidence of hepatic toxicity and early death in the buffy-coat group, obscuring any beneficial effects this intervention may have had on leukemia relapse.

Kolb et al initially described the antileukemic effects of unmanipulated donor peripheral blood leukocytes in patients who had relapsed after allogeneic BMT. Other reports confirming this observation are summarized in Table 3. Results from the largest reported series suggest that patients with CML recurring as isolated cytogenetic relapse or chronic phase respond better to this treatment than patients with more advanced disease or acute leukemia. Thirty one of 39 patients with isolated cytogenetic relapse or chronic phase relapse of CML achieved cytogenetic remissions compared with 5 of 12 patients with more advanced CML and 8 of 23 patients with acute leukemia. GVHD occurs in 80% and marrow aplasia in 56% of the patients treated with donor lymphocyte infusions. GVHD and marrow aplasia have been important causes of treatment failure, contributing to the 22% treatment-related mortality associated with this therapy. Aplasia may develop coincidentally with clinical relapse or in those infused during isolated cytogenetic relapse.

The effector cells and mechanisms of response to donor lymphocyte infusion are not understood, but are presumed to involve T cells and/or NK cells with antileukemic activity. It is likely that the aplasia seen in some of these patients was caused by a direct immune effect of donor cells against both normal and leukemic recipient cells, similar to what has been observed in transfusion-associated GVHD. Donor cells reactive against recipient nonleukemic cells have been identified, and have been shown to inhibit colony formation in vitro. The efficacy of donor lymphocyte infusions in inducing remissions should encourage exploration of this strategy as a method for preventing relapse. Recent studies have shown that it is possible to safely infuse increasing numbers of donor lymphocytes in animals receiving TCD transplants by prolonging the time period between the initial transplant and the donor lymphocyte infusion. It may be possible to perform a TCD transplant to prevent GVHD, and later infuse donor lymphocytes to provide GVL activity.

**Summary and Therapeutic Recommendations**

The chimeric state after allogeneic BMT allows for innovative strategies in treating patients with leukemia relapse. Given the persistence of donor-derived immunity in most transplant recipients, an initial trial of IFNa or donor lymphocyte infusions is a reasonable approach for patients experiencing chronic phase CML recurrence, reserving high-dose chemotherapy and second BMT for patients who fail to respond.

Young patients who relapse with advanced CML or acute leukemia relapsing at least 1 year after initial transplant, who have a good performance status, and who had no major complications during their first transplant should be considered for a second marrow or blood stem cell transplant. This could possibly be followed by some form of investigational therapy to prevent relapse. Patients who relapse less than 1 year from initial transplantation represent a more serious problem because of their resistance to therapy and generally debilitated condition. These patients have occasionally responded to innovative approaches, such as G-CSF, cytokines, or buffy-coat infusions. These approaches need to be explored systematically in clinical trials to determine their true value in the setting of relapse postallogeneic transplantation.

The best treatment for relapse should act:illy be its prevention after the initial transplant. More effective preparative regimens may be possible using novel chemotherapy or targeted radiotherapy approaches. Relapse prevention with maintenance chemotherapy or immunotherapy after BMT is being actively explored, but no definite conclusions as to their efficacy and utility can be made at this time.

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<table>
<thead>
<tr>
<th>Reference</th>
<th>CYTOKINES, T-CELL DEPLET. in BWMT</th>
<th>Time to Relapse, mo</th>
<th>Stage at Relapse/N</th>
<th>IFNα Dose 10^6 U/m2</th>
<th>Toxicity</th>
<th>Outcome</th>
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<tr>
<td>79</td>
<td>50/64</td>
<td>2-85 (9)</td>
<td>CP 28, AP 8, BC 4, Cytogenetic relapse 24</td>
<td>0-5-5 tiw to daily</td>
<td>NS</td>
<td>16% Complete cytogenetic remission, 50% survival at 5 years</td>
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<td>82</td>
<td>9/9</td>
<td>6-21 (13)</td>
<td>CP 6, Cytogenetic relapse 3</td>
<td>1-5 daily</td>
<td>NS</td>
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<td>106</td>
<td>18/18</td>
<td>4-24 (12)</td>
<td>CP 3, AP 1, Cytogenetic relapse 14</td>
<td>5 tiw to 5 daily</td>
<td>7/18 Gd 3-4</td>
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<td>107</td>
<td>1/18</td>
<td>1-48 (11)</td>
<td>CP/18</td>
<td>3-6 daily</td>
<td>6/18 Gd 3-4</td>
<td>9 No response, 4 progression, 9 hematologic remissions, 6 cytogenetic remissions</td>
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Abbreviations: BMT1, Bone marrow transplant 1; N, number, IFNa, interferon α; CP, chronic phase; AP, accelerated phase; BC, blast crisis; tiw, three times a week; NS, not stated; Gd, grade; CGVHD, chronic graft-versus-host disease; AGVHD, acute graft-versus-host disease.
Table 3. Donor Leukocyte Infusions for Relapse After Allogeneic BMT

<table>
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<tr>
<th>Reference</th>
<th>N</th>
<th>Dx</th>
<th>TCD in BMT</th>
<th>Stage Relapse</th>
<th>Time to Relapse (mo)</th>
<th>10^6 Cells Infused/ kg</th>
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<td>3</td>
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<td>No</td>
<td>CP</td>
<td>24-36</td>
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Abbreviations: N, number; Dx, diagnosis; TCD, T-cell depletion; BMT1, bone marrow transplant 1; Rx, treatment; GVHD, graft-versus-host disease; CML, chronic myelogenous leukemia; CP, chronic phase; IFNα, interferon α; NS, not stated; AL, acute leukemia; MM, multiple myeloma; AML, acute myelogenous leukemia; AP, accelerated phase; BC, blast crisis; AMSA, amascrine; ARα-C, cytosine arabinoside; CG, isolated cytogenetic relapse; BU, busulfan.

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