FEATURE ARTICLE

Graft Failure Following Allogeneic Blood and Marrow Transplant: Evidence-Based Nursing Case Study Review

Christine Wilson, PhD, APRN, BC, NP-C, and Terry Sylvanus, MSN, APRN, BC, AOCN®

When a patient requires an hematopoietic stem cell transplant, engraftment of the donor cells must occur for the transplant to be successful. Engraftment results when the infused donor marrow, cord blood, or peripheral blood stem cells begin to grow and reproduce in the host’s marrow. Engraftment can be defined as the first of three consecutive days with an absolute neutrophil count higher than 500 cells/mcl but also, more practically, as the first day that a patient’s peripheral blood neutrophil count is sustained at or above 500 x 10⁶/L (Wolff, 2002). If engraftment does not occur or is not sustained over time, the patient is said to have experienced graft failure (DeVita, Hellman, & Rosenberg, 2001).

No consistent definition of graft failure is found in the literature. Terminology used to describe problems with engraftment includes delayed engraftment, graft failure, primary graft failure, graft rejection, secondary graft failure, graft dysfunction, and failure to engraft. Primary graft failure, graft failure, or failure to engraft are synonymous terms meaning that the defined number of neutrophils has not been achieved by 21 or 28 days after the transplant. Graft dysfunction, or secondary or late graft failure, occurs when donor engraftment takes place initially but is unable to be sustained (Mehta et al., 1997). The marrow may or may not then be repopulated with cells from the host. Graft failure that results from immunocompetent host cells’ action on donor cells, with disease reoccurrence, is called graft rejection (DeVita et al., 2001).

Despite the advances made since the earliest days of transplant therapy, graft failure following allogeneic blood and marrow transplant is still a life-threatening complication. This article reviews the science of graft failure and uses a case study presentation to address how an oncology nursing staff was motivated by a patient's experience of graft failure. An evidence-based literature review was undertaken to answer three relevant clinical questions: (a) What factors contribute to graft failure in patients receiving allogeneic hematopoietic stem cell transplants? (b) What interventions are appropriate for these patients? and (c) How can this information assist nursing staff in providing improved care for these patients? An example of the table of evidence is provided.

Despite the advances made since the earliest days of transplant therapy, graft failure following allogeneic blood and marrow transplant is still a life-threatening complication. This article reviews the science of graft failure and uses a case study presentation to address how an oncology nursing staff was motivated by a patient's experience of graft failure. An evidence-based literature review was undertaken to answer three relevant clinical questions: (a) What factors contribute to graft failure in patients receiving allogeneic hematopoietic stem cell transplants? (b) What interventions are appropriate for these patients? and (c) How can this information assist nursing staff in providing improved care for these patients? An example of the table of evidence is provided.

One Unit’s Experience With Graft Failure

Mrs. C, a 39-year-old married woman, was treated successfully with vincristine, methotrexate, mechlorethamine, and prednisone and mediastinal radiation at the age of 28 for stage IIIB Hodgkin disease. Eight years later, she developed a secondary malignancy: acute myeloid leukemia (AML). Induction chemotherapy consisting of idarubicin and cytarabine, followed by consolidation with high-dose cytarabine alone, resulted in a complete remission for three years. Upon relapse, Mrs. C received salvage chemotherapy, again with idarubicin and cytarabine, but her disease progressed. Further treatment with idarubicine and cytarabine was complicated by multiple infections, including Pseudomonas bacterial pneumonia and positive cytomegalovirus (CMV) blood cultures, for which she received ganciclovir. Because neither of her two brothers was a match for her, a human leukocyte antigen- (HLA-) matched unrelated donor was found through the National...
Marrow Donor Registry and was a 5/6 allele match. Mrs. C received conditioning with cyclophosphamide and total body irradiation followed by peripheral blood stem cell infusion of 5.24 x 10^9 total viable cells. She received standard graft-versus-host disease (GVHD) prophylaxis with continuous IV infusion of tacrolimus and methotrexate on days 1, 3, 6, and 11. She had a prolonged period of neutropenia that failed to respond to therapy with granulocyte-colony-stimulating factor and was complicated by grade III–IV mucositis, fever, pancreatitis, and severe headaches, CMV retinitis, and intractable nausea and vomiting. A bone marrow biopsy at day +25 showed a total lack of donor hematopoietic cells in the collection, processing, or storage. During her post-transplant phase, she received standard graft-versus-host disease (GVHD) prophylaxis with continuous IV infusion of 5.24 x 10^9 total viable cells. Fifteen days after the DLI, Mrs. C’s white blood cell count began to rise; this was hoped to be a sign of engraftment. Unfortunately, blast cells were noted in her peripheral smear. A second bone marrow biopsy revealed 100% autologous cells, residual disease, and no evidence of donor cells. During her post-transplant phase, she had received levofloxacin, acyclovir, fluconazole, vancomycin, cefepime, voriconazole, foscamet, meropenem, timentin, and septrin for prophylaxis and treatment of febrile neutropenia. She remained febrile throughout her hospitalization, eventually developing pneumonia with positive sputum and blood cultures for Stenotrophomonas. At this point, Mrs. C’s prognosis was discussed with her and her spouse, and treatment options, including hospice care, were offered. Based on information about her poor prognosis, Mrs. C elected to have no further aggressive treatments. Preparations were started to allow her to return home with her husband, but her condition deteriorated rapidly and she died 10 days later.

The medical and nursing staff was surprised by this patient’s experience of graft failure. Two similar cases occurred during the same time period and were the only cases of primary graft failure the nursing staff of this blood and marrow transplant unit experienced in two calendar years. Although the staff was knowledgeable about the usual toxicities of the transplant process, the nurses were concerned about such poor outcomes. Many members of the staff worried that “something” had happened to these patients’ stem cells in the collection, processing, or administration process that resulted in the unprecedented number of graft failures. Fear was expressed that further graft failures, resulting in more patient deaths, would occur. One nurse stated that she would never again blithely tell a patient, “You should begin to engraft,” but instead would say, “We hope you will begin to engraft.” The staff questioned, What happened? Why did it happen to this patient? Did we do something wrong? Could we have done something to prevent this? What more could we have done to alleviate the suffering experienced by this patient and her family? What can be done to provide better care in the future?

**Evidence-Based Nursing Practice**

Evidence-based nursing can be defined as the integration of the best research evidence available, nursing expertise, and the values and preferences of the individuals, families, and communities that are served. The best nursing research evidence available means clinically relevant, scientifically sound studies regarding the effectiveness and safety of interventions, the specificity of nursing assessment measures, the strength of relationships with prognostic and causative factors, the cost-effectiveness of interventions, and the meaning of patient experiences or disease (Sigeta Theta Tau International Evidence-Based Practice Task Force, 2004).

The process of evidence-based nursing practice generally involves an organized approach to asking accurate and specific clinical questions, systematically searching for evidence, evaluating the relevancy and applicability of the evidence, making recommendations for practice based on the best evidence available, and evaluating the effectiveness of the practice on the basis of clinical outcomes (Rutledge & Grant, 2002). Although this concept usually is applied in relation to planned or concurrent care, it also can be a useful tool for the retrospective analysis of patient outcomes.

In this case study, the relevant clinical questions asked by the nursing staff were (a) What factors contribute to graft failure in patients receiving allogeneic hematopoietic stem cell transplants? (b) What interventions are appropriate for patients experiencing graft failure? and (c) How can this information assist nursing staff in providing improved care for similar patients in the future?

A systematic literature search was initiated to seek answers to these questions. The MEDLINE® and Cumulative Index to Nursing and Allied Health Literature® computerized databases were searched using the index terms “bone marrow transplantation,” “stem cell transplantation,” “graft failure,” “engraftment,” “outcomes,” and “quality of life.” The references of pertinent articles also were reviewed to determine whether any articles existed that were not indexed in either of the aforementioned databases or if any “classic” research articles consistently were referenced. More than 60 English-language research articles and reviews of articles available through the institution’s library and published from January 1994–January 2004 were selected. Each article was reviewed and summarized on a form created to help organize pertinent information: author, title of study, year published, type of study, description (study aims, design, and population), analysis, comments or discussion (critique), and clinical implications or relevance to the question under consideration. The resulting summaries then were evaluated for “quality” of the evidence: Results from large, multicenter studies ranked higher than case studies, and reviews of large amounts of well-correlated data ranked higher than studies carried out on small or limited populations. Finally, the results were displayed in an evidence table. An example of the table used to display the factors associated with graft failure is displayed in Table 1. This useful exercise helped to clarify the factors, if present in future patients, that should alert the staff to the possibility of graft failure, as well as appropriate treatment for this devastating complication. Relevant nursing research on this complication of blood and marrow transplant was the most difficult to find, perhaps because of the specificity of the topic. The review demonstrated a need for further clinically relevant research in the nursing care of hematopoietic transplant recipients.

**Factors Related to Graft Failure**

Data from the National Marrow Donor Program of more than 5,000 matched, unrelated bone marrow transplant recipients from 1991–1999 were reviewed. Approximately 4% of the recipients experienced primary graft failure, and another 10% developed secondary graft failure (Davies et al., 2000). A search of the literature revealed that no general agreement exists on which factors definitively contribute to graft failure; in fact, the literature often is contradictory. The most accurate statement would be that it seems to be a multifactorial phenomenon. For this review, an evidence table was used to organize and rank the studies and summarize data, patient outcomes, and clinical recommendations or implications for practice. The evidence table gives examples of the format, as well as some of the studies and reviews summarized to
### Table 1. Table of Evidence

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<tr>
<th>Author and Year</th>
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<tr>
<td>Abdallah et al., 2003</td>
<td>Descriptive correlative</td>
<td>16 adults with hematologic malignancies (8 stem cell transplant recipients) diagnosed with respiratory syncytial virus (RSV) infection were analyzed for patient characteristics, clinical presentation, and outcomes.</td>
<td>Two patients died; three patients showed delayed engraftment or graft failure.</td>
<td>Small population; association was observational. Mechanism of how RSV may affect engraftment is understood poorly; except for cell dose, other possible causes of graft failure were not examined.</td>
<td>This research supports the observation that RSV infection may delay engraftment or cause graft failure, but no definitive conclusion can be made.</td>
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<td>Awaya et al., 2002</td>
<td>Review, case studies</td>
<td>Summary of reports on telomere shortening that occurs as a result of cell doublings; report of two patients who experienced graft failure associated with telomere shortening.</td>
<td>Case 1 was a child who received marrow from 61-year-old. Case 2 had hypocellular marrow 25 years after transplant.</td>
<td>Measurement of telomere length in both cases showed lengths significantly shorter than (a) age-matched control or (b) donor of original marrow. Postulated that telomere shortening was related to both cases of late graft failure.</td>
<td>Higher cell dose means fewer cell divisions, thus less telomere shortening and less chance of graft failure.</td>
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<td>Bornhauser et al., 2002</td>
<td>Correlative</td>
<td>51 patients with hematologic malignancies received peripheral blood stem cell transplants (PBSCTs) from unrelated donors; antithymocyte globulin was infused in all patients to reduce graft-versus-host disease (GVHD). Donor lymphocyte infusions (DLIs) were administered to 33 patients on day +21 prophylactically to promote engraftment. Early graft failure occurred in 16% of patients (n = 8).</td>
<td>DLIs did not reduce the number of infections, graft failure, or relapse, and the incidence of GVHD was high.</td>
<td>Neither cell dose nor diagnosis was related to the eight cases of graft failure in this study, and despite retransplant, all patients with graft failure died.</td>
<td>T-cell depletion with antithymocyte globulin increased the risk of graft failure.</td>
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<td>Carvallo et al., 2003</td>
<td>Correlative</td>
<td>36 patients with metastatic solid tumors received allogeneic PBSCT and nonmyeloablative conditioning. Donor T-cell and myeloid engraftment were analyzed by polymerase chain reaction to find degree of chimerism. Relationships were examined among degree of chimerism, age, sex, history of chemotherapy, CD34+ and CD3+ dose, pretransplant absolute neutrophil count, GVHD prophylaxis, and donor-patient sex mismatch.</td>
<td>Patients who had received prior chemotherapy engrafted faster than did those who were chemotherapy naive. This was true for myeloid and T cells. Higher CD34+ cell dose also was associated with earlier, higher degree of chimerism.</td>
<td>No patient experienced graft failure, but rate and pattern of engraftment varied with exposure to previous chemotherapy. Because this engraftment is a gradual change over from host to donor, as opposed to ablating the host and replacing it with donor cells, results may be applicable only to this population. Authors suggested that a less myeloablative regimen could be used for patients with previous chemotherapy exposure.</td>
<td>Higher dose of CD34+ cells were associated with faster engraftment and less chance of graft failure.</td>
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<td>Castro-Malaspina et al., 2002</td>
<td>Correlative</td>
<td>510 patients had matched, unrelated bone marrow transplants (BMTs) from 1988–1998 for myelodysplastic syndromes. Factors studied for relationship to outcomes were myelodysplastic syndrome subtype, age, GVHD, sex, human leukocyte antigen (HLA) match, conditioning regimen, and cell dose cytomegalovirus (CMV) status.</td>
<td>73 patients died before engrafting. Of 437 evaluable for engraftment, 57 (13%) had graft failure, 24 had primary graft failure, and 33 had late graft failure. Higher cell dose, female sex of host, and male sex of donor were associated with higher rates of engraftment. Late graft failure was associated with lower cell dose.</td>
<td>Association of graft failure with HLA disparity was not found; however, the authors noted that HLA typing was not possible at the same level over this time period, so more disparities may have occurred than noted.</td>
<td>Cell dose closely was associated with development of primary and late graft failure.</td>
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<td>Dominietto et al., 2002</td>
<td>Correlative</td>
<td>905 patients stratified into low-, medium-, or high-dose groups by number of unmanipulated cells received in allogeneic BMT from 1976–2000; correlated cell dose with graft function (as indicated by platelet and white blood cell counts) and transplant-related mortality.</td>
<td>Patients receiving highest cell dose had higher platelet and white blood cell counts over time as compared with the other two groups and lowest transplant-related mortality.</td>
<td>The positive effect of cell dose was more obvious in patients older than 30 or with advanced disease, chronic myeloid leukemia (CML), or other than matched, related donors. Authors suggested that graft function is not exclusively a function of CD34+ cell dose but also of other cell subpopulations.</td>
<td>Study did not give specific data on percentage of patients with graft failure, only inferred that if higher dose produces best graft function, lower dose may contribute to graft failure.</td>
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<td>Grewal et al., 2003</td>
<td>Review</td>
<td>Review of more than 150 studies of factors related to outcomes in PBSCT and/or umbilical cord blood stem cell transplant (UCBT). Compared engraftment, GVHD, immune reconstitution, and survival.</td>
<td>UCBT graft failures were associated with lower doses of CD34+ cells. PBSCT graft failure was associated with HLA-C disparity, T-cell graft depletion, CML, and autoimmune disorders.</td>
<td>Comparison of other issues (search time, availability, potential for disease transmission to recipient) also were noted.</td>
<td>Cell dose was the most critical factor for graft failure in UCBT. Experience with UCBT was limited for most nonmalignant diseases; therefore, further study is recommended.</td>
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<td>Johnston et al., 1999</td>
<td>Case study</td>
<td>11-year-old boy who received allogeneic BMT for relapsed acute lymphocytic leukemia (ALL) developed marrow aplasia on day +45.</td>
<td>Human herpes virus-6 was detected in blood and bone marrow. Patient was treated with foscarnet and gancyclovir, and bone marrow recovered.</td>
<td>Bone marrow depression, not actual graft failure, occurred as marrow recovered without further infusion of leukocytes.</td>
<td>If unrecognized and/or untreated, bone marrow depression of this magnitude could lead to graft failure. Needs further study.</td>
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<td>McDonough et al., 2003</td>
<td>Quasi experimental</td>
<td>Phase II clinical trial of 64 pediatric patients who received allogeneic BMT from 1995–2000 using stem cells augmented with CD34+ cells. 40 patients were treated for hematologic malignancy and 14 for nonmalignant disease.</td>
<td>10 of 54 children experienced graft failure; this was significantly associated with nonmalignant disease diagnosis. Gender mismatch (female donor/male host) and degree of HLA disparity also approached significance.</td>
<td>Graft failure was not associated with CMV seropositivity. 7 of 10 patients had primary graft failure, 3 experienced late graft failure after initial donor engraftment but were treated successfully with DLI.</td>
<td>Application of data to adult population is questionable.</td>
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<td>Mehta et al., 1997</td>
<td>Correlative</td>
<td>712 recipients of allogeneic BMT from 1980–1994 were analyzed for factors as related to survival: age, gender, diagnosis, conditioning regimen, donor match, GVHD prophylaxis, cell dose, use of growth factor, and leukocyte count on day +15.</td>
<td>Factors negatively influencing survival included lower leukocyte count on day +15, unrelated donor, female gender, age &gt; 35, T-cell depletion, and methotrexate not used in GVHD prophylaxis.</td>
<td>52 of 712 patients died from hemorrhage, infection, or graft failure within three months of transplant without relapse. An additional 47 experienced graft failure within two months, required retransplantation, or died from hemorrhage, infection, or graft failure.</td>
<td>Study was completed before many current antibiotics were available for treatment of infection. Statistics for factors associated with graft failure were not separate from others associated with death.</td>
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| Petersdorf et al., 1997 | Matched case control, correlative | 21 of 521 patients experienced graft failure and were treated for hematologic disorders from 1985–1994 with cyclophosphamide and total body irradiation conditioning and cyclosporine and methotrexate. GVHD prophylaxis was analyzed. For each patient with graft failure, two patients were 15 of 21 triads were mismatched for one HLA-C allele and one for both. In addition, 7 donor-host pairs were mismatched at HLA-A, and 16 pairs were mismatched at HLA-B. Multivariate conditional logistic regression was used to account for the amount of graft failure attributed to HLA-C mismatch. | Results indicated that HLA-C mismatch was associated with an increased risk for graft failure independent of the effect of HLA-A and HLA-B mismatch. Lower cell dose also was associated with higher rates of graft failure, independent of HLA-C mismatch. In addition, more patients with CML diagnosis | Mismatch of any of the HLA-A, HLA-B, or HLA-C alleles can increase the risk for graft failure in addition to the diagnosis of CML. | (Continued on next page)
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<td>Urbano-Ispizua et al., 2001</td>
<td>Correlative</td>
<td>Analyzed factors (gender, age, ABO compatibility, diagnosis, conditioning regimen, CMV serology, disease status, CD34+ cells and CD3+ cells infused, and cryopreservation), for 257 HLA-identical sibling (allogeneic) transplant recipients; 24 (11%) developed graft failure.</td>
<td>23 of 155 patients who received T-cell doses less than 0.2 x 106 experienced graft failure. Probability of graft failure increased as the number of CD3+ cells in the graft decreased. Also, patients with CML and busulfan-based regimen had higher risk ratio for graft failure.</td>
<td>Authors concluded that “graft quality,” as determined by number of CFUs present in allograft, was highly associated with risk of graft failure (fewer CFUs lead to greater risk of graft failure).</td>
<td>Number of donor CD3+ and CD34+ cells correlated with success of allografting. Despite subsequent treatment, initial graft failure was associated with poorer outcome (death) in 67% of patients.</td>
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<td>Van Hennik et al., 2000</td>
<td>Comparative</td>
<td>Blood samples from 21 patients with hematologic malignancies who received either autologous or allogeneic transplants and experienced graft failure were compared to 26 successfully engrafted similar patients. Factors related to graft function included type of conditioning regimen, number of chemotherapy cycles prior to transplant, number of colony-forming cells (CFUs), number of CD34+ cells, and number of cobblestone area-forming cells present in the allograft. PBSCT and BMT recipients were included.</td>
<td>Authors concluded that “graft quality,” as determined by number of CFUs present in allograft, was highly associated with risk of graft failure (fewer CFUs lead to greater risk of graft failure).</td>
<td>Observed that engrafted autologous patients had received more cycles of alkylating agents than patients who experienced graft failure. Also noted that patients with AML were more likely to have graft failure after BMT than those with non-stem cell disorders. Because patient data were not matched to account for these discrepancies, some of the differences observed between graft failure and engrafted patients may have been from underlying disease rather than allograft quality.</td>
<td>Inconclusive, but supports previous findings that severity of disease and cell dose are related to development of graft failure.</td>
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<td>Wadlow &amp; Porter, 2002</td>
<td>Review</td>
<td>Authors reviewed studies of UCBT as related to the advantages and disadvantages compared to PBSCT or BMT.</td>
<td>Advantages of UCBT included potential for “limitless” supply, including all races and ethnicities, reduced rates of GVHD, reduced disease transmission, and viral contamination.</td>
<td>Disadvantages of UCBT were “insufficient cell dose” that produced delayed engraftment and higher rates of graft failure. Graft failure rates were averaged from 10%–20%. Other related factors included underlying disease, patient age, degree of HLA difference, and number of leukocytes in graft. Myeloid engraftment occurred later than neutrophil engraftment.</td>
<td>Primary factor affecting graft failure was the number of cells or cell dose from cord blood donor. Cord blood T cells have limited alloreactivity, which may contribute to graft failure by the same mechanism as T-cell depletion.</td>
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assist the nursing staff in understanding the multifactorial components that contributed to their patients’ outcomes.

Factors related to graft failure can be classified loosely as those related to the donor, the host, or the interaction of both. Donor factors may include increased patient age (Kollman et al., 2001; Small et al., 1999); female gender (Kollman et al.); HLA type (mismatch with host), especially HLA-A, HLA-B, HLA-DRB1, or HLA-C (Petersdorf et al., 1997); reduced number of CD34+ cells (less than 5 x 10^6) (Dominietto et al., 2002); reduced number of CD3+ cells (T-cell dose of less than 0.2 x 10^6) (Champlin et al., 2000; Urbano-Ispizua et al., 2001); T-cell depletion of graft by antithymocyte globulin (Green et al., 1999; Papadopoulos et al., 1998); use of Campath®-1G (Berlex Laboratories, Montville, NJ) (Chakrabarti et al., 2003; Hale et al., 1998); telomere length shortening (Awaya et al., 2002; de Pauw et al., 2002); and type of stem cell source (stem cell, cord blood, or bone marrow) (Cohen & Nagler, 2003; Storek et al., 2001).

Typical host factors included patients with hereditary, nonmalignant hematologic disease (McDonough, Jacobsohn, Vogelsang, Noga, & Chen, 2003); antithymocyte antibodies caused by pregnancy or extensive transfusion support prior to transplant (especially in the absence of immunosuppressive chemotherapy) (Zakrzewski, 2002); conditioning regimen (less intense for nonmalignant disease or no radiation) (Carvallo et al., 2003; Grandage et al., 1998); use of immunosuppressants (cyclosporine A, tacrolimus, methotrexate, or high-dose steroids) (Davies et al., 2000; Stucki et al., 1998); diagnosis of chronic myeloid leukemia (McGlave et al., 2000; Storb, 1985; Wiesmann et al., 2003); second transplant or transplant for a secondary malignancy (Stucki et al.; Wolff, 2002); viral infection (human herpes virus-6 [HHV-6]) (Johnston et al., 1999); post-transplant CMV reactivation or infection (Small et al., 1999; Torok-Storb et al., 1997); varicella zoster virus, herpes simplex virus, or respiratory syncitial virus (after transplant) (Abdallah, Rowland, Scheperjuk, To, & Bardy, 2003); and grade II–IV GVHD and the autoimmune disorder systemic lupus erythematosus (Shaughnessy et al., 2001).

In the case study cited, the nursing staff learned through a literature review that there were a number of factors that were related to graft failure. Mrs. C’s malignancy (AML) was a secondary one that developed eight years after receiving chemotherapy for the primary disease of lymphoma. In addition, she was heavily pretreated because she experienced multiple relapses. GVHD prophylaxis resulting from a mismatch of one HLA allele in her unrelated donor graft was appropriate, but it also was known to be related to the occurrence of graft failure. CMV infection and subsequent treatment with the immunosuppressant antiviral ganciclovir were additional factors that could have contributed to her failure to engraft.

### Treatment Options for Graft Failure

When an allogeneic graft fails, the patient will have a disease relapse and/or profound pancytopenia, either of which can be ultimately fatal. Mrs. C suffered both of these conditions as a result of the failure of her hematopoietic graft. She was treated with cytokine growth factors, and, when graft failure was confirmed, she was reconditioned with fludarabine and given a DLI from her original donor. Through review of the literature, as with the factors related to graft failure, the staff confirmed that the medical treatment Mrs. C received was appropriate and current.

Treatment alternatives for graft failure that have been attempted are administration of additional cytokine growth factors, infusion of peripheral blood stem cells, or DLI (Keil et al., 1996; Remberger et al., 1998; Wolff, 2002). Cytokine growth factors include either granulocyte–colony-stimulating factor and/or granulocyte macrophage–colony-stimulating factor (Dreger et al., 1993; Nemnaitis et al., 1990). Although use of additional growth factors still is controversial, healthcare providers currently are less concerned that stimulation of malignant myeloid cell lines may occur (Rowe et al., 1994). Prophylactic administration of donor leukocytes at day +21 has been tried, but results showed the incidence of primary graft failure, relapse, or infectious complications was not reduced. Additionally, an increased rate of early graft failure occurred in 16% of patients, and disease-free survival at 31 months was only 36% (Bornhauser, Platzbecker, Theusser, Holig, & Ehninger, 2002).

A second peripheral blood stem cell transplant is not common for graft failure, although one European study reported favorable results with second stem cell transplants if retransplant was performed more than 80 days after the initial therapy and patients received cyclosporine A for prevention of GVHD (Guardiola et al., 2000). More often, DLIs or “booster” cells are given as treatment for graft failure or disease relapse and administered as soon as they are available. The source of additional stem cells is usually the donor of the original allograft, but alternative donors, or multiple donors in the case of umbilical cord blood transplant, may be used (Byrne, Musuka, Davy, Donovan, & Russell, 2001).

DLI alone may be used for graft failure with disease relapse (graft rejection) in an attempt to provoke graft-versus-leukemia effect, especially in patients who may not be able to tolerate additional chemotherapy (Hashino et al., 2004; Min, Kim, Lee, Min, & Kim, 2000; Redei, Waller, Holland, Devine, & Wingard, 1997). In primary or secondary graft failure, preparing the patient with immunosuppressive and/or cytotoxic therapy is more common (Byrne et al., 2001). Antithymocyte globulin is used frequently to reduce the activity of T cells against the new allograft (Kroger et al., 2001), but patients have received Campath-1G for this purpose as well (Grandage et al., 1998). Some of the preparative regimens used to recondition patients prior to DLI have included total body irradiation, busulfan, or cyclophosphamide (Grandage et al.). In recent years, more common cytotoxic therapies used before DLI are IV agents such as fludarabine with cyclophosphamide or fludarabine alone if the patient does not tolerate the effects of the combined regimen (Ambulkar, Parikh, & Saikia, 2003). Finally, palliative therapy with oral hydroxyurea, oral Gleevec® (Novartis, East Hanover, NJ), interferon, or IV Mylotarg® (Wyeth, Madison, NJ) may be offered if a patient with graft failure or rejection is too ill or is unwilling to undergo further treatment (Higano, Raskind, & Singer, 1992; Kantarjian et al., 2002; Tsimeridou et al., 2003).

### Nursing Implications

When a patient fails to engraft, he or she faces the imminent possibility of death and will grieve this loss accordingly. Despite other interventions that may be offered, the patient has lost the opportunity for remission or cure with a considerable cost of suffering. Anger, betrayal, grief, depression, and hopelessness are all feelings that may be experienced and expressed. Healthcare personnel involved in the patient’s care similarly may feel a sense of failure and grief. Kelly, Ross, Gray, and Smith (2000) noted that the majority of nursing research with blood and marrow transplant recipients has focused on effective nursing care for symptom management and quantitative measure of quality of life after transplantation. Very little has been published on patients who do not achieve the therapeutic goal of remission or die from either disease or transplant therapy. When therapeutic goals cannot be met, a need exists for open and honest discussion of what has occurred, which options are available, and
which outcomes can be anticipated. Nurses can be instrumental in assisting patients to make informed decisions to undertake or forgo additional therapy and in providing support for whatever decision the patient makes. Patients report that they try to find meaning in what has happened to them throughout the illness and transplant experience. In addition to whatever social support the patient may have, religious or spiritual support often is important at this juncture (Xuereb & Dunlop, 2003).

General nursing care for individuals who experience graft failure in an acute care setting remains the same as that for any patient undergoing stem cell or bone marrow transplant. Neutropenic precautions include strict hand washing for all individuals before entering and after leaving a patient’s room. Any individual, including healthcare personnel, with a transmissible disease such as varicella zoster virus, infectious gastroenteritis, herpes simplex virus, or upper-respiratory infections should not come in direct contact with the patient (Shelton, 2003). Prophylactic antibiotics generally are administered, but Centers for Disease Control and Prevention guidelines caution that vancomycin and other antianerobic agents should be used only “judiciously” to avoid the emergence of resistant bacteria (Sullivan et al., 2001).

Nurses need to continuously monitor patients carefully for complications of disease and therapies. Blood product support, including red blood cell and platelet transfusions, is imperative because pancytopenia is a result of graft failure. It commonly includes red blood cell and platelet transfusions; the threshold for administration of products may vary according to protocol or patient symptoms. Frequent, astute assessment of major symptoms, is imperative because pancytopenia is a result of graft failure. It commonly includes red blood cell and platelet transfusions; the threshold for administration of products may vary according to protocol or patient symptoms. Nurses need to continuously monitor patients carefully for complications of disease and therapies. Blood product support, including red blood cell and platelet transfusions, is imperative because pancytopenia is a result of graft failure. It commonly includes red blood cell and platelet transfusions; the threshold for administration of products may vary according to protocol or patient symptoms. Frequent, astute assessment of major symptoms.

In choosing to undergo a bone marrow transplant, individuals are balancing the hope for survival with the very real fear that they will suffer and die from the rigors of the treatment. Patients have stated that they experience fear of pain and other physical discomforts, disfigurement, loss of function, recurrence of disease, and death, among others. These fears can be compounded when a patient feels unprepared physically, emotionally, spiritually, or cognitively for events that transpire during the experience of transplantation (Cohen & Ley, 2000).

Nurses and patients agreed that no amount of preparation could produce complete understanding of the physical and emotional events that might occur. However, patients reported feeling angry and betrayed when accurate information was not presented. During the post-transplantation phase, de Carvalho, Goncalves, Bontempo, and Soler (2000) found that patients believed that their interpersonal needs for inclusion, control, and affection were neglected most often by their nursing team. Patients were interested in specific information about ways the disease and transplant would affect their daily lives and didn’t want this information couched in terms of statistics and percentages (Xuereb & Dunlop, 2003). They reported frustration with the “vague” responses they received concerning duration, frequency, normalcy, and “meaning” of symptoms that they were experiencing (Cohen & Ley; Xuereb & Dunlop).

In one study, only 33% of patients with primary graft failure at day +100 survived three years or more regardless of a second transplant or DLI. In the group experiencing late graft failure, only 18% survived three or more years. The authors of the study concluded that quality of engraftment was a crucial indicator of survival following matched, unrelated bone marrow transplantation (Mehta et al., 1997). Overall three-year survival rates are similar for patients who receive peripheral blood stem cell or umbilical cord transplant and require DLI for graft failure (30%–35%). For patients with graft rejection, the three-year survival rate is 5%–20% (Davies et al., 2000).

Patients who engraft only after additional treatment are more likely to experience acute GVHD because immunosuppressant medications may be withheld or reduced to prevent a second occurrence of graft failure or graft rejection. They also are more susceptible to major organ dysfunction as a result of additional cytotoxic or antimicrobial therapy. Finally, these patients are at increased risk for complications from hemorrhage and infection, particularly from opportunistic organisms such as fungi, as a result of a more prolonged period of pancytopenia.

Nurses can help to reduce patients’ fears by providing accurate, timely information about procedures, symptoms, and feelings that the transplant recipient may experience or is experiencing. Information must be tailored individually because patients have reported a broad spectrum of need for information as well as a fear of “knowing too much” (Tarzian, Iwata, & Cohen, 1999). Active listening, encouraging patients to express fears and hopes, and arranging for them to meet with others who have been through a similar experience are other methods to help them cope with fears. However, because the incidence of graft failure is so low, it often is overlooked; if mentioned at all, it is rarely explained in any detail to patients undergoing transplant for malignant diseases. Medical and nursing staff members need to ensure that patients know that a possibility of graft failure exists when they sign an informed consent. Then, if graft failure does occur, the patient is more prepared to deal with the situation and better able to assess other available treatment options and their probable consequences.

The death of Mrs. C focused the nursing staff of one blood and marrow transplant unit on the factors associated with graft failure. They learned which factors could be identified before and during the transplant experience through an evidence-based literature review and how recognition of these factors could alert the nurse to be cautious, as well as honest, in their interactions with the patient and family. Review of treatment options cited in the literature assured them that medical treatments and nursing interventions for this patient had been appropriate. In addition, they identified several areas in the informational and emotional needs of their patients that could be improved.

Author Contact: Christine Wilson, PhD, APRN, BC, NP-C, can be reached at cwilson11@tampabay.rr.com, with copy to editor at CJONeditor@janel.com.

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Rapid Recap

Graft Failure Following Allogeneic Blood and Marrow Transplant: Evidence-Based Nursing Case Study Review

- **Graft failure following allogeneic bone and marrow transplant is still a life-threatening complication and seems to be a multifactorial phenomenon.**
- **General nursing care for individuals who experience graft failure in an acute care setting remains the same as that for any patient undergoing stem cell or bone marrow transplant.**
- **Support for the psychosocial, spiritual, and informational needs of these patients and families includes providing accurate, timely information about procedures, symptoms, and feelings that transplant recipients may experience and encouraging them to find meaning in their experiences.**
- **Systematic literature review and objective examination of the evidence related to a nursing inquiry can be useful exercises in evaluating patient care.**