1. INTRODUCTION

The original rationale of bone marrow transplantation (BMT) was solely based on the concept of dose intensity. The logic was as follows: the ability to deliver anticancer therapy (chemotherapy and/or radiation therapy) is limited by dose toxicities, primarily toxicity to normal bone marrow; tumors not susceptible to repetitive doses of modest amounts of chemotherapy might be completely obliterated with one extremely large dose of chemotherapy and/or radiation therapy; a consequence of one large dose of therapy is destruction of normal hematopoiesis, resulting in permanent aplasia; if normal matched marrow were available for transplantation, then these “lethal” doses of chemotherapy could be administered to a patient, the tumor might be eradicated, and the infusion of donor allogeneic bone marrow would restore normal hematopoiesis and save the patient from iatrogenic death. Clinical success with autologous BMT has shown validity of this theory of dose intensity. However, it has become clear throughout the past 20 yr that powerful immunologic forces contribute to the potential for cure in allogeneic BMT (alloBMT). The immunologic reaction by which donor cells from the graft generate an anticancer effect...
is known as the graft vs leukemia (GVL) or graft vs tumor (GVT) effect. This chapter focuses on clinical aspects of the GVL effect: the relationship between graft vs host disease (GVHD) and the GVL effect, T-cell depletion and its relationship to the GVL effect, donor leukocyte infusions (DLI) as a treatment of disease relapse after alloBMT, and current results of nonmyeloablative allogeneic transplantation.

2. THE RELATIONSHIP OF GRAFT VS HOST DISEASE WITH THE GRAFT VS LEUKEMIA EFFECT

One of the major complications of alloBMT is GVHD. GVHD is an immunologic phenomenon occurring when immunocompetent donor cells perceive host tissues to be “foreign” and mount an immunologic attack against them. Acute GVHD usually occurs within the first 100 d after transplantation and affects the skin, liver, and gastrointestinal tract. Chronic GVHD occurs 100 or more d after transplantation and is generally believed to be less of a fulminate disorder; clinical manifestations can affect almost any organ but commonly involve the liver, skin, eyes, bone marrow, mouth (sicca syndrome), and lungs. GVHD prophylaxis and treatment employ potent immunosuppressive therapy directed toward reducing lymphocyte number and function. Unfortunately, the immunosuppressive therapy predisposes patients to opportunistic infections. Therefore, both the development of GVHD and its treatment are clinically vexing problems associated with significant morbidity and mortality. Despite these toxicities, the development of GVHD may be beneficial, because GVHD is frequently associated with the GVL effect, resulting in a lower risk of disease relapse after transplantation.

Although it was originally postulated more than 40 yr ago that donor hematopoietic cells might generate an anticancer effect (1,2), the clinical relationship of GVHD with leukemic relapse was not documented until the 1970s and early 1980s. Odom et al. described two children with acute lymphoblastic leukemia (ALL) who relapsed after alloBMT. When clinical GVHD developed, the children subsequently developed a remission (3). Weiden et al. compared leukemic patients undergoing a syngeneic BMT with those receiving an alloBMT and observed differences in the relative relapse rates for those with and without clinical GVHD (4). The patients with clinical GVHD had a relapse rate 2.5 times less than patients without GVHD. Additionally, the relapse rate was higher in syngeneic patients than in allogeneic transplantation recipients who did not develop GVHD. This finding suggested that cells in the allogeneic graft produced a GVL effect.

Subsequent studies by the Seattle transplantation group further defined the relationship between GVHD and leukemic relapse. One study of patients with leukemia receiving an alloBMT showed that clinical GVHD augmented the
GVT effect, because patients with clinically significant chronic GVHD had a 27% risk of long-term relapse, compared with a 55% risk of relapse for patients with subclinical GVHD \( (p = 0.0003) \) \( (5) \). Thus, clinical chronic GVHD was strongly associated with a long-term GVL effect. A second study of more than 1200 recipients of alloBMT reported that patients with acute leukemia transplanted when in relapse had a lower relapse rate if they subsequently developed either acute or chronic GVHD \( (6) \). The conclusion was, again, that chronic GVHD leads to a durable antileukemic, or GVL, effect.

The International Bone Marrow Transplant Registry reported a landmark analysis of more than 2000 recipients of human leukocyte antigen (HLA)-identical sibling BMTs, examining the relationship between GVHD and disease relapse. Decreased risk of relapse was observed in recipients of non-T-cell-depleted allografts with acute (relative risk 0.68, \( p = 0.03 \)), chronic (relative risk 0.43, \( p = 0.01 \)), and both acute and chronic GVHD (relative risk 0.33, \( p = 0.0001 \)) when compared with recipients without GVHD \( (7) \). This large multi-institutional trial confirmed an unequivocal relationship of both acute and chronic GVHD with decreased leukemic relapse. Many trials have substantiated these findings, including specific associations with a GVT effect in leukemia, lymphoma, and myeloma \( (8–17) \).

In summary, abundant data emerged from 1978 to 1992 describing a strong relationship between the development of clinical GVHD, both acute and chronic, with reduced risk of relapse following alloBMT. The logical conclusion of these observations was that cells in the donor graft, which resulted in GVHD, also led to a profound antitumor effect.

### 3. THE RELATIONSHIP OF T-CELL DEPLETION WITH THE GVL VS LEUKEMIA EFFECT

Although it was evident by 1990 that a relationship existed between GVHD and reduced risk of leukemic relapse, the development of GVHD itself was unfortunately associated with significant morbidity and mortality. Therapeutic options to treat and prevent GVHD were limited. Mortality from GVHD could overshadow the risks of leukemic relapse for some patients. Therefore, many centers began clinical trials of T-cell depletion in alloBMT to reduce the incidence and severity of GVHD. It was believed that the T-cells in the donor graft were, in part, responsible for the development of clinical GVHD. Removing these T-cells might reduce the risk of morbidity and mortality from clinical GVHD. Unfortunately, many studies subsequently showed that T-cell depletion was associated with an increased risk of leukemic relapse.

Several small studies of T-cell-depleted alloBMT showed a trend toward increased risk of relapse after transplantation \( (18,19) \). Two large reports sub-
sequently demonstrated an association of an increased risk of disease relapse following alloBMT in patients receiving T-cell-depleted bone marrow. Goldman et al. described 405 patients with chronic myelogenous leukemia (CML) receiving alloBMTs when they were in the chronic phase. The probability of relapse was higher for recipients of T-cell-depleted marrow compared with non-T-cell-depleted marrow (relative risk 5.4, $p < 0.0001$) (20).

The International Bone Marrow Transplant Registry compared more than 731 recipients of T-cell-depleted HLA-identical sibling BMT with 2480 recipients of non-T-cell-depleted marrow. Although T-cell depletion did reduce the risk of acute and chronic GVHD leukemic relapse increased. Leukemic relapse was 2.75 times more likely after T-cell depletion for patients with acute leukemia in first remission or patients with CML in chronic phase ($p < 0.0001$) (21). Thus, although T-cell depletion did reduce the risk of GVHD, leukemia-free survival was not enhanced because of the loss of the GVL effect.

Most of these studies used pan T-cell depletion, or removal of all T-cell subsets from the HLA-matched sibling donor graft. Subsequent reports have suggested that less-than-full T-cell depletion might reduce the risk of GVHD while retaining a GVL effect. In particular, selective CD8+ T-cell depletion has been reported to reduce the risk of GVHD without losing the GVL effect (22,23). Additionally, it has been suggested that T-cell depletion in recipients of unrelated BMTs might reduce the risk of GVHD without losing the GVL effect (24). Strategies in which T-cell depletion is used to reduce the risk of acute GVHD have also been described, but T cells are then subsequently infused (“add back”) to generate a GVL effect (25,26). However, no large multicenter trial has investigated these strategies and such data remains preliminary.

In summary, data concerning T-cell depletion demonstrates that manipulating the cellular composition of the allogeneic marrow graft can influence the risk of leukemic relapse. These powerful data confirm that the cells themselves, specifically the donor T-cells, have the capacity to mount an antileukemic effect.

Given the relationship of clinical GVHD with the GVL effect and because T-cell depletion reduces the GVL effect, it is clear that T-cells are critical mediators in the GVL effect. The precise cellular mechanism, however, remains unknown. In particular, a fundamental question is whether the GVL effect is independent of the GVHD effect. Thus, is the GVL effect simply immunologic GVHD directed against alloantigens shared by host tissues and leukemia cells, or, alternatively, are there donor cells that specifically recognize tumor antigens and generate the GVL effect? The association of clinical GVHD with the GVL effect would strongly imply that the GVL effect is simply an alloantigen reaction directed against all host tissues, both normal and leukemic. However, abundant data exist suggesting that it is possible to sepa-
rate the GVL effect from the alloantigen GVHD reaction (27–33). Both natural killer cells and different T-cell subsets, may have a role in the GVL effect (34–35). An ongoing up-to-date elusive goal is to harness the GVL effect and minimize clinical GVHD toxicity.

Theoretically, if one accepts the hypothesis that the GVL effect operates through mechanisms other than simple alloantigen recognition, one might decrease the morbidity and mortality of GVHD if a state of immune tolerance could be obtained. Therefore, if both donor and recipient cells are present in a given host, without clinical GVHD, then a state of immune tolerance would theoretically exist and hopefully the donor cells might still be able to generate a GVL effect. This situation has been described clinically and is known as mixed hematopoietic chimerism. It is generally defined as the coexistence of both donor and recipient cells after alloBMT.

Mixed hematopoietic chimerism has long been known to exist after transplantation, with conflicting clinical implications. Although some authors have found that the detection of mixed chimerism may be associated with increased risk of relapse in certain disease states (36–38), others have found that mixed hematopoietic chimerism after alloBMT is common and is not necessarily associated with an increased risk of disease relapse (39–44). For example, Huss and Deeg described mixed hematopoietic chimerism in patients with aplastic anemia or CML undergoing alloBMT; the incidence of rejection was higher (but not significantly) in patients with aplastic anemia with mixed chimeras. Intriguingly, among patients with CML, both overall survival and relapse-free survival were superior in mixed as opposed to complete chimeras (45). The development of stable mixed chimerism is theoretically attractive; however, in clinical practice, the majority of patients undergoing either an ablative or a nonmyeloablative allogeneic transplantation clinically either evolve into a fully chimeric state or experience disease relapse (46).

4. DONOR LEUKOCYTE INFUSIONS

The use of the GVL effect as adoptive immunotherapy was proven conclusively with results obtained from a treatment known as DLI. The use of DLI was pioneered in patients who relapsed after alloBMT. The theory was straightforward: if a patient relapsed after receiving an ablative alloBMT, and if that patient also did not have overt clinical GVHD, then the infusion of additional donor cells (DLI) might be sufficient to produce a cellular immunotherapeutic effect and result in clinical remission. Initially, small studies investigated the use of donor buffy coat leukocytes for patients with CML who relapsed after alloBMT and found that a combination of α interferon and DLI resulted in both clinical and cytogenetic remissions (47,48).
The largest series examining the efficacy of DLI was a survey of 25 North American BMT programs regarding their use of DLIs (49). One-hundred forty patients who received DLI relapsed after alloBMT. Diseases included CML \( (n = 56) \), acute myeloid leukemia (AML) \( (n = 46) \), ALL \( (n = 15) \), myelodysplastic syndrome (MDS) \( (n = 6) \), non-Hodgkin’s lymphoma (NHL) \( (n = 6) \), multiple myeloma \( (n = 5) \), Hodgkin’s disease \( (n = 2) \), and other \( (n = 4) \). Donor leukocytes were obtained by leukopheresis from nonprimed donors in a median of leukopheresis sessions during a median 7-d period. The leukocytes were not manipulated in vitro. The cell yield was variable, but most centers obtained a mean mononuclear cell (MNC) dose of approx \( 5 \times 10^8 \) MNCs per kilogram. CML responded best to DLIs. Of the 55 evaluable patients with CML, 60% achieved a complete response to DLI. Patients who relapsed in chronic phase had a 74% chance of achieving a remission with DLI, patients in accelerated phase had a 33% response rate, and only one of six patients in blast crisis achieved a remission. Responses were more modest in other diseases. Fifteen percent of the patients with AML who relapsed achieved a complete response, 18% of patients with ALL, 40% of MDS, and 50% of myeloma. Median time to remission in patients with CML was 85 d, and 34 d for patients with AML. Sixty percent of evaluable patients developed acute GVHD and 61% developed chronic GVHD. The median time to development of acute GVHD was 32 d. Eighteen percent developed pancytopenia related to DLI at a median of 21 d after infusion. This pancytopenia resolved without treatment in 13 patients, resolved with granulocyte colony-stimulation factor (G-CSF) treatment in 8, resolved after bone marrow boost in 2, and did not resolve in 3. Importantly, there was a clear correlation of disease response with development of clinical GVHD. Of 45 evaluable completely responding patients, 42 developed acute GVHD, and 36 of 41 developed chronic GVHD. The correlation of acute and chronic GVHD with complete remission was statistically significant \( (p < 0.0001) \). Of the 23 patients who did not develop either acute or chronic GVHD, only 3 obtained a complete response to DLI.

This landmark study by Collins et al. conclusively demonstrated that adoptive immunotherapy with DLIs in a large series of patients has the potential to lead to clinical and cytogenetic remissions in several diseases, with CML appearing to be the most amenable to this therapy. Correlation of clinical response with GVHD was strong.

Long-term follow-up of this cohort of patients was recently published (50). Seventy-three patients achieved a complete remission after DLI, and long-term follow-up was available for 66, with a median follow-up of 32 mo. The probability of survival at 1, 2, and 3 yr was 83%, 71%, and 61%, respectively. Patients with CML had 1-, 2-, and 3-yr survival rates of 87%, 76%, and 73%; for other diseases, survival probability at 1 and 2 yr was 77% and 65%. This
follow-up study concluded that the majority of remissions achieved with DLI persist for years. Additional data have confirmed that DLI-induced remissions are durable (51).

Although adoptive immunotherapy with DLI has excellent efficacy in patients with CML, its efficacy is somewhat more modest in patients with lymphoid malignancies. Fewer than 50% of patients with ALL or multiple myeloma have been reported to achieve complete responses with DLI (55,56).

The use of G-CSF (filgrastim) for the treatment of relapse after allogeneic BMT has been described as a potential alternative to DLI (57,58). The largest series reported 14 patients relapsing after allogeneic transplantation (n = 5 CML, n = 5 AML, n = 2 MDS, n = 1 Chronic lymphocytic leukemia [CLL], n = 1 ALL). Filgrastim was given at 5µg/kg subcutaneously for 21 d. Of the participant, 43% achieved a complete response. Most patients developed chronic GVHD.

In summary, infusions of donor leukocytes induce remission in the absence of any other therapy, proving that donor hematopoietic cells have the capacity to generate a GVL or GVT effect and resulting in meaningful and potentially durable clinical remissions.

5. NONMYELOABLATIVE ALLOGENEIC TRANSPLANTATIONS

We now know that a major component of cure in alloBMT is the GVT effect. Indeed, some chemotherapy-resistant malignancies are potentially cured by alloBMT. In this setting, the GVL effect may be the most important contributor to cure. Therefore, if one were to hypothesize that a given group of patients might be cured by the GVL effect but would probably not benefit by high doses of chemotherapy, then why should such patients receive high-dose chemotherapy? Instead, it would make more sense to significantly decrease the intensity of the pretransplant conditioning regimen and simply deliver enough immunosuppressive therapy to prohibit graft rejection. One would then infuse donor hematopoietic cells and rely entirely on the GVT effect to generate a tumor response. This is the fundamental concept of non-myeloablative (“mini”) allogeneic transplantation. To summarize, the rationale is straightforward:

1. Some malignancies will not be cured by high-dose chemotherapy.
2. Some malignancies may be cured by the GVT effect.
3. If so, a minimal BMT preparative regimen would be desirable to prevent graft rejection and minimize toxicity.
4. Once the donor cells engraft, a GVT effect will hopefully result, leading to a clinical remission.

Mini-transplantations are attractive for several reasons. A significant reduction in the ablative preparative regimen will generate less acute toxicity for patients undergoing alloBMT. Regimen-related toxicity of the traditional abla-
tive BMT preparative regimen can be severe (57), and it has been suggested that gastrointestinal mucosal damage can result in a release in inflammatory cytokines and actually stimulate the production of acute GVHD (58). A mini-transplantation could avoid many of these regimen-related toxicities. Reduction in treatment-related morbidity and mortality might also facilitate alloBMT in older patients and patients with concurrent medical illnesses who might be otherwise ineligible for fully ablative transplantation regimens. Additionally, some mini-transplantation regimens allow the procedure to be performed as an outpatient, which is certainly attractive for some patients undergoing transplantation.

Early data have suggested that a mini-transplantation is feasible and often effective. Slavin et al. reported data on 26 patients with a variety of disorders who underwent a nonmyeloablative transplant using fludarabine, anti-T-lymphocyte globulin, and moderate dose busulfan (8 mg/kg) (59). The patients then received G-CSF mobilized peripheral blood progenitor cell (PBPC) allogeneic transplantation, with cyclosporine as the sole GVHD prophylactic agent. Of the 26 patients, 17 achieved complete chimerism and the remainder partial chimerism. Fourteen patients did not experience GVHD; severe GVHD was the cause of death for four patients. With a median follow-up of 8 mo, 85% of patients were alive and 81% were disease free. The conclusion was that nonmyeloablative allogeneic transplants were well tolerated and offered exciting promise. Giralt et al. reported on 15 patients undergoing nonmyeloablative stem cell transplantation to treat refractory AML or MDS (60). The nonmyeloablative regimen was not uniform. GVHD prophylaxis consisted of cyclosporine and methylprednisolone. Acute GVHD occurred in only three patients. Bone marrow chimerism (greater than 90% donor cells) occurred in 75 patients by d 30 after infusion. The procedure was well tolerated, and again, the conclusion was that nonmyeloablative transplantation offered exciting promise for a generally elderly (median age 59 yr; range 27–71 yr) patient population.

Although reported follow-up for most nonmyeloablative allogeneic transplantations is relatively brief, several series do have somewhat mature follow-up. The M.D. Anderson experience with mini-transplantations was recently reported (61). Seventy-eight patients received fludarabine and melphalan as a preparative regimen, and eight received cladribine and melphalan. The median patient age was 52 yr (22–70 yr range). Most patients had advanced hematologic malignancies. The median percentage of donor cells at 1 mo in 75 patients was 100%. The probability of grades 2–4 and 3–4 acute GVHD was 0.49 and 0.29, respectively. Disease-free survival at 1 yr was 57% for patients in first remission and 49% for patients with more advanced disease. The conclusion was that disease control can be achieved by nonmyeloablative alloBMT.

McSweeney et al. reported on 45 patients with hematologic malignancies in HLA-identical sibling donors receiving low-dose total body irradiation
(200 cGy) and cyclosporine plus mycophenolate for GVHD prophylaxis (62). Of the eligible patients 53% had the transplantation performed entirely as an outpatient. Nonfatal graft rejection occurred in 20% of patients, and fludarabine was later added to this preparative regimen to control graft rejection. The incidence of grade 2–3 acute GVHD was 47%. With a median follow-up of 417 d, overall survival was 67%, nonrelapse mortality was 7%, and relapse mortality was 27%. This minimally ablative regimen was extremely well tolerated and demonstrated significant potential efficacy for elderly patients in need of alloBMT.

Possibly the prototypic experience of mini-allogeneic transplantations was reported by Childs et al. using mini-transplantations for metastatic renal cell carcinoma (63). Renal cell carcinoma is refractory to chemotherapy but occasionally responds to immunologic therapy such as IL-2. Because some patients respond to immunologic therapy and because the GVT effect is potentially powerful immunologic therapy, the goal of this trial was to use the GVT effect to treat metastatic renal cell carcinoma. Nineteen patients with refractory metastatic renal cell carcinoma received a preparative regimen of cyclophosphamide and fludarabine followed by infusion of peripheral blood stem cell allograft from HLA-identical siblings or a sibling with a one HLA antigen mismatch. The median follow-up was 402 d. Of the 19 patients, 9 survived, 2 died of transplant-related causes, and 8 died of progressive disease. Of the 19 patients, 53% showed disease regression. Of these patients, 30% had a complete response and 70% had a partial response. There was a dramatic correlation of development of disease response with the development of clinical GVHD. Prolonged tumor regression occurred in the majority of patients with grade 2–4 acute GVHD (9 of 10 patients) and in a minority of those without acute GVHD (1 of 9, \( p = .005 \)). The conclusion was that mini-allogeneic stem cell transplantation can lead to sustained tumor regression in patients with refractory metastatic renal cell carcinoma and was strongly associated with the development of clinical GVHD. This group has also emphasized the development of full donor chimerism of T-cells as a requirement for the GVT response (64).

Early data concerning the use of nonmyeloablative alloBMT is exciting. The initial toxicity is diminished compared with a traditional ablative transplantation. However, it is not certain whether mini-transplantation will be as effective as fully ablative transplantation in controlling disease relapse. A retrospective study comparing ablative and nonmyeloablative patients with hematologic malignancies showed that survival was actually decreased in nonmyeloablative recipients (52% vs 28%), with the majority of deaths secondary to disease relapse (65).

From January 2000 through September 2001, 20 evaluable patients received a nonmyeloablative alloBMT using a uniform preparative regimen at the
Cleveland Clinic Foundation. The patient characteristics and clinical outcomes are shown in Table 1. All patients were treated with a nonmyeloablative preparative regimen consisting of fludarabine (30 mg/m²/d for 3 d), followed by TBI (200 cGy). The patients received donor PBPCs the day after TBI completion. The median patient age was 52 yr (range 28–62, with seven patients older than 60). All patients initially experienced prompt hematopoietic engraftment with neutrophil recovery by day +10 after transplantation, and most patients were treated as outpatients. As shown in Table 1, 6 patients achieved either a complete response or an excellent partial response, 8 patients were alive with progressive disease, and 6 died. The most common cause of death was chronic GVHD. Infection complications have been common, especially cytomegalovirus viremia (66).

Lineage-specific chimerism analysis has shown a significant difference in the kinetics of peripheral blood-nucleated cell chimerism and T-cell

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at Transplantation, Yr</th>
<th>Disease Status at Transplantation</th>
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<tr>
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<td>AML–CR 2</td>
<td>Dead (acute GVHD)</td>
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<td>51</td>
<td>CLL–Refractory</td>
<td>PR</td>
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<tr>
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<tr>
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<td>CR</td>
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<td>62</td>
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<td>CR</td>
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<td>MDS–RA</td>
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<td>18</td>
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<tr>
<td>20</td>
<td>48</td>
<td>CLL–Rel 2</td>
<td>Progressive disease</td>
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AML = acute myeloid leukemia; GVHD = graft vs host disease; CLL = chronic lymphocytic leukemia; PR = partial remission; NHL = non-Hodgkin’s lymphoma; Rel = relapse; CR = complete remission; MM = multiple myeloma; MDS = myelodysplastic syndrome; RA = refractory anemia; RCC = renal cell carcinoma; MFB = myelofibrosis; RAEB = refractory anemia with excess blasts.
chimerism. The mean peripheral buffy coat donor chimerism, using all nucleated cells, is 95% donor cells by day +21. In contrast, the kinetics of T-cell chimerism are more variable. Most patients ultimately achieve 100% donor T-cell chimerism; however, some patients experience rapid T-cell chimerism by day +49, and others do not experience complete T-cell chimerism until day +200 or longer. Five patients never achieved 100% donor T-cell chimerism, and all five patients relapsed. Fifteen patients achieved 100% T-cell chimerism; nevertheless, 5 of these patients developed progressive disease, including 3 with multiple myeloma. All patients who achieved a complete or an excellent partial response achieved 100% T-cell chimerism.

Several conclusions can be drawn from this data. First, the preparative regimen described is associated with limited early toxicity and reduced treatment-related mortality compared with an ablative allogeneic transplantation. Peripheral blood–nucleated cell chimerism develops rapidly. Complete T-cell chimerism appears to be a requirement for an ongoing disease response, although the development of complete T-cell chimerism does not guarantee absence of progressive disease. The leading cause of death in our small cohort of patients is chronic GVHD. Our experience demonstrates the feasibility of minitransplantations even for an elderly population. Continued obstacles are disease relapse and clinical GVHD.

6. SUMMARY

The author believes that the GVL effect is the most potent immunologic therapy ever described in man. The GVL effect associated with DLI can save patients who are relapsing after alloBMT who would otherwise be incurable. The clinical outcome data of nonmyeloblative allogeneic transplantation, although preliminary, demonstrate the exciting therapeutic promise of the GVL effect.

The single biggest clinical problem of the GVL effect is its almost universal association with clinical GVHD. GVHD remains the major cause of morbidity and mortality after alloBMT. Those who perform basic and clinical research involving alloBMT have a simple and straightforward research goal: to separate the GVL effect from GVHD in a clinically meaningful way. To date, we have been unable to achieve this goal. As we become more knowledgeable about the biochemical nature of the GVL effect, graft engineering, and the causes and treatments of clinical GVHD, our ability to maximize the GVL effect and minimize the toxicity of GVHD will result in better and more powerful oncologic immunotherapy.

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