Manipulating the Immunologic Characteristics of Both Graft and Host to Improve Transplant Outcome

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The depletion and purging of T cells, improvements in hematopoietic engraftment, and modulation of host immune attributes in graft engineering are reviewed.

Background: Several critical outcomes of allogeneic stem cell transplantation for hematologic malignancies such as engraftment, incidence of graft-vs-host disease (GVHD) and disease-free survival depend on a balance between residual host and infused donor T cells and on chemosensitivity of the underlying disorder. Manipulating cell compartments of the allograft does affect long-term outcome.

Methods: The authors review investigations on the effect of blood and marrow graft components, treatment regimens, and immunologic interventions on eventual transplant outcome, an approach termed "graft engineering." Results: Major advances in graft engineering over the last decade are presented as a series of related developments or levels that derive from the goals of reducing GVHD and minimal residual disease.

Conclusions: Morbidity and mortality of GVHD have decreased markedly by methods of T-cell depletion but at the expense of recurrent disease. Cellular therapy and immunotherapy show promise in potentially eradicating residual disease posttransplant.

Introduction: The Basis for Graft Engineering

Once considered experimental therapy for patients without any other therapeutic recourse, bone marrow transplantation (BMT) has become an accepted treatment modality for a variety of disease states. Its expansion into many new areas including solid tumors (eg, breast cancer, ovarian cancer, lung cancer, melanoma) and its much earlier use in the treatment schema are in the investigational stages pending completion of clinical trials. A major advance in the last decade has been the identification of alternative stem cells sources including peripheral blood stem cells (PBSC), cord blood, ex vivo expanded products, and alternative donors. The generic term, hematopoietic stem cell transplantation (HSCT), is used throughout this document to denote the use of myeloablative therapy requiring stem cell (of any source) rescue except when discussing a specific therapeutic modality (ie, BMT, cord blood, or PBSC transplantation). Originally, BMT started with an allogeneic approach. However, there has been increasing development in autologous sources of hematopoietic stem cells over the last two decades. Besides a restricted donor pool (only fully HLA-identical sibling donors were initially used), allogeneic BMT was associated with high posttransplant morbidity and mortality. Initially, 70% of allogeneic BMT patients receiving unmanipulated hematopoietic grafts develop acute graft-vs-host disease (GVHD) with one third of these patients rapidly succumbing to this complication or associated immunosuppressive syndromes or infections. Of patients surviving more than 100 days, half will later develop chronic GVHD, which has an attendant mortality of almost 50%. These complications increase still further for those individuals who receive an HLA-mismatched or HLA-unrelated donor graft.

With all these risks, why is allogeneic HSCT still used as first priority in many instances? To date, allogeneic BMT still generates the highest cure rates, largely due to its inherent antitumor (or graft-vs-leukemia) properties that result in low relapse rates.2,3 Autologous HSCT carries no morbidity related to GVHD or its associated complications. In fact, use of autologous PBSC results in decreased morbidity with mortality rates in the peritransplant period being <5% in many studies. However, the major long-term complication of autologous HSCT is relapse, which can be as high as 100% over time in some disease states.

As improvements in supportive care, antimicrobial and immunosuppressant therapy, growth factor utilization, and health care delivery are assimilated into transplantation schema, increasing emphasis has been placed on improved quality of life. In the next decade, transplant, as a modality, must reconcile the differences between stem cell sources with a resultant improvement in the quality of life and converge on exploiting the antitumor properties of the hematopoietic stem cell (HSC) graft and host to decrease relapse. For allogeneic BMT, T-cell depletion (TCD) of donor marrow was initially viewed as a major advance toward conquering the above problems since both animal and human studies implicated T cells as the primary mediators of GVHD. Surprisingly, the few randomized TCD trials did not show improved overall disease-free survival (DFS) over those patients receiving an unmanipulated graft. While the latter showed high death rates from GVHD, TCD marrow...
recipients were dying from graft failure, leukemic relapse, and B-cell lymphoproliferative disease—all previously low incidence complications. Subsequent studies have confirmed that ancillary marrow (other than pluripotent stem) cell populations do mediate GVHD but that they and/or other cells also facilitate engraftment and possess antileukemic properties. Many of the TCD techniques radically deplete ancillary cell populations (including committed progenitor cells) via nonspecific loss.

Problems such as these underscored the need for a systematic approach for investigating the effect of various HSC graft components, treatment regimens, and immunologic interventions (including the use of cytokines and immunomodulators) on eventual outcome. This approach, which was originally pioneered in allogeneic BMT, was termed graft engineering and relied on a series of interdependent phase I and II clinical trials used in succession to systematically alter the lymphohematopoietic characteristics of the graft and/or the host to improve long-term survival. This design also facilitated the incorporation of new technology (investigational devices) whose characteristics could be easily evaluated and compared to the previous study that did not include this step. This also allowed a direct comparison of various graft characteristics, such as stem cell content, lymphocyte subsets, or natural killer (NK) cell activity, to "performance" characteristics that are represented in patient outcomes such as acute and chronic GVHD, engraftment, inpatient hospitalization stay, infections, blood product utilization, relapse, performance status, and overall quality of life. Of course, not all clinical trials or transplant programs followed this format, although there has been a striking convergence over the last decade in the major programs. Most now focus on reducing relapse, increasing the donor pool, and extending this modality into new vistas, such as neurologic diseases, autoimmune disorders, and solid organ transplantation. We have attempted to stratify progress in this field as a series of levels that may not be in actual time sequence but exemplify the major advances in graft engineering.

Level I: T-Cell Depletion and Purging

Prevention of GVHD

Initially, various pharmacologic means were used to decrease the incidence and severity of GVHD. In general, the immunosuppressive agents such as cyclosporine A, methotrexate, and corticosteroids are effective in reducing the incidence of GVHD but have little impact on patients who develop extensive GVHD that does not respond or that recurs after initial treatment. As discussed above, TCD in itself did little to improve outcome because of the new complications introduced by this manipulation. Not all TCD techniques are equal, however. Physical separation methods such as soybean agglutinin/T-cell rosetting, elutriation, and specific monoclonal antibody (ie, anti-CD8) depletion continue to be used successfully in several centers (Table 1). In general, the physical methods of TCD by themselves are sufficient for the acute leukemias and lymphomas, but relapse is still problematic in chronic myelogenous leukemia (CML), myelodysplastic syndrome, and multiple myeloma.

<table>
<thead>
<tr>
<th>Table 1. -- Methods of Lymphocyte Depletion</th>
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<tr>
<td>Physical Separation (Nonspecific T and B cells)</td>
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<tr>
<td>Counterflow centrifugal elutriation</td>
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<tr>
<td>Soybean agglutinin/E-rosetting formation</td>
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<tr>
<td>Density gradient centrifugation</td>
</tr>
</tbody>
</table>

Immunological

- Monoclonal antibodies* (ie, anti-CD2, 3, 4, 5, 6, 8)
- T-cell specific: anti-CD2, 3, 4, 5, 6, 8
- Non-specific (T and B cells): CAMPATH-1

*Used (1) alone or in combination with complement or (2) conjugated with toxins, biotin, or magnetic beads to permit negative or positive selection of cells.

Purging Autografts

During this same time period, methods were developed to purge tumor cells from autologous graft products in an effort to reduce the high rate of relapse inherent in autologous BMT. Several single and multiple antibody cocktail combinations have been used against specific tumors with varying success. Tumors of similar type differ in their antigen density among individuals and even within the host itself. It is increasingly difficult to remove the low antigen expressing cells without high, nonspecific cell loss. Most of these trials were single-institution trials using reagents not available to other centers. A more general approach was taken with pharmacologic purging. Drugs such as 4-hydroperoxycyclophosphamide (4HC) and mefosphamide preferentially destroy a wide spectrum of tumor cells while sparing a significant proportion of pluripotent stem cells. Unlike tumor cells, these cells contain high levels of aldehyde dehydrogenase that rapidly detoxify the active metabolites. Almost all committed progenitor cells are destroyed in this process, which leads to prolonged periods of aplasia while their numbers are reconstituted from the pluripotent stem cells. Several clinical trials in Europe and the United States showed a reduction in relapse, especially in patients with acute myelogenous leukemia without excessive morbidity. However, the rising costs of health care are at odds with methodologies that lead to six- to eight-week hospitalizations for aplasia. The Food and Drug Administration (FDA) did not approve 4HC for clinical use because of the lack of a prospective, randomized, clinical trial; this lead to its unavailability for several years. Further development of 4HC is under review by the National Cancer Institute and a pharmaceutical sponsor.

Level II: Improving Hematopoietic Engraftment

Autologous PBSC Transplantation

Initially, collection of PBSC products in "steady state" were unimpressive; they were mostly performed in patients with low yield marrow harvests or in whom significant marrow disease existed. Large numbers of apheresis procedures were required, and engraftment, especially platelets, was significantly prolonged. Collecting products following hematopoietic rebound post-chemotherapy and later, the addition of hematopoietic growth factors, reduced the number of products required for durable engraftment. Later, the CD34 epitope found on early human HSC was found to be an adequate surrogate marker to determine graft adequacy. It was felt that PBSC transplantation provided a means of "in vivo purging" because grossly, the products appeared to have less tumor cell contamination than their marrow harvest counterparts. The use of PBSC along with posttransplant growth factors also significantly reduced posttransplant morbidity by reducing the aplastic period and reduced inpatient hospitalization time, antibiotic days, and blood product utilization. Unfortunately, it is now obvious that tumor cells
CD34+ Stem Cell Selection

An alternative approach to tumor depletion is to isolate the HSC themselves via positive selection and allow the passive washout of all other cells, including tumor. Positive selection technology using monoclonal antibodies directed against the CD34 epitope has eloquently demonstrated that CD34+ cells alone are sufficient for hematopoietic reconstitution in the autologous setting.26-27 Engraftment times can be shortened by using CD34+ selected PBSC alone or in combination with similarly selected marrow followed by posttransplant growth factors.28 A recently completed phase III clinical trial using CD34+ PBSC selection in multiple myeloma has demonstrated rapid engraftment, low morbidity, and a mean 3 log reduction in contaminating tumor cells when compared with the unselected study arm.29,30 It is still too early to determine the impact, if any, on DFS. Of course, tumors bearing the CD34 epitope will be captured and concentrated by this approach, reducing its usefulness in myeloid disorders. It is doubtful whether this technology will show a significant reduction in posttransplant relapse, but it opens enormous potential for combining several engineering approaches and for further advancement in positive selection technology.

Allogeneic Stem Cell Augmentation

Delayed engraftment kinetics were commonly seen with the physical TCD methods.4,31,32 This was accompanied by mixed hematopoietic chimerism. Low total HSC following manipulation and unopposed host-vs.-graft responses are thought to be responsible for these observations. Use of these methodologies in unrelated or mismatched HSCT could result in high graft failure rates. Slow engraftment may also provide a growth advantage to residual tumor. Animal data suggested that increasing the stem cell dose may overcome these problems.33 Small-sized CD34+ cells are depleted along with lymphocytes during elutriation.34,35 Positive selection technology using immunomagnetic columns can be used to capture these CD34+ cells and augment the stem cell complement of the graft. Cells in the small-sized fraction first are reacted with biotinylated anti-CD34 antibody and then passed over a column of avidin-coated beads (CEPRATE SC, CellPro, Inc, Bothell, Wash), which binds CD34+ cells selectively. Bound cells then are eluted from the column by gentle agitation of the beads (Figure). We have used this approach successfully to double the CD34+ stem cell content of elutriated allografts.36 Selected outcomes of elutriation trials at The Johns Hopkins Oncology Center over the past decade are shown in Table 2. Engraftment is rapid in both the HLA-matched and -mismatched setting using both sibling and unrelated donors. Full donor chimerism is now demonstrated by day 100. The reappearance of host cells once full chimerism is demonstrated now represents relapse.37 This approach has dramatically reduced inpatient hospitalization times, blood product and antibiotic usage, and acuity, and it has been associated with a 40% reduction in hospital charges. Fifteen percent of our allogeneic (including matched unrelated donor) recipients undergo myeloablative therapy and HSC as outpatients without ever requiring inpatient hospitalization.

<table>
<thead>
<tr>
<th>Graft</th>
<th>T-cells/kg</th>
<th>Days to Engraftmenta</th>
<th>Percentage:</th>
<th>Failure</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Neutrophils</td>
<td>Platelets</td>
<td>Acute GVHD</td>
</tr>
<tr>
<td>Elutriation R/O Fraction</td>
<td>5 x 10^5</td>
<td>21</td>
<td>41</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>1 x 10^6</td>
<td>18</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>R/O + CD34+ Fractions</td>
<td>5 x 10^5</td>
<td>16</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Unmanipulated BM</td>
<td>5 x 10^6</td>
<td>17</td>
<td>25</td>
<td>50</td>
</tr>
</tbody>
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1. neutrophils, ANC >500; platelets, >50,000 unsupported
2. clinically significant (> grade 1)
R/O = rotor off
BM = bone marrow
TRM = transplant-related (nonrelapse) mortality

Mobilization of allogeneic donors results in large numbers of HSC that have been used in a similar fashion.37-39 While unmanipulated PBSC products engraft rapidly, they are associated with significant morbidity related to acute and chronic GVHD. These products contain large numbers of T cells. The use of TCD has had mixed results. Apparently, T-cell numbers are still too high using CD34+ selection.28 However, use of soybean agglutinin/T-cell rosetting to concentrate the HSC in combination with similarly treated marrow has been used in the unrelated and mismatched setting with considerable success.40 It appears that allogeneic PBSC products will require manipulation similar to their marrow counterparts. The composition of mobilized products is still under study and may lend important clues for the engineering process.

Level III: Modulating Host Immune Attributes
Despite the advances discussed above, relapse still remains the major complication for autologous HSCT as well as for allogeneic HSCT where manipulated grafts are used. It is generally agreed that preparative regimens currently used for myeloablation leave behind at least low numbers of tumor cells, often possessing multiple drug-resistance characteristics. Host immunity is severely depressed following HSCT\(^41\) and is incapable of dealing with even small levels of minimal residual disease. Acceleration of immune reconstitution or specific augmentation of graft-vs-leukemia effectors would be expected to impact on minimal residual disease and translate to lower relapse rates.

**Induction of Autologous GVHD**

Early human clinical data suggested that there was an association with lower relapse rates in patients who had developed chronic but not acute GVHD.\(^2,42\) An autoimmune syndrome is reproducibly induced in both animals and humans following autologous HSCT that is morphologically and mechanistically similar to chronic GVHD.\(^43,44\) Unfortunately, the antitumor activity was low even in histologically documented cases. The use of biologic response modifiers was investigated, first in animal models, to determine if the graft-vs-leukemia response induced by this syndrome could be augmented. Interferon can force the surface expression of class II (in addition to class I) antigens in low-expressing tumors, while IL-2 will expand the autoimmune effector cells specific to these antigens. Several phase I trials to determine maximum tolerated dose of these agents alone and in combination have now been completed\(^45,46\) (G.B. Vogelsang, personal communication, 1998). Current trials in patients transplanted with resistant disease or \(\geq 2\) relapse show a 30% to 40% increase in DFS at 4 years compared with historical controls (G. Vogelsang, personal communication, 1998). A similar phase II trial in metastatic breast cancer failed to show improvement in DFS (M.J. Kennedy, personal communication, 1998). There is concern that the tumor burden derived from the infused graft may still overwhelm the immune response. A randomized trial using CD34+ selected PBSC with autologous GVHD induction is now underway at this institution for metastatic breast cancer. It is uncertain whether the graft-vs-leukemia benefit is active in the solid tumor setting.

**Use of Cytokines in the Autologous Setting**

Several groups have used cytokines such as IL-2 to boost immune effector activity posttransplant.\(^47,50\) Although increased NK and cytolytic activity can be easily demonstrated in vitro, it is still uncertain whether this translates into a survival benefit in terms of relapse reduction. Newer cytokines are being explored such as IL-12 and IL-15, alone and in combination with IL-2. A new agent in early trial development is FLT-3 ligand.\(^51\) This multipotential growth factor also expands the dendritic cell pool in both animals and humans.\(^52,53\) It is hoped that this will further augment antitumor responses, especially in the settings described above.

Cytokines can also be used as antitumor agents themselves. In CML, the tumor cells are growth factor independent. In fact, laboratory studies show that increased concentrations of growth factor hastens apoptosis in these cells while augmenting the growth of normal stem cells.\(^54\) The current clinical trial in CML at this institution exploits these properties. Patients with CML undergo an autologous marrow harvest. These cells are elutriated to obtain the small-sized, lymphoid-rich fraction that also contains the majority of pluripotent CD34+ BCR-ABL– stem cells (along with the contaminating BCR-ABL+ cohorts). This fraction is ex vivo expanded in the presence of GM-CSF for 72 hours before cryopreservation. The patient then receives daily GM-CSF for 60 days posttransplant in a similar effort to promote the growth of the normal stem cell pool and differentiation of the abnormal component. As expected, engraftment kinetics are significantly delayed due to the depletion of committed progenitor cells from the graft. Two or three cycles of pseudo-engraftment have been observed wherein peripheral counts begin to recover and then dissipate. Analysis of these time points reveals the presence of BCR-ABL+ clones. At approximately day 40, true engraftment is achieved. To date, 12 patients have been entered into this study. At a median follow-up of 9 months, four of eight evaluable patients are in full molecular remission. To date, four patients have died of various causes (veno-occlusive disease, graft failure, relapse) (R. Jones, personal communication, 1998).

**Adaptive Immunotherapy: Donor Leukocyte Infusion**

Allogeneic graft manipulation has significantly decreased posttransplant-related morbidity, which has extended this modality to older age patients, more disease states (including nonhematologic diagnoses), and across HLA barriers. Unfortunately, with more patients surviving transplant, an ever-increasing number will relapse. Immunologic tolerance conferred by allogeneic transplant is not adversely affected by current graft manipulation methods. Donor leukocyte infusions (DLI) at the time of relapse has been associated with remissions, especially in CML and multiple myeloma.\(^55-57\) Complications of this therapy include aplasia (graft failure, infection) and acute and chronic GVHD. It is suspected that high tumor burdens in the acute leukemias and aggressive lymphomas hinder its effectiveness in these situations. Currently, induction therapy in combination with DLI is being investigated for acute leukemia in the United States and Europe. It is almost impossible to infuse donor leukocytes in the immediate transplant period in conjunction with unmanipulated donor grafts because of the additive toxicities resulting from GVHD. However, TCD grafts are ideal substrates to conduct studies of prophylactic DLI. Antitumor augmentation should be more effective closer to transplant (in the minimal residual disease state) than at the time of relapse. Very few groups have studied the effect of specific donor leukocyte populations for reducing these complications while maintaining antitumor activity. Chaplin and colleagues\(^58\) have demonstrated that CD8 depletion of donor lymphocyte grafts can achieve molecular remissions in CML patients who have relapsed following TCD BMT. The use of CD8-depleted DLI products is associated with a lower incidence of GVHD and aplastic complications. It is unclear which cells are responsible for achieving remission in this setting since CD4+ T cells, CD56+ NK cells and other rarer cell populations are all still present in the donor graft. These data support previous trials showing that specific CD8 depletion of the initial marrow graft can be equally effective in reducing relapse in CML.\(^59\) Animal data suggest that CD56+ NK cells may also provide effective antitumor activity in acute myelogenous leukemia and other diseases.\(^60\) Together, these clinical trials suggest that modulation or enhancement of specific ancillary cell populations following TCD may reduce the incidence of relapse in patients at high risk for relapse.

**Adaptive Immunotherapy: Using Ancillary Cells to Augment Antitumor Activity**

More benefit may be derived from administering specific ancillary cell populations prophylactically. Unmanipulated donor leukocytes have been infused in specified time points following transplantation with an elutriated graft.\(^61\) Unfortunately, stem cell numbers were unusually low in this trial, which did not include CD34+ augmented grafts resulting in a high frequency of graft failure. Another approach would be to utilize the ancillary cells that remain after graft TCD. These graft-derived ancillary cells may include beneficial antitumor subpopulations in higher frequency than those available via donor leukopheresis. New developments in positive selection technology now permit sequential selection of ancillary cell populations from the graft. One can envision the complete dissection of the hematopoietic graft into specific CD34+ fractions that can be either used immediately to construct the engineered graft or stored for later use. Preliminary large-scale experiments using the CD34– cells that are not infused following CD34+ augmentation/elutriation show that CD4+, CD8+, and CD56+ cells can be sequentially obtained in high purity and yield using the respective biotinylated monoclonal antibodies and the CellPro CEPRATE avidin column.\(^62,63\) In vitro functional (cytolytic) activity can be demonstrated against appropriate targets using the purified CD4+ and CD56+ cells, even after control rate freezing, cryopreservation, and thawing. There is some concern that “uncaptured” antibody–coated cells from the first selection will be carried over into the sequential selection. We have shown that this does occur with the avidin–biotin selection, but this “contamination” can be beneficial depending on the initial positive selection performed. If the cells were first selected for CD34, which is the most likely process, the
contaminating population is composed of stem cells. Although representing only a small percentage of the total selected product, they would still equal as much as 20% to 40% of the initial CD34+ cells applied to the column. Use of both selected products results in near total recovery of all the CD34+ cells contained in the unmanipulated graft. Few would argue that this type of contamination is detrimental to clinical outcome. The full potential of adoptive immunotherapy cannot be gauged at this time, but it offers many promising opportunities for graft engineering.

Augmenting Allogeneic Immune Response

Initially, investigators were reticent to use immune modulators in the allogeneic setting because of unwanted exacerbation of GVHD. The use of TCD grafts allows the use of posttransplant cytokines such as IL-2 because of the relatively low frequency of donor GVHD effector cells. Current experimental data suggest that IL-2 used at low dose (<=1 x 10^6 IU/m^2) will be sufficient to stimulate NK/LAK cells but will not trigger the abundant low-affinity receptors found on T cells, thus preventing their participation in a GVHD reaction. The use of a TCD or “cytotoxic effector modulated graft” also reduces the life-threatening side effects that would otherwise occur from protracted T-cell stimulation. Several recent studies have demonstrated that the use of post-BMT IL-2 can increase NK function and absolute peripheral blood CD56+ cell counts. An earlier study by Soiffer et al also showed that low-dose continuous infusion (CI) IL-2 could be safely started 60 days post-BMT (mean) with compliance to 12 weeks of therapy. Follow-up was sufficient in the latter study to show a significant decrease in relapse rates in patients who completed the course of posttransplant IL-2 therapy. We have currently opened an optimal dose–finding trial of post-BMT IL-2 in patients at high risk of relapse to determine if NK function and CD56+ cell numbers can be increased without incurring increased morbidity. All patients first receive a CD34+ augmented/elutriated graft to minimize post-BMT complications. We are also accruing patients with high-risk CML to receive CD34+ augmented/elutriated grafts and post-BMT GM-CSF. Previously (and not discussed to this point), patients with a diagnosis of CML who received an elutriated graft alone had unacceptably high relapse rates (nearly 100%). Increased stem cell dose (CD34+ augmentation) and the apoptotic effect (on BCR/ABL+ stem cells) of high-dose myeloid growth factors are expected to significantly decrease this risk. The 12 patients (9 evaluable: 2 patients <day 50) currently enrolled (median follow-up: 18 months) remain both cytogenetically and molecularly free of disease. Other than the first patient who started cyclosporine A late and developed fatal GVHD, no patient has developed acute or chronic GVHD, and all have 100% performance status (R. Jones, personal communication, 1998).

Level IV: Beyond Current Graft Engineering Protocols

Further Approaches to Reducing Relapse

If toxicity remains acceptable on trials such as these but sufficient cytolytic activity has not been achieved, future studies may incorporate positively selected ancillary cell populations (ie, CD56+ NK cells, CD4+ T cells) along with cytokines (IL-2, IL-12, IL-15, etc) to further augment activity. Specific ancillary cell populations can also be expanded ex vivo using various cytokine combinations. These effectors can be used fresh and/or cryopreserved for use at relapse, or they can be given back at defined times post-BMT. Currently, we and other investigators are expanding Epstein-Barr virus–specific donor lymphocyte clones for use against B-cell lymphoproliferative disorders. While this has not been a complication of elutriation, it has a high incidence with solid organ transplantation and also with other forms of TCD. It is likely that different disease states will require different ancillary effectors and cytokine combinations. Current DLI trials (especially those employing selected subpopulations) may help to define this disease hierarchy for future up-front graft engineering studies.

The Future

A systematic approach to hematopoietic graft manipulation can significantly impact on morbidity and quality of life following HSCT. Acute and chronic GVHD, blood product and antibiotic usage, inpatient hospitalization, acuity, costs, and survival (especially in patients older than 40 years of age) have been improved. There are still many problems encountered with HLA-mismatched or -unrelated donor transplants that must be resolved. It is not totally clear why children under 18 years of age have significantly better survival than adults in this setting. The use of cord blood (which has not been discussed to this point) is fraught with its own set of problems. Current trials sponsored by the National Heart, Lung, and Blood Institute may help resolve several of these issues. It is expected that stem cell sources eventually will be interchangeable and that they will be used in conjunction with various ancillary cell populations and/or cytokine combinations that will provide augmented antitumor properties. It is likely that these purified stem or ancillary cells will be genetically engineered to further enhance their performance characteristics. Although unimaginable a decade ago, the possibility of a genetically engineered universal stem cell is not that intangible in the near future. In the meantime, small inroads into decreasing relapse provide reassurance that we are making progress; the present difficulty encountered in plotting DFS for engineered graft recipients is a case in point. At many centers, patients who had relapsed and thus removed from DFS curves are now in long-term remission following DLI and are maintaining a good quality of life. It is hoped that future graft engineering objectives directed towards relapse will be accomplished with a similar success rate as our previous endeavors.

References


