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Non-Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Objective—To review the literature related to nonmyeloablative stem cell transplantation, and the unique characteristics and patient population to which it applies.

Data Sources—Research studies, research and clinical reviews, clinical experience

Conclusion—Nonmyeloablative stem cell transplantation has demonstrated effective and safe application in a heterogeneous population not otherwise eligible for an allogeneic transplantation. Although many principles are based on those of conventional myeloablative transplantation, the engraftment kinetics, patient selection and regimen related complications are distinct.

Implications for Nursing Practice—Nurses must be knowledgeable about nonmyeloablative stem cell transplantation including the provision of individualized care for a heterogeneous population. This can include non-traditional transplant indications, elderly cancer patients and those with comorbidities.

Keywords

Regimen Intensity; Transplant Engraftment; Chimerism; Comorbidities; Elderly

Allogeneic hematopoietic stem cell transplantation (HSCT) is a treatment option with curative potential for patients with malignant, non-malignant, and genetically determined hematologic diseases.¹ Conventional myeloablative transplantation includes myeloablative conditioning with high dose chemo- and radio-therapy to eradicate residual disease and recipient (host) immunity in preparation for healthy donor-derived hematopoietic stem cells (graft). The graft not only provides bone marrow reconstitution, but has an added benefit when the donor-derived lymphocytes mount a specific immune response to eradicate residual disease initially labeled the graft versus leukemia (GVL) effect. Despite these obvious benefits, the regimen related toxicity from the myeloablative conditioning makes conventional myeloablative transplantation a high risk treatment option for the majority of patients with hematologic malignancies due to older age, comorbidities, and an extensive treatment history.²

Nonmyeloablative allogeneic stem cell transplantation (NST) has emerged as an alternative to conventional myeloablative transplantation.³ NST includes the use of nonmyeloablative conditioning (NMC) or reduced intensity conditioning (RIC) that consists of low dose chemo- and/or radio-therapy thus decreasing regimen-related toxicity.⁴ The less intense regimens are

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generally better tolerated by those normally excluded from conventional myeloablative transplantation, while maintaining engraftment of the donor-derived hematopoietic stem cells and the unique benefit of an immune effect against residual disease (Table 1).⁴⁻⁹

Transplant outcomes following NST are still being studied. Improved overall survival for patients undergoing NST has been reported compared to those undergoing conventional myeloablative transplantation^{2,10,11} while others have reported survival outcomes to be similar.¹²⁻¹⁵ Consequently, improved survival and safety is attributed to lower regimen related toxicity; however, the influence of baseline health status, may offset this benefit. Overall survival and non-relapse mortality are reported to be negatively influenced by older donor and recipient age, poor recipient performance status, high risk disease, and extensive treatment history.¹⁶

The purpose of this article is to highlight the uniqueness of NST and the population to which it is applied. Many underlying principles of allogeneic HSCT are similar among the various levels of regimen intensity (e.g. marrow replacement); however, unique characteristics exist. The biologic and clinical aspects of NST along with the impact and individualized needs of the transplant recipient will be discussed.

Engraftment Kinetics

The distinguishing characteristic of a NST is the composition of hematopoietic recovery known as engraftment. Four evidence-based principles associated with successful NST engraftment include: 1) a conditioning regimen with sufficient immunoablation to overcome residual host immunity not eradicated by the less intense regimen;^{2,4,17,18} 2) allowing host and donor hematopoietic cells to co-exist;¹⁷ 3) higher stem cell and lymphocyte dose to facilitate engraftment;^{2,17,18} and 4) dependence on immune reactivity, versus the conditioning regimen, to control residual disease.^{2,4,17}

In NST, the recipient hematopoietic stem cells are not eradicated by the conditioning regimen. Consequently, NST utilizes a conditioning regimen that emphasizes immunosuppression to decrease the risk of rejection by residual recipient immunity. As a result, the first phase of engraftment is generally autologous myeloid cells occurring as early as day 7 post transplant,^{17,19} and is influenced by the stem cell source. The average recovery of an absolute neutrophil count (ANC) over 500 is 13 days, while some regimens maintain an ANC over 500 at all times. Platelet engraftment generally occurs by day 14, demonstrated by a decrease in platelet transfusion requirements.²

The next phase of engraftment involves donor lymphoid recovery. Specifically, donor-derived T-cells will engraft as early as day 14 with the majority engrafted by day 30.¹⁷ If donor lymphoid recovery is not achieved as desired, additional donor lymphocytes may be administered as a donor lymphocyte infusion (DLI). Another approach to facilitate full donor engraftment is to taper the immunosuppressive medications enhancing the activity of the donor T-cells.⁶ Full T-cell engraftment creates a graft versus marrow effect, eradicating remaining host hematopoietic stem cells allowing those of donor origin to seed. Donor myeloid engraftment, the final phase of recovery, can then occur with donor stem cell proliferation and differentiation within the host.

To monitor NST engraftment, recipient blood samples are evaluated to determine the chimerism which quantifies what percentage of hematopoietic cell recovery is of donor or recipient origin (Table 2).⁹ Mixed chimerism describes a state when both the recipient and donor hematopoietic stem cells co-exist. Polymerase chain reaction (PCR) testing identifies and quantifies polymorphic DNA markers, thus determining the origin (donor or host) of the recipient's immunity. Real-time quantitative PCR is the most rapid and sensitive technique,

yet costly, therefore other techniques such as fluorescent in situ hybridization (FISH) and chromosome markers can be used.⁷

In the setting of incomplete chimerism, disease progression, or relapse, a post transplant donor lymphocyte infusion can be used as adjuvant therapy to enhance the immune response through the graft versus malignancy effect.⁵ Disease progression and relapse continue to impact overall survival after NST with an incidence similar to conventional myeloablative transplantation.^{2, 14} This strategy requires careful monitoring as the benefit of an immune response can be offset by the development of significant acute graft versus host disease (GVHD).

Indications

The successful application of nonmyeloablative allogeneic stem cell transplantation has revolutionized the care of individuals with hematological malignancies who are older or who otherwise experience debility. Data reported by the Center for International Blood and Marrow Transplant Research (CIBMTR) reveal a steady increase in the use of NST in the treatment of malignant and non-malignant diseases, accounting for 25% of all allogeneic HSCT in 2002.⁸ Although there are numerous published studies evaluating the safety and efficacy of NMC and RIC regimens in various terminal and more recently chronic diseases, the most common indication is acute myelogenous leukemia.²⁰ Current applications under study include hematological malignancy in the subgroup of individuals not eligible for conventional myeloablative transplantation, solid tumors and non-malignant diseases (Table 3).^{2,18,21}

Initially, NST was applied to patients with hematological malignancies who were unsuitable candidates for conventional myeloablative transplantation. The objective was to optimize the graft versus leukemia effect, while improving the safety of allogeneic HSCT through the use of less toxic regimens. Initial reports were positive, paving the way for expansion of NST application beyond hematologic diseases. The application of NST to patients with solid tumors demonstrated the graft versus malignancy (GVM) or graft versus tumor (GVT) effect.²² In this population, the goal of NST was to establish donor immunity as an approach to controlling and eliminating recipient residual disease.

More recent studies have emerged applying NST to patients with non-malignant diseases.²¹ This indication expanded the NST population to include children. The goal in non-malignant diseases is to achieve sufficient donor cell engraftment to eradicate the underlying genetic disease,²¹ through the graft versus marrow effect.¹⁷ Achieving immune tolerance, a stable mixed chimeric state, is sufficient for a disease response.

Regimen Intensity and Stem Cell Sources

The two categories of NST conditioning regimens, NMC and RIC, can be further defined by the potential for autologous recovery. NMC does not eradicate hematopoiesis and recipient immunity, thus autologous recovery occurs within 28 days should engraftment fail.^{2,4} RIC, while not fully ablative, results in prolonged bone marrow aplasia should donor engraftment fail.^{2,4} In a review of 39 studies, 28 different conditioning regimens were documented (Table 3).² Fludarabine, a purine analog, was used in over 50% of these regimens as it provides an effective immunosuppressive effect, a key principle in NST. Approximately half of the 28 regimens were NMC, with fludarabine-melphalan 140mg/m² (with or without campath-1H or antithymocyte globulin equine (ATG)) the most frequently used NMC regimen. Fludarabine-total body irradiation 200cGy (with or without ATG) was the most common RIC regimen. A definitive dose of total body irradiation in NST has yet to be determined, with a majority of regimens using 200cGy, and some as high as 700cGy.^{2,23} The impact of NMC and RIC regimens on engraftment continues to be studied.

Various allogeneic stem cell sources are used in NST. Matched related donors are the most common source of stem cells in NST, followed by a matched-unrelated donor and unrelated cord blood respectively.^{2,24} Peripheral blood is reported as the most frequent source of hematopoietic stem cells in both related and unrelated NST.²⁵ Studies indicate a higher rate of graft rejection and poor donor T-cell chimerism in recipients that receive bone marrow derived stem cells.²⁶ Higher stem cell (CD34+) doses, ranging from $4.65 - 4.74 \times 10^6/\text{kg}$ in both NMC and RIC, are suggested for successful engraftment in the setting of mixed chimerism.² Healthy donors who are older have been documented to yield a lower CD34+ count during mobilization.^{27,28} One study suggests that NST recipients who receive a graft from younger donors (≤ 45 years) have better transplant outcomes.²⁹

Complications

Despite the lower toxicity profile associated with NST, toxicities associated with conventional myeloablative transplantation along with unique complications can occur. As with a conventional myeloablative transplantation, recipients may still experience myelosuppression, GVHD, and other regimen related toxicities, however the overall severity is less.¹¹ The degree and length of anemia, thrombocytopenia, and neutropenia have been reported as less in NST recipients than conventional myeloablative transplant recipients.¹¹ This translates into fewer red cell and platelet transfusions, decreased overall risk of infection, and shorter duration of intravenous antibiotics. In addition, NST conditioning regimens are overall less emetogenic in addition to being associated with fewer cases of regimen related mucositis.¹¹ Absence of mucositis allows the recipient to maintain a reasonable nutritional status, reducing the need for total parenteral nutrition as compared to the conventional myeloablative transplant recipient.

The presentation of GVHD is not unique in the setting of NST however the time of onset can be quite variable. Acute GVHD after NST commonly occurs 6 – 12 months after transplant compared to a more immediate onset, as early as one month, following conventional myeloablative transplantation.³⁰ This delay and variability in onset is related to the gradual engraftment of donor lymphocytes and any subsequent donor lymphocyte infusions. Similar to acute GVHD, the onset of chronic GVHD in NST may be slightly delayed with more extensive disease.³¹

Although the onset of GVHD in NST varies compared to conventional myeloablative transplantation, the overall incidence appears to be similar or slightly lower.^{14,30} The lower incidence of acute GVHD may be due to the less intense conditioning regimen resulting in lower toxicity and tissue damage, thus minimizing the release of inflammatory cytokines that may contribute to the development to acute GVHD.³⁰ In NST recipients, the incidence of grade II-IV acute GVHD ranges from 41 to 50%, with a lower incidence of grade III & IV than conventional myeloablative transplantation.¹³ The incidence of chronic GVHD is approximately 39% with about 20% classified as extensive.¹³ Despite the older age and comorbidities of NST recipients, treatment related mortality attributed to GVHD is reported as similar or lower to that of conventional myeloablative transplantation. Incidence of GVHD mortality in NST ranges between 27% - 37%, with the highest rates in patients over the age of 50.^{2,5}

Although many toxicities have been documented to be less prevalent in NST recipients,³² an increased risk of graft rejection, and unique complications such as ABO incompatibility, have been documented and are primarily related to the mixed chimeric state during engraftment. The NST regimen preserves some host T-cells and creates an increased risk of rejection compared to conventional myeloablative transplantation. Therefore, the NST conditioning regimen includes strategies that target host residual immunity to limit graft rejection. Despite

this risk, successful rates of engraftment average 94% across various NST regimens with a slightly higher rate in RIC compared to NMC.²

A unique complication, as a result of a mixed chimeric state, is ABO incompatibility. Hemolysis and pure red cell aplasia have been identified with major and minor ABO incompatibilities in NST.^{33,34} The first, a delayed hemolysis, is a “major” ABO incompatibility, which presents when persistent recipient B-lymphocytes produce antibodies (anti-donor isohemagglutinins) against emerging donor red cells. For example, in a donor with type ‘A’ blood and a recipient with type ‘O’ blood, the recipient produces anti-A isohemagglutinins that react against the donor type A red blood cells. The result is a gradual hemolysis as delayed donor erythropoiesis increases, resulting in red cell aplasia approximately 20-30 days after transplant. Patients with a major ABO incompatibility should be monitored for falling hematocrit and receive red blood cell transfusions if hemolysis is suspected.

The second category of ABO incompatibility is more acute and occasionally fatal.³³ This “minor” ABO incompatibility presents as early as 7-14 days after transplant. In this case the donor B-lymphocytes contained in the peripheral blood stem cell product produce antibodies (anti-host isohemagglutinins) against the residual recipient red blood cells. For example, in a donor with type ‘O’ blood and a recipient with type ‘A’ blood, the transplanted donor anti-A isohemagglutinins react against the recipient type ‘A’ red blood cells. The result is an acute hemolysis requiring aggressive management. Management of hemolysis requires frequent monitoring to evaluate the presence of hemolysis and if necessary, red blood cell transfusions. Peripheral blood stem cells contain significantly more B-lymphocytes than bone marrow and therefore may trigger a higher production of donor anti-host isohemagglutinins and thus a more intense hemolysis.³⁴ Bi-directional ABO incompatibility may also occur; where both minor and major incompatibilities are present (e.g. donor type ‘A’ and recipient type ‘B’).

Complications following NST might also include those resulting from older age, pre-existing debility, or advanced disease. In transplant recipients it has been documented that older age and high levels of symptom distress at the time of HSCT were associated with higher levels of distressing symptoms at time of hospital discharge.³⁵ Although NST patients experience less regimen related toxicity than conventional myeloablative transplant patients,¹³ individuals selected for RIC regimens report high levels of symptom distress prior to HSCT.³⁶ In addition, solid tumor recipients may present for HSCT after surgical resections while older more debilitated recipients may have mild organ dysfunction, diabetes, vascular disease, hyperlipidemia, or other factors that impact their response and tolerance to medications and routine complications. Moreover, patients with chronic diseases may present in a de-conditioned state with mild organ dysfunction due to a history of multiple treatments prior to allogeneic HSCT. A thorough knowledge of an individual's baseline status is essential to identifying and managing subsequent transplant related complications.

Patient Selection

Attention to the overall health status of allogeneic HSCT recipients has changed with the inclusion of older and more debilitated individuals. Differences between the demographic and clinical characteristics of individuals selected for NST as compared to conventional myeloablative transplantation are well documented.^{11,14,37-39} Often NST recipients are older, have an extensive treatment history, mild organ dysfunction and/or limited performance status. In addition, individuals are more commonly classified as having high-risk disease with residual or metastatic disease present at time of HSCT. Established criteria have been widely applied in the setting of conventional myeloablative transplantation considering individual criteria such as age,^{40,41} performance status,⁴² single organ function,⁴³ and disease stage as predictors of

tolerance and outcome. These criteria inherently classify the potential NST recipient at high risk for allogeneic HSCT therefore additional criteria are required to refine patient selection.

To address the pervasive variation of recipient characteristics in the evolving field of allogeneic HSCT, the application of a more comprehensive measure of health status such as a comorbidity index has surfaced to guide decision making.⁴³ A measure adapted from the Charleston Comorbidity Index (CCI) specifically for HSCT recipients is the most widely published measure. The HSCT-Comorbidity index (HSCT-CI) expands the CCI adding components to include obesity, peri-transplant infection, and psychiatric disturbances. Good reliability and validity has been demonstrated,⁴⁴ however broad application is still a concern.⁴⁵ Specific to NST recipients, individuals with comorbidities, despite age, have better survival when compared to those with the same level of debility undergoing myeloablative conditioning.^{14, 46} In recipients with no comorbidities, despite conditioning intensity, transplant outcomes do not differ.^{38,39}

The clinical utilization of a comorbidity index along with existing measures such as performance status and chronological age is in its infancy for NST patient selection. Weak correlations between measures of comorbidity, performance status and age, support a comprehensive approach in the NST recipient.⁴⁶ Non-relapse mortality and overall survival can be successfully predicted when poor performance status is consolidated with the level of comorbidity and transplant toxicity.^{46,47} Disease status combined with comorbidity scores has also been shown to serve as a valid prognostic factor in acute myelogenous leukemia and myelodysplastic patients receiving allogeneic HSCT.³⁸

The application of health status assessment has also changed as it applies to NST donors. The safety of stem cell collection has improved with the use of peripheral collections; however, the impact on the older donor has not been examined. As the recipient age increases, donor age increases as well in the setting of a matched related HSCT. Although assessment of the donor's health prior to mobilization is not new, the impact of mobilization on the older donor is unknown.

Patient Reported Outcomes & Reintegration

Understanding the experience of cancer patients extends beyond the objective measures generated by clinicians.⁴⁸ The value of patient reported outcomes has been recognized by the Food and Drug Administration⁴⁹ and the National Institutes of Health.⁵⁰ This includes measurement of health-related quality of life (HRQL), functional status, psychosocial adjustment and symptom experience. Current evidence suggests that survivors of a conventional myeloablative transplantation report greater levels of physical and psychosocial distress compared to healthy populations.^{51,52} The experience of NST recipients is less well understood.

Functional limitations increase sharply with age in cancer patients⁵³ which suggests that the NST population may innately be at high risk for greater limitations before and after allogeneic transplantation. In one study, NST recipients reported poor physical function pre-transplant compared to the general population and those preparing for conventional myeloablative transplantation.⁵⁴ NST recipients however, appear to manage pre-existing deficits well through the transplant⁵⁵ with a return to baseline within the first 100 days.⁵⁴ These results suggest that NST may spare individuals from some of the acute functional limitations associated with an intense conditioning regimen.

In addition, older age and poor performance status have been documented to negatively influence HRQL outcomes in allogeneic HSCT recipients.^{51,56,57} Despite these projections, HRQL has been documented to improve over time in survivors of NST.^{54,55} When NST and

conventional myeloablative transplant recipients were compared, there was no difference between groups during early recovery.⁵⁴ These results suggest that RIC patients, despite an initial decline in HRQL, report early HRQL recovery.

HSCT survivors have also reported challenges associated with reintegration into their prior lives including stigmatization, interpersonal relationships difficulties and financial problems.⁵⁸ NST survivors have reported that physical function limitations lead to difficulties with work and maintaining regular daily activities despite an improvement in their mental health that exceeds that of an age-adjusted general population norm.⁵⁴ Elderly cancer patients, however, are characterized as having poor social networks⁵³ which has been associated with poor survival in HSCT recipients.⁵⁹ Although there may be less toxicity and a shorter in-patient hospitalization, these challenges have not been explored in the older or more debilitated NST recipient and caregiver.

Interventions, such as NST, that decrease transplant complications are likely to yield a favorable cost-benefit ratio.⁶⁰ The cost for conventional myeloablative transplantation has been reported to range from \$50,000 to \$300,000.⁶¹ Most of the variability in costs is related to the incidence of transplantation related complications which are documented as less frequent in NST recipients. The cost reduction includes decreases in total inpatient days, number of support personnel needed, and number of intravenous medications. The quantification of cost reduction is complicated by the different conditioning regimens, GVHD prophylaxis, and comorbidities of patients receiving NST, compared to the more homogeneous costs of conventional myeloablative transplantation. However, a cost saving of approximately \$53,000 was reported for the NST recipient compared to the conventional myeloablative transplant recipient⁶² with the major expenses for this population concentrated 6 to 12 months post transplant.⁶³

In response to NST demonstrating fewer regimen related complications, transplant centers are using different organizational systems to support outpatient HSCT programs.⁶⁴ The safety of outpatient transplantation has been reported using daily outpatient visits to an infusion center/day hospital setting and home health care visits.⁶⁵ The daily visits allow for blood count monitoring and early identification of complications. Limitations to outpatient transplantation management can include distance from the transplant center, caregiver resources, and home health care agency availability.

Conclusion

Nonmyeloablative allogeneic stem cell transplantation has demonstrated effective and safe application in a heterogeneous population not otherwise eligible for allogeneic transplantation. Although many principles for NST are based on those of conventional myeloablative transplantation, the engraftment kinetics, patient selection, regimen related complications and patient experience are distinct. Despite the rapid expansion and application of NST, comparing transplant outcomes are difficult due to the numerous conditioning regimens currently being studied.

Although the overall toxicity profile is improved for NST recipients, unique complications and tolerance of routine complications deserve attention. The chronological age and overall health status play a significant role in the approach to managing NST recipients. The effects of age alone on the recovery time and resiliency of the elderly cancer patient has been well documented.⁶⁶ In addition, the effect of delayed donor engraftment and the mixed chimeric state on transplant outcomes, especially GVHD, require further study.

These factors obligate the interdisciplinary transplant team to individualize care with an understanding of the expanded applications of NST. Nurses must be knowledgeable about non-

traditional the diseases, elderly cancer patients and those with disabilities to provide quality care for this heterogeneous population. The nursing assessment and interventions used in conventional myeloablative transplant recipients need to be intensified for the NST recipients. Minor deviations in physical and psychological function often have a significant impact on transplant outcomes. Ultimately transplant nurses are accountable for the identification of nurse sensitive outcomes in this population to ensure best practice, quality physical and psychosocial care.

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Table 1

Categories of Graft Immune Effect

Effect	Application	Definition
Graft versus marrow	All diseases	Donor immunity eradicates the recipient marrow
Graft versus leukemia/lymphoma (GVL)	Leukemia and lymphoma	Donor immunity provides a response toward residual leukemia, malignancy, or tumor to achieve and maintain a disease free status
Graft versus malignancy (GVM)	Malignancy	
Graft versus tumor (GVT)	Solid tumors	

Data from ^{ref 4-9}. Champlin et al 2000, Childs et al 1999, McCann et al 2005, Khan et al 2004, Battiwalla et al 2001.

Table 2

Chimerism Terminology

Donor Chimerism (DC)	Cells detected are of donor origin
Transient Mixed Chimerism (TMC)	A short-lived, mixed cell profile including a small proportion (1-5%) of recipient cells, which eventually converts to full donor
Stable Mixed Chimerism (SMC)	A constant, mixed cell profile consisting of 1-20% recipient cells
Progressive Mixed Chimerism (PMC)	A mixed profile with increasing numbers of recipient cells over time.

Adapted from McCann et al, 2005 ⁽⁹⁾

Table 3**Highlights of Current NST Approaches**

Common conditioning agents	Fludarabine, Cyclophosphamide, Busulfan, Antithymocyte Globulin Equine, Thiopeta, Melphalan, Alemtuzumab, Cladribine, Idarubicin, Cytarabine, Cisplatin
Radiation	Low dose total body irradiation or thymic only
GVHD Prophylaxis	Cyclosporine, Mycophenolate Mofetil, Methotrexate, Tacrolimus, Methyl-prednisolone
Disease	<p><u>Hematologic Malignancies</u></p> <ul style="list-style-type: none"> • Acute leukemia • Chronic leukemia • Myelodysplastic syndrome • Multiple myeloma • Non-hodgkin lymphoma • Hodgkin disease <p><u>Solid Tumor</u></p> <ul style="list-style-type: none"> • Melanoma • Renal cell carcinoma • Ewing's sarcoma • Small cell lung cancer • Neuroblastoma • Rhabdomyosarcoma • Ovarian cancer • Pancreatic • Breast <p><u>Non-Malignant Diseases</u></p> <ul style="list-style-type: none"> • Waldenström's macroglobulinemia • Severe aplastic anemia • Paroxysmal nocturnal hemoglobinuria • β-Thalassemia • Franconi's anemia • Gaucher's disease • Diamond blackfan anemia • Chronic granulomatous disease • Leukocyte adhesion disorder • Systemic lupus erythematosus • Rheumatoid arthritis • System scleroderma • Juvenile idiopathic arthritis
Median Age	6 months-73 years (median 49 years)

Data from (2,18,21) Satwani, 2008; Banna, 2004; Anagnostopoulos, 2002