

Related and Unrelated Nonmyeloablative Hematopoietic Stem Cell Transplantation for Malignant Diseases

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Abstract

Patients with advanced hematological malignancies ineligible for conventional myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) due to advanced age or medical contraindications were enrolled in a multi-center study to investigate the safety and efficacy of nonmyeloablative HSCT using a 2 Gy total body irradiation (TBI)-based regimen. A total of 192 patients (median age 55) were treated with HLA-matched sibling peripheral blood stem cell (PBSC) grafts, and 63 patients (median age 53) received a 10 of 10 HLA-antigen matched unrelated donor (URD) HSCT (PBSC graft, n=48; marrow graft, n=15). Diagnoses included multiple myeloma (n=61), myelodysplastic syndrome (n=55), chronic myeloid leukemia (n= 31), non-Hodgkin lymphoma (n=31), acute myeloid leukemia (n=28), chronic lymphocytic leukemia (n=24), Hodgkin Disease (n=14). The conditioning regimen was fludarabine 30 mg/m²/d x 3 days and 2 Gy TBI. Ninety-five related HSCT patients received 2 Gy TBI without fludarabine. Postgrafting immunosuppression was combined mycophenolate mofetil and cyclosporine. Transplants were well tolerated with a median of 0 days of hospitalization in the first 60 days for eligible patients. For related HSCT recipients, median follow-up was 289 (100-1188) days. Nonfatal graft rejection occurred in 6.8%. Of those with sustained engraftment, graft-versus-host disease (GVHD) occurred in 49% (33% grade II, 11% grade III, 5% grade IV). Day-100 non-relapse mortality was 6%. Overall, 59% (114/192) of patients were alive. The relapse/disease progression mortality was 18%, and non-relapse mortality was 22%. The projected 2-year survival and progression-free survival were 50% and 40%. For the URD HSCT recipients, median follow-up was 190 (100-468) days. Graft rejection occurred in 27% (17/63) of patients, mostly in recipients of marrow grafts (9/15). Acute GVHD occurred in 63% (50% grade II, 13% grade III) of 46 engrafted patients. Chronic GVHD requiring therapy occurred in 50% of patients. Of the 63 URD HSCT patients, 54% were alive, 37% in CR, 3% PR, and 14% with disease progression or relapse. Related and unrelated nonmyeloablative HSCT is feasible and potentially curative in patients with advanced hematological malignancies who have no other treatment options.

1. Background

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative therapy for a variety of malignant and nonmalignant hematological diseases. Conventional allogeneic HSCT involves the use of maximally tolerated myeloablative chemotherapy and/or radiotherapy conditioning regimens to eradicate the underlying disease while the allograft serves to rescue patients from marrow aplasia induced by the treatment. One of the major limitations of this approach is the high degree of toxicity associated with the myeloablative conditioning regimens. This toxicity has limited the use of allogeneic HSCT to younger, medically fit patients [1,2]. However, the majority of patients presenting with hematologic malignancies that might be cured with allogeneic HSCT are older than the upper age limit of 50 to 55 years that is typically recommended for patients referred for conventional allogeneic HSCT.

Over time, two important observations related to conventional myeloablative HSCT have emerged. First, even the most intensive or toxic conditioning regimens do not typically cure many hematological malignancies [1]. Second, allografts provide a graft-versus-leukemia (GVL) effect that is responsible for many of the observed cures [3-5]. These two observations, combined with a better understanding of how to control immune cell functions, has led to a radical rethinking of how HSCT might be done in the future. Specifically, the emphasis is moving away from relying on toxic, high-dose chemoradiotherapy towards using donor immune cells for eradicating the underlying malignancy.

In the histocompatible allogeneic HSCT setting, T cells mediate both the host-versus-graft (HVG) and graft-versus-host (GVH) reactions [6]. It follows that optimal post-grafting pharmacologic immunosuppression that modulates T cells could be used to control both HVG and GVH reactions. Intensified post-grafting immunosuppression could be used to permit donor engraftment and decrease the intensity of the conditioning regimen. This hypothesis was tested in histocompatible canine HSCT studies, which showed that the synergistic combination of the antimetabolite mycophenolate mofetil (MMF) and the T-cell activation blocker cyclosporine (CSP) prevented both graft-versus-host disease (GVHD) and graft rejection. With combined MMF/CSP postgrafting immunosuppression for 4 and 5 weeks, respectively, the myeloablative radiation dose of 9.2 Gy total body irradiation (TBI) required for sustained donor engraftment was reduced to a nonmyeloablative dose of 2 Gy [7]. Dogs transplanted with this nonmyeloablative regimen experienced minimal toxicities and mild pancytopenia and became stable mixed hematopoietic chimeras. These results in the canine model, combined with the knowledge of the GVL effect of allografts, were translated to clinical studies of nonmyeloablative allogeneic HSCT for patients not eligible for treatment with a conventional allotransplant.

2. Clinical Results with a Nonmyeloablative Transplant Regimen

Multi-center nonmyeloablative HSCT studies were first conducted in patients with an HLA-matched family member. After the documented success of this approach, a multi-center study of 10 of 10 HLA-antigen matched unrelated donors was initiated. This manuscript will first review the results for related donor studies followed by the unrelated donor HSCT studies. The consortium of transplant centers participating in the nonmyeloablative transplant studies now includes the Fred Hutchinson Cancer Research Center, University of Washington, Seattle Children's Hospital, Seattle Veterans Administration Medical Center, Stanford University, City of Hope National Medical Center, University of Leipzig, Germany, University of Torino, Italy, University of Colorado, Baylor University, Oregon Health Sciences University, University of Arizona, University of Utah, and the Medical College of Wisconsin.

2.1. Initial Clinical Experience with HLA-matched Sibling Nonmyeloablative HSCT

The first clinical study of the nonmyeloablative HSCT regimen consisted of 45 patients (median age 56 years) with hematological malignancies [8]. The transplant regimen was identical to that developed in the dog model and consisted of 2 Gy TBI (0.07 Gy/min) given as a single fraction on day 0. Postgrafting immunosuppression was MMF 15 mg/kg given orally twice daily from day 0 to 27 combined with CSP, 6.25 mg/kg given orally twice daily from day 1 to 35. Granulocyte colony stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSC) were collected from HLA-identical sibling donors and administered within four hours after TBI.

Patients in this initial study had the following diseases: acute myeloid leukemia (AML [n=11]), multiple myeloma (MM [n=8]), chronic myeloid leukemia (CML [n=9]), Hodgkin Disease (HD [n=4]), chronic lymphocytic leukemia (CLL [n=8]), non-Hodgkin lymphoma (NHL [n=3]), acute lymphocytic leukemia (ALL [n=1]) and myelodysplasia (MDS [n=1]). All patients were either age greater than 50 years or, if younger, had significant medical contraindications to conventional HSCT. Participating centers included the Fred Hutchinson Cancer Research Center, University of Washington, Veterans Administration Medical Center, Seattle, WA, University of Leipzig and Stanford University.

2.2. Low Degree of Treatment-Related Toxicity

The nonmyeloablative HSCT regimen was very well tolerated. No patient experienced regimen-related painful mucositis, severe nausea and vomiting, pulmonary toxicity, cardiac toxicity hemorrhagic cystitis or new-onset alopecia. Mild to moderate nausea and diarrhea due to MMF/CSP were common. Serum creatinine elevations to twice baseline values occurred in 60% of patients because of targeting high serum CSP levels. One MM

patient with pre-existing renal dysfunction (serum creatinine 2.3 mg/dL) required hemodialysis. Reversible hyperbilirubinemia to more than 10 mg/dL occurred in 3 patients because of preexisting liver cirrhosis (n=1), concurrent Amphotericin B treatment (n=1), and isolated liver acute GVHD (n=1). Over half of the eligible patients had all their transplant therapy in the outpatient clinic setting.

Myelosuppression was mild with most patients not developing severe neutropenia or thrombocytopenia. Patients with abnormal marrow function at the time of transplant required more blood product transfusions compared to patients with normal marrow function. A retrospective cohort study demonstrated that recipients of this nonmyeloablative transplant regimen had significantly reduced red blood cell and platelet transfusion requirements compared to conventional HSCT recipients [9].

2.3. Mixed Hematopoietic Chimerism Established in All Patients

All 45 patients had initial donor engraftment. Based on T-cell chimerism analysis, 86% were mixed chimeras, and 14% were complete donor chimeras on day 28. This changed to 79% and 21%, respectively, on day 56. Nine (20%) of the first 45 patients had graft rejection after discontinuation of MMF/CSP immunosuppression, between 2 and 4 months after transplant. Four of the patients with graft rejection had CML, two MM, one AML, one MDS and one CLL. Graft rejection was nonfatal and was typically associated with minor changes in blood counts. This observation was unlike the usually fatal outcome of graft rejection that may occur following conventional HSCT. Most all patients with sustained donor engraftment developed spontaneous conversion to complete donor chimerism, and thus the use of donor lymphocyte infusion was usually not needed. Pretransplant factors predictive of graft rejection were a lack of intensive preceding therapy and a diagnosis of CML. Low donor T-cell chimerism at day 28 predicted rejections.

2.4. Addition of Fludarabine to Prevent Graft Rejection

To prevent graft rejection, the conditioning regimen was modified to increase pretransplant host T-cell immunosuppression. Fludarabine 30 mg/m²/day on days 4, 3 and 2 was added to the 2 Gy TBI conditioning regimen. Because of concern of possible toxicity associated with the addition of fludarabine, patients with extensive prior therapy were initially not treated with fludarabine. However, as it became clear that all patients tolerated fludarabine without additional toxicities, the regimen was subsequently modified to include fludarabine plus 2 Gy TBI for all patients treated in the multicenter study with a nonmyeloablative allogeneic HSCT.

2.5. Updated Results of HLA-Matched Related Donor Nonmyeloablative HSCT

A recent update of results from seven collaborating institutions included 192 patients (inclusive of the first 45 reported patients) with hematologic malignancies given nonmyeloablative HLA-matched related donor HSCT using the 2 Gy TBI-based regimen [10]. As with the initial study, patients were not eligible for conventional myeloablative allogeneic HSCT due to advanced age or medical contraindications. The median age of patients was 55 (range 18-73) years. For 58 patients, conditioning consisted of 2 Gy TBI alone. In 87 patients, the conditioning regimen consisted of fludarabine 30 mg/m²/d for three days followed by 2 Gy TBI. Forty-seven patients received nonmyeloablative allogeneic HSCT as planned consolidation therapy following an autologous HSCT. Ten of these 47 patients received fludarabine in addition to TBI, 37 received 2 Gy TBI alone. Diagnoses of these patients included MM (n=57), MDS/myeloproliferative syndrome (MPS) (n=33), CLL (n=23), NHL (n=21), AML (n=21), CML (n=20), HD (n=12), and others (n=5). The median follow-up after allogeneic HSCT was 289 days (range 100-1177).

2.6. Stable Engraftment Enhanced with Addition of Fludarabine To 2 Gy TBI

Transplants were well tolerated with a median of 0 days of hospitalization in the first 60 days after transplant. Neutropenia, when it developed, was typically not prolonged, with a median of 2 days of absolute neutrophil count (ANC) less than 500/ μ L. Platelet counts remained above 20,000/ μ L for the majority of patients. The median donor T-cell chimerism on days 28, 56 and 84 were 79%, 86% and 90%, respectively, consistent with progressive increase in donor chimerism for most patients. Among the 192 patients transplanted, there were 13 nonfatal graft rejections (6.8%). Most of the rejections occurred in the group conditioned with 2 Gy TBI alone without prior autologous HSCT (10 patients, 17%). There were three patients (all three with MDS/CMML) with graft rejection among those conditioned with fludarabine plus 2 Gy TBI for an overall rejection incidence of 3.4% in this group. There were no rejections seen in the group treated following a planned autologous HSCT. The addition of fludarabine to the TBI resulted in higher donor chimerism by day 28, and the group treated with tandem autologous and nonmyeloablative allogeneic HSCT had the highest overall donor chimerism.

2.7. Incidence of GVHD

The overall incidence of GVHD was 49% in patients with stable engraftment with an incidence of grades II, III and IV GVHD of 33%, 11%, and 5%, respectively. There was no increase in the incidence of acute GVHD for patients who received fludarabine in the conditioning regimen. With decrease in rejection without increase in

toxicity or GVHD, the addition of fludarabine to 2 Gy TBI was consistent with an improved transplant outcome.

2.8. Survival and Complete Remission of Disease

For the 192 patients, the non-relapse mortality before day 100 was 6%. With a median follow-up of 9.6 months, overall survival was 59%, nonrelapse mortality was 22% and death from disease progression/relapse was 18%. Based on actuarial Kaplan-Maier analysis, the projected 2-year survival and progression free survival was 50% and 40%, respectively.

Complete remission (CR) of disease was observed in a majority of patients because of the potent GVL effect. Molecular remissions were seen in patients with CML and CLL, and morphologic remissions were seen in patients with AML, ALL, MDS, MM, NHL, and HD. Molecular remissions in patients with CML were observed at a median of 5.5 months (range, 320) after transplant [11]. These observations are consistent with an important feature of the GVL effect of nonmyeloablative allogeneic HSCT. After mixed chimerism is established and withdrawal of immunosuppression is initiated, the graft-versus-host effect of the T-cell-replete graft results in a progressive increase in donor chimerism followed by a subsequent GVL effect with eradication of underlying disease, which can take up to several months to accomplish.

2.9. Tandem Autologous and Nonmyeloablative Allogeneic HSCT

Combining cytoreduction by autologous HSCT followed several weeks later with nonmyeloablative allogeneic HSCT is a highly promising area of investigation for patients with MM. The rationale for this approach in patients with MM is that myeloablative allogeneic HSCT, while potentially curative due to the graft-versus-myeloma effect, has been historically associated with unacceptably high transplant-related mortality for a majority of MM patients. High-dose therapy with autologous PBSC support results in effective cytoreduction of disease with low transplant-related mortality, but eventually nearly all patients develop disease relapse or progression. The approach of separating the high-dose conditioning regimen from the immunotherapeutic effect of the allograft serves to decrease the transplant-related mortality yet provides the curative allogeneic effect of graft-versus-myeloma. Of the 32 MM patients (median age of 55 years) transplanted with a tandem autologous/nonmyeloablative allogeneic HSCT with a median follow-up of 328 days from the allograft, overall survival was 81%. CR was observed in 53%, with partial response in 31% of patients [12].

2.10. Donor Lymphocyte Infusion

The use of donor lymphocyte infusions (DLI) was initially thought to be an important component to the

nonmyeloablative allogeneic HSCT. However, given the nearly uniform spontaneous conversion to complete donor chimerism, DLI are no longer included in the treatment protocols. DLI were given to 32 patients a median of 88 days after nonmyeloablative HSCT [13]. The indications for DLI were mixed chimerism (n=18) or disease progression (n=14). For 10 patients with less than 50% donor T-cell chimerism at day +56, or +84, DLI did not result in increasing donor chimerism and did not prevent subsequent graft rejection. Three patients with greater than 50% donor T-cell chimerism had an increase in donor chimerism after DLI. DLI were given to 14 patients with relapsed or progressive or persistent disease, resulting in two CR, two PR, one stable disease and nine disease progressions. Four patients developed acute GVHD and four others developed chronic GVHD. In summary, DLI after nonmyeloablative HSCT had rather poor efficacy in increasing low degree of donor chimerism and in treating morphologic disease relapse/progression.

2.11. Unrelated Donor Nonmyeloablative HSCT

Encouraged by the success of the nonmyeloablative HSCT with HLA-matched related donors, a multi-center study of 10 of 10 HLA-antigen matched unrelated donor was initiated [14]. Sixty-three patients with hematological malignancies received a nonmyeloablative regimen of fludarabine 30 mg/m²/day for 3 days and 2 Gy TBI followed by unrelated donor HSCT and postgrafting immunosuppression with MMF and CSP. The source of hematopoietic stem cells were PBSC (n=48) and marrow (n=15). Unrelated donors were selected on the basis of serologic matching for HLA-A, -B, and -C and allele level matching for HLA-DRB1 and -DQB1. The diagnoses for the 63 study participants included MDS (n=22), CML (n=11), NHL (n=10), AML (n=7), MM (n=4), ALL (n=2), HD (n=2) and Waldenstrom's macroglobulinemia (n=1). The median age was 53 (range 4-69) years with a median follow-up of 5.5 (range 0.6-15.6) months. Over 30% of patients had failed previous autologous or allogeneic HSCT, and all were at high risk for treatment-related mortality based on either age, medical co-morbidities or diagnoses of advanced-stage disease.

2.12. Stable Engraftment of PBSC Versus Marrow

Sustained donor engraftment was observed in 46 of 63 (73%) patients. Rejection was highly associated with diagnoses of CML/CLL and MDS. Recipients of PBSC grafts had improved rates of sustained engraftment (37/48) compared to recipients of marrow (9/15). Graft rejection resulted in prolonged marrow aplasia in 5 of 17 patients, which contributed to the deaths of three patients. The remaining 12 patients with graft rejection had autologous reconstitution. Pharmacokinetic studies in a subset of patients showed that mycophenolic acid, the active metabolite of MMF, had a half-life of 3.6 hours. The short half-life of mycophenolic acid and the rapidly

reversible binding of the target enzyme inosine monophosphate dehydrogenase, suggested that the twice daily MMF dosing schedule may have been suboptimal for recipients of unrelated donor grafts.

2.13. GVHD, Survival and Disease Remission for Nonmyeloablative URD HSCT

Acute GVHD of grades II, III and IV occurred in 50%, 13% and 0%, respectively, among the 46 patients with sustained donor engraftment. Chronic GVHD requiring therapy occurred in 50% of patients with stable grafts. Of the 63 patients enrolled, 46% had died: 32% due to underlying disease and 14% from nonrelapse causes. Fifty-four percent of patients were alive: 37% were in CR, 3% in PR and 14% with disease progression or relapse. Significant differences were seen in the 1-year Kaplan-Meier estimates of survival (45% versus 9%; $P=0.02$) and the progression-free survival (36% versus 7%; $P=0.002$) for recipients of PBSC compared to marrow. This study showed that unrelated donor nonmyeloablative HSCT was feasible and relatively safe for patients with advanced hematological malignancies not eligible for conventional HSCT. Important findings were the poor rates of donor engraftment and worse survival in recipients of marrow compared to PBSC. Because of these results, PBSC has become the only acceptable stem cell product for unrelated donor nonmyeloablative HSCT protocols. In addition, three times per day MMF dosing may improve both engraftment rates and GVHD control in this patient population.

3. Summary and Future Challenges

Taken together, the nonmyeloablative allogeneic HSCT results with either HLA-matched related or unrelated donors represent a significant advance in the treatment of patients with hematological malignancies. Nonmyeloablative transplantation provides the potentially curative therapy of an allograft with a low transplant-related mortality for patients who were previously ineligible for conventional HSCT. However, complications after nonmyeloablative HSCT include the problems of disease relapse, infectious complications and GVHD. These will continue to require development of new strategies to improve upon outcome after allogeneic HSCT.

GVHD remains a potentially significant complication following nonmyeloablative HSCT. Initially in the first 45 patients treated with HLA-identical related PBSC grafts, the postgrafting immunosuppression regimen of MMF and CSP extended to days 28 and 35, respectively. To reduce the risk of subsequent GVHD without compromising the GVL effect, the treatment protocol for recipients of HLA-identical related grafts was modified to extend the CSP immunosuppression depending on the risk of disease progression. For patients with aggressive disease, CSP was tapered from day 56 to day 75. For those with indolent disease, CSP was tapered from day 56 to 180. Current experience with MMF/CSP immunosuppression following the nonmyeloablative HSCT sug-

gests that for most patients, when GVHD develops it can be controlled with the addition of standard immunosuppressive therapy such as prednisone [8]. The onset of acute GVHD following nonmyeloablative HSCT appears to be delayed compared with myeloablative HSCT. However, the potentially prolonged use of immunosuppression results in delayed, potentially life-threatening infectious complications. Future efforts to facilitate the GVL effect of the allograft while effectively preventing acute and chronic GVHD remain a significant challenge.

While the precise tumor response profiles are still being defined, certain diseases appear to be more susceptible to the GVL effect. It appears that indolent lymphoid and myeloid malignancies are more susceptible to the allograft effect following nonmyeloablative transplant, while certain aggressive malignancies in advanced stages (relapsed AML and advanced MDS) have higher incidences of disease recurrence. The exact reasons for these differences in GVL response are unclear, but may be related to the rapid rate of clonal expansion of tumor cells in advanced malignancies that may outgrow the rate of donor T-cell tumor cell killing. The choice and duration of postgrafting immunosuppression for GVHD prophylaxis is likely to affect the ability of donor cytotoxic T cells to develop and sustain anti-tumor responses. Thus while intensive or prolonged postgrafting immunosuppression may decrease the incidence of GVHD, it may also decrease the GVL effect. Alternatively, intensive cytoreduction with autologous HSCT followed by nonmyeloablative allogeneic HSCT may circumvent the problem of rapid tumor growth relative to the GVL response. To further improve upon the GVL effect in the future, nonmyeloablative HSCT may be used as a platform for adoptive immunotherapy for the infusion of cytotoxic T cells directed at tumor-specific or hematopoietic-restricted minor histocompatibility antigens [15], dendritic cell therapies [16] or tumor vaccination strategies.

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References

1. Thomas ED, Storb R, Clift RA, et al. Bone-marrow transplantation. *N Engl J Med.* 1975;292:832-843, 895-902.
2. Ringden O, Horowitz MM, Gale RP, et al. Outcome after allogeneic bone marrow transplant for leukemia in older adults. *JAMA.* 1993;270:57-60.
3. Math G, Amiel JL, Schwarzenberg L, Catton A, Schneider M. Adoptive immunotherapy of acute leukemia: Experimental and clinical results. *Cancer Res.* 1965;25:1525-1531.
4. Weiden PL, Flournoy N, Thomas ED, et al. Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. *N Engl J Med.* 1979;300:1068-1073.
5. Horowitz MM, Gale RP, Sondel PM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood.*

- 1990;75:555-562.
6. Martin PJ. Overview of marrow transplantation immunology. In: Thomas ED, Blume KG, Forman SJ (eds): Hematopoietic Cell Transplantation. Boston: Blackwell Science, p.19-27, 1999.
 7. Storb R, Yu C, Wagner JL, et al. Stable mixed hematopoietic chimerism in DLA-identical littermate dogs given sublethal total body irradiation before and pharmacological immunosuppression after marrow transplantation. *Blood*. 1997;89:3048-3054.
 8. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood*. 2001;97:3390-3400.
 9. Weissinger F, Sandmaier BM, Maloney DG, Bensinger WI, Gooley T, Storb R. Decreased transfusion requirements for patients receiving nonmyeloablative compared with conventional peripheral blood stem cell transplants from HLA-identical siblings. *Blood*. 2001;98:3584-3588.
 10. Sandmaier BM, Maloney DG, Gooley T, et al. Nonmyeloablative hematopoietic stem cell transplants (HSCT) from HLA-matched related donors for patients with hematologic malignancies: clinical results of a TBI-based conditioning regimen [abstract]. *Blood*. 2001;98 (Part 1):742a-743a.
 11. Sandmaier BM, Hegenbart U, Shizuru J, et al. Nonmyeloablative hematopoietic stem cell transplantation (HSCT) from HLA-identical siblings for treatment of chronic myelogenous leukemia (CML): induction of molecular remissions [Abstract]. *Blood*. 2001;98(Part 2):371b.
 12. Maloney DG, Sahebi F, Stockerl-Goldstein KE, et al. Combining an allogeneic graft-vs- myeloma effect with high-dose autologous stem cell rescue in the treatment of multiple myeloma [Abstract]. *Blood*. 200;98(Part 1):434a-435a.
 13. Maris MB, Sandmaier BM, Niederwieser D, et al. The effect of donor lymphocyte infusions (DLI) on chimerism and persistent disease after nonmyeloablative hematopoietic stem cell transplant (HSCT) [Abstract]. *Blood*. 2000;96(Part 1):477a.
 14. Maris M, Niederwieser D, Sandmaier B, et al. Nonmyeloablative hematopoietic stem cell transplants (HSCT) using 10/10 HLA antigen matched unrelated donors (URDs) for patients with advanced hematologic malignancies ineligible for conventional HSCT [abstract]. *Blood*. 2001;98(Part 1):858a.
 15. Warren EH, Gavin M, Greenberg PD, Riddell SR. Minor histocompatibility antigens as targets for T-cell therapy after bone marrow transplantation. *Curr Opin Hematol*. 1998;5:429-433.
 16. Greenberg PD, Riddell SR. Cellular Therapy. In: Austen KF, Burakoff SJ, Rosen FS, Strom TB (eds): Therapeutic Immunology. Malden, MA: Blackwell Science, Inc, p.550-573, 2001.