



Draft

Non-myeloablative  
Stem Cell Transplantation

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The Health Resources Commission  
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## **Health Resources Commission**

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative and two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

## ***Overview***

In 2007 the Oregon Health Resources Commission (HRC) appointed a technology subcommittee to perform evidence-based reviews of medical technologies. Members of the subcommittee for this review consisted of five physicians, and an attorney who serves as the consumer representative. All meetings were held in public with appropriate notice provided. The technologies chosen for review are chosen according to the Technology Assessment process which takes into account stakeholder input when deciding on topics to consider as well as the needs of the State of Oregon. The HRC utilizes source documents from sources previously approved by the Commission. In conducting the review process and when working with our source providers the HRC defines the patient populations of interest, technologies to be studied and outcome measures for analysis,

considering both effectiveness and safety. Evidence is specifically sought for subgroups of patients based on race, ethnicity and age, demographics. Using standardized methods, our source document providers review systematic databases, and the medical literature. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The Center for Evidence Based Policy through their subcontractors and the “Participant Inquiry” process provided the HRC with materials to complete the report, “reduced Intensity Marrow Transplantation, November, 2009”. This identified our major source document from Hayes Inc. “*Nonmyeloablative Transplantation for Hematological Malignancies*” Feb, 2006 with updates from 2007, 2008 and 2009.

Hayes, Inc.

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This report was circulated to subcommittee members and the reference and contact information for Hayes, Inc. was posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings and input from the HRC. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the source documents, the subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. This report may be updated if indicated at the discretion of the Health Resources Commission

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Health Resources Commission website:

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## ***Critical Policy***

### *Health Resources Commission*

- “Clinical outcomes are the most important indicators of comparative effectiveness”
- “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

## ***Clinical Overview***

### ***Myeloablative conditioning with Stem Cell Transplantation (Myeloablative)***

The goal of high-dose chemotherapy (HDC) is to completely eradicate all of the cancer cells in the patient by using extremely high doses of medications; sometimes irradiation is used in addition to chemotherapy. However, the dosages required in HDC to eradicate cancer cells also destroy the patient’s healthy bone marrow stem cells (myeloablation), which are the progenitors of many types of blood and immune cells. Destruction of the bone marrow stem cells is fatal. However, patients can be treated with HDC if the destroyed bone marrow stem cells can be replaced after treatment to reconstitute the blood-cell producing system. Stem cells can be obtained from the patient’s circulating peripheral blood or bone marrow before administering HDC, stored, and re-infused after the chemotherapy is completed, a process called autologous stem cell transplant (SCT). However, even if HDC eradicates the tumor cells in the body, the replacement autologous stem cells may be contaminated with tumor cells that may then be able to re-establish the cancer.

Stem cells can also be collected from a donor and used to replenish the bone marrow stem cells, a process referred to as an allogeneic SCT. Allogeneic transplants from healthy donors are not contaminated with tumor cells, and in addition they have the potential to induce a beneficial graft-versus-tumor effect where the transplanted cells destroy cancer cells in the patient. However, traditional HDC/allogeneic transplants are associated with a high treatment related mortality rate, due to a combination of the toxicity of the myeloablation regimen and to damaging graft vs. host disease.

### ***Non myeloablative conditioning with Stem Cell Transplantation***

Nonmyeloablative (NMA) transplantation (also sometimes called mini-transplantation or low/reduced-intensity transplantation) involves a lower dose and less intensive conditioning regimen for hematopoietic stem cell transplantation (HSCT) than that used for conventional, myeloablative (MA) transplantation. NMA transplantation is under investigation for the treatment of several types of cancer, including leukemia, lymphoma, multiple myeloma (MM), and other several cancers of the blood. NMA transplantation may be considered for two general categories of patients, those who would otherwise be considered candidates for a conventional MA transplantation and those who would not be considered candidates for conventional MA transplantation due to age or other contraindications. NMA conditioning may also be used in tandem transplantation, in which a MA conditioning regimen with autologous HSCT is followed several months later by a NMA conditioning regimen and allogeneic HSCT. NMA transplantation was developed as an alternative to MA transplantation for older, heavily pretreated, and/or less medically fit patients. Definitions of the term “nonmyeloablative” vary widely in the literature but have been tentatively defined as those conditioning regimens that meet the

following criteria: (1) do not eradicate the patient's hematopoietic ability; (2) allow prompt endogenous hematologic recovery (< 4 weeks) without transplant; and (3) have presence of mixed chimerism (i.e., coexistence of hematopoietic cells of host and donor origin) upon engraftment. There is no standardized NMA regimen, and the approaches that are found in the literature are highly variable.

NMA conditioning regimens must be distinguished from low/reduced-intensity conditioning regimens, as the latter typically require a transplant of stem cells to restore hematopoiesis, produce major antitumor effects, and reduce graft-versus-host reactions. In contrast to the low/reduced-intensity conditioning regimens, NMA regimens rely on optimization of pretransplant and posttransplant immunosuppression to overcome graft-versus-host reactions and allow engraftment, thereby relying upon eradication of tumors by the graft-versus-tumor (GVT) effect. The use of lower doses of anticancer drugs and radiation results in relatively little toxicity and produces only mild myelosuppression (Luznik et al., 2003; ACS, 2004b; NCI, 2004; Baron et al., 2005a; Baron and Storb, 2006).

NMA transplantation protocols are based on a two-pronged approach. First, immunosuppressive (but NMA) conditioning regimens are used to provide sufficient immunosuppression to achieve engraftment of hematopoietic stem cells. The second aspect of a NMA transplant involves the destruction of malignant cells by the GVT effect. Unlike with MA transplantation, cells from both the donor and the patient exist in the patient's body for some time following NMA transplantation (mixed chimerism). Once the cells from the donor begin to engraft, they may cause the GVT effect and work to destroy the cancer cells that were not eliminated by the lower-dose anticancer drugs and/or radiation. To boost the GVT effect, the NMA transplant patient may be given an injection of their donor's white blood cells (donor lymphocyte infusion). Most patients will eventually convert to full-donor or complete chimerism. NMA conditioning regimens depend largely or solely on GVT effects rather than high-dose therapy to eliminate malignant cells. The less intensive preparative regimen produces less toxicity and, therefore, is tolerated by less medically fit patients (Djulgovic et al., 2003; Luznik et al., 2003; ACS, 2004b; NCI, 2004; Baron et al., 2005a; Baron and Storb, 2006).

### ***Hematological Malignancies***

Hematological malignancies comprise a varied group of neoplasms that arise through malignant transformation of bone marrow-derived cells. The diversity that is seen in this group of disorders is a reflection of the complexity of normal hematopoiesis and the immune system. A number of classifications have been devised in an attempt to subdivide hematological malignancies in a clinically and biologically relevant way. The primary basis of classification is the distinction between tumors of lymphocytes (the primary cell of the immune system) and myeloid malignancies (relating to the bone marrow). To date, most of the studies evaluating nonmyeloablative (NMA) transplantation have focused on the following hematological malignancies: lymphoma (Hodgkin's lymphoma and non-Hodgkin's lymphoma), multiple myeloma, myelodysplastic syndrome, and leukemia (acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia).

**Scope:**

This report will look at non-myeloablative transplantation for hematological malignancies.

**Key Questions:**

1. How effective is reduced intensity transplantation in the treatment of hematological malignancies or autoimmune diseases vs. standard transplant protocols?
2. What is the relative safety of reduced intensity transplants vs. standard transplantation protocols for hematological malignancies or autoimmune diseases?
3. Are there any subpopulations for which there are differences in effectiveness or safety for reduced intensity transplantation vs. standard transplantation protocols in treatment for hematological malignancies or autoimmune diseases?

**Conclusions:***Limitations of the evidence:*

1. Most of the studies are retrospective, with insufficient sample size, and do not have adequate follow up duration or control groups.
2. There are no prospective randomized Head to Head trials of NMA vs MA SCT in comparable patient populations.
3. NMA conditioning regimens and hematopoietic stem cell transplantation (HSCT) protocols were variable between studies and within a single study.
4. Patients undergoing NMA tended to be older, have more advanced disease, more comorbidities, and generally had more pretreatment prior to undergoing transplantation making comparisons between NMA and MA protocols very difficult.
5. No large, prospective, randomized controlled trials that addressed specific questions regarding safety and efficacy of nonmyeloablative (NMA) transplantation for single malignancies were available.
6. No studies reported mortality directly related to the NMA regimen.

**Conclusions: Subject to the limitations listed above**

1. Evidence suggests that NMA transplantation may reduce the duration of the initial neutropenic phase, reduce blood transfusion requirements, and decrease transplant-related mortality.
2. Evidence suggests that NMA transplantation may result in an acceptable outcome for patients with no other treatment alternatives.
3. Serious and life-threatening complications such as graft rejection, graft versus-host disease (GVHD), and opportunistic infections are often associated with NMA transplantation.
4. Evidence suggests that the toxicity profiles of NMA conditioning regimens are lower with fewer myelosuppression and gastrointestinal toxicities than those caused by conventional MA conditioning regimens.
5. Further research is needed to determine whether that NMA transplantation significantly reduces the incidence of disease progression or prolongs survival.

6. Evidence suggests that initial (first 100 days) infections and infectious complications are lower for NMA regimens vs MA regimens, however at the one year point evidence suggests there is no clinically significant difference.
7. One study (Sorrer 2004, n=64) determined that lower mean numbers of hematologic ( $P<0.0001$ ), gastrointestinal ( $P<0.0001$ ), hepatic ( $P=0.005$ ), infection related ( $P=0.02$ ), and hemorrhagic ( $P=0.02$ ) adverse events were seen in NMA compared with MA patients; however there was no comparative difference for cardiovascular, metabolic, pulmonary, and renal toxicities between in NMA compared with MA patients.
8. There was considerable variation in length of hospital stay for patients undergoing NMA transplantation, with studies reporting median duration of stay ranging from 8 days up to 40 days. Initial hospitalization was typically of shorter duration for patients undergoing NMA transplantation compared with those undergoing MA transplantation, and several studies reported that NMA transplantation was completed on an outpatient basis for some patients. There is insufficient evidence to determine a difference for number of hospital days over a 1 year period.
9. The limited evidence available suggests that outcomes from NMA transplantation are comparable with conventional MA transplantation.

### ***Supporting Evidence:***

#### Non-myeloablative (NMA) Transplantation for Mixed Hematological Diseases:

Bornhäuser et al. (2001) performed a retrospective study (n=42) to assess the safety and efficacy of allogeneic NMA transplantation from unrelated donors. All of the patients included in this study had hematological malignancies. The patients were grafted with bone marrow (n=13) or peripheral blood stem cells either unmanipulated (n=20) or CD34+ selected (n=9). With a median follow-up of 13 months (range, 5 to 26), the actuarial disease-free survival (DFS) was 64% for patients with lymphoid malignancies and 38% for patients with standard risk leukemia compared with 14% for patients with high-risk disease. The main cause of treatment failure was relapse of disease in high-risk patients (n=14). Primary graft failure occurred in 1 patient with CML; autologous peripheral stem cells were reinfused to rescue the patient. Secondary graft failure was observed in 8 patients; autologous peripheral stem cell graft was reinfused in 6 of 8 patients to reconstitute hematopoiesis (2 patients died from infectious complications). The overall day 100 treatment-related mortality was 12%. At 1 year post-transplant, 14 patients had died due to relapsing disease, 7 from opportunistic infections, 3 from early toxicity (sepsis, GVHD, pneumonitis), and 1 from heart failure. The researchers concluded that unrelated NMA transplantation was associated with a high risk of graft failure.

McSweeney et al. (2001) described the initial results of NMA transplantation in consecutive patients (n=45) with hematological malignancies who were ineligible for conventional MA transplantation due to age or medical contraindications. The regimen toxicities and myelosuppression were mild, allowing 17 of 32 (53%) eligible patients to

have entirely outpatient transplantations. The remainder were hospitalized a median of 8 days (range, 1 to 35). Nonfatal graft rejection occurred in 9 of 44 (20%) patients at 2 to 4 months. Grades II to III acute GVHD occurred in 17 of 36 (47%) patients with sustained engraftment. With a median followup of 417 days (range, 310 to 769), 30 of 45 (66.7%) patients were alive; 12 (26.7%) died of progressive disease; and 3 (6.7%) died of transplantation complications without disease progression. Of patients with sustained engraftment, 19 of 36 (53%) were in complete remission, including 8 with molecular remissions. The authors of this study concluded that the NMA transplantation approach used in this study reduced the acute toxicities that are associated with MA transplantation, and that the induction of potent GVT effects can be performed in previously ineligible patients, largely in an outpatient setting.

Weissinger et al. (2001) examined the platelet and red blood cell (RBC) transfusion requirements in patients given NMA transplantation and compared results to patients treated with standard MA transplantation. The patients in the NMA group (n=40) had mixed hematological malignancies, myelodysplasia, or myeloproliferative diseases and were ineligible for conventional MA transplantation due to age or medical contraindications. All of the patients were given peripheral blood stem cell grafts from genotypically HLA-identical siblings. None of the grafts were processed before transplantation. Among patients given NMA transplants, 23% required platelet transfusions compared with 100% among patients given conventional MA grafts ( $P<0.0001$ ). In addition, the number of platelet units given to NMA recipients was reduced, with a median of 0 (range, 0 to 214) compared with a median of 24 (range, 4 to 358) following MA transplantation ( $P<0.0001$ ). Among NMA recipients, 63% required RBC transfusions compared with 96% of those with conventional grafts ( $P=0.0001$ ). The number of RBC units transfused was also reduced, with a median of 2 (range, 0 to 50) for the NMA group compared with 6 (range, 0 to 34) for the MA group ( $P=0.0001$ ). Although neither significantly influenced the outcome of the analysis, high transfusion requirements before transplantation and donor-recipient ABO incompatibility increased the transfusion requirements in both patient groups. Patient age, splenomegaly at transplantation, development of GVHD, post-transplantation cytomegalovirus antigenemia or cytomegalovirus disease did not have statistically significant influences on post transplantation transfusions.

Feinstein et al. (2003) performed a retrospective study (n=55) of patients who received NMA transplantation from either related or unrelated HLA-matched donors after failing conventional MA transplantation. The patients in this study had mixed hematological malignancies and were ineligible for conventional MA transplantation due to age or medical infirmity, or high risk of transplantation related death. The patients had failed conventional autologous (n=49), allogeneic (n=4), or syngeneic (n=2) MA transplantation, and were treated with HLA-matched related (n=31) or unrelated (n=24) donor allografts following NMA conditioning. One patient with refractory secondary AML rejected the unrelated donor marrow graft 33 days following NMA transplantation and died of relapse. The remaining 45 patients for whom chimerism data were available all had sustained engraftment. Regarding transfusions, 31 patients required no platelet transfusions and 17 patients required no RBC transfusions. Data regarding hospitalization

were available for 51 of 52 patients who were eligible for outpatient transplantation; 11 patients did not require hospitalization within the first 60 days following HSCT. The remainder was hospitalized for a median of 8 days (range, 1 to 60). The incidence of grades II, III, and IV acute GVHD for 31 patients with HLA-matched related donors was 29%, 13%, and 6%, respectively. Among 21 patients with related donors and > 100 days follow-up, 14 (67%) patients required extended immunosuppressive treatment for chronic GVHD. The incidence of grades II, III, and IV acute GVHD for 24 patients with HLA-matched unrelated donors was 38%, 8%, and 4%, respectively. Among 18 patients with unrelated donors and > 100 days follow-up, 10 (56%) patients required treatment for chronic GVHD. Thirty-three patients died a median of 127 days (range, 7 to 834) following NMA transplantation: 21 due to relapse, 11 due to transplant-related mortality (TRM), and 1 due to suicide. The TRM rate on day 100 was 11%, with an estimated 1-year TRM rate of 20%. The median follow-up among 22 survivors was 368 days (range, 173 to 796). Of 22 survivors, 17 were progression free. One-year estimates of overall and progression-free survival rates were 49% and 28%, respectively. Untreated disease at the time of NMA transplantation increased the risk of death ( $P=0.04$ ). The authors concluded that encouraging outcomes could be achieved with NMA transplantation in patients who are expected to have poor outcomes with conventional MA transplantation.

Maris et al. (2003) performed a retrospective study ( $n=89$ ) that evaluated engraftment, GVHD, and GVT effects in patients with advanced hematologic malignancies who received NMA transplantation using transplants from unrelated donors matched for HLA-A, HLA-B, HLA-C antigens and DRB1 and DQB1 alleles transplanted with Marrow ( $n=18$ ) or granulocyte colony-stimulating factor (G-CSF)-stimulated peripheral blood mononuclear cells (G-PBMCs;  $n=71$ ). The sustained engraftment rate was higher for recipients of G-PBMC (60 of 71 [85%] patients) than those given marrow (10 of 18 [56%] patients;  $P=0.007$ ). Overall, 19 patients experienced graft rejection. The transfusions of platelets and RBCs were not required in 19 (21%) and 13 (15%) patients, respectively. Most of the (91%) patients required hospitalization at some point following HSCT, while 8 patients were hospitalized overnight for the infusion of the unrelated donor grafts. The median time of hospitalization over the first 2 months was 8.5 days (range, 0-60). The cumulative probabilities of grades II, III, and IV acute GVHD were 42%, 8%, and 2%, respectively. Chronic GVHD requiring therapy occurred in 40 patients. Nonrelapse mortality at day 100 and at 1 year was 11% and 16%, respectively. One-year overall survivals and progression free survivals were 52% and 38%, respectively. G-PBMC recipients had improved survival (57% versus 33%) and progression-free survival (44% versus 17%) compared with marrow recipients. The authors of this study concluded that HLA-matched unrelated donor NMA transplantation is feasible in patients who are ineligible for conventional MA transplantation; and that G-PBMCs conferred higher donor T-cell chimerism, greater durable engraftment, and better progression-free and overall survivals compared with marrow.

Niederwieser et al. (2003) retrospectively examined NMA transplantation from HLA-matched or mismatched unrelated donors in patients with hematological diseases ( $n=52$ ). Most of the (88%) patients were considered high risk, and 42% had failed previous autologous or allogeneic HSCT. The patients received 2 Gy of TBI on day 0 and fludarabine (30 mg/m<sup>2</sup>) on days -4 to -2. GVHD prophylaxis was performed with

cyclosporine and mycophenolate mofetil. Regarding transfusions, 9 (17%) patients did not require any transfusions; 16 did not require platelet transfusions, and 9 did not require RBC transfusions. The median hospital stay for 22 patients who were treated in the United States and were eligible for outpatient therapy was 16 days (range, 0 to 56), while 30 patients who received transplants in Germany and were ineligible for outpatient treatment had a median hospital stay of 40 days (range, 13 to 122). Durable donor chimerism was attained in 88% of patients. Complete donor chimerism was generally attained by day 28 for natural killer (NK) cells, by day 56 for granulocytes, and by day 180 for CD3+ cells (range, 55% to 100%). Of 52 patients, 3 died too early to be evaluable for engraftment. Of the remaining 49 patients, 6 (12%) rejected their grafts between 21 and 56 days following NMA transplantation and had autologous marrow recoveries. The factors predictive of graft rejection in univariate analysis were low T-cell contents in the grafts ( $P=0.04$ ) and diagnosis of MDS ( $P=0.03$ ). Grade II acute GVHD was seen in 22 (42%) patients; grade III in 4 (8%); and grade IV in 7 (13%). Of 43 evaluable patients, 13 (30%) developed chronic GVHD that required systemic immunosuppressive therapy; 8 died from complications that were associated with either acute or chronic GVHD (15%). The 100-day transplantation-related mortality was 11%. Complete remissions, including molecular remissions, were seen in 45% of patients with measurable disease before transplantation. The mortality from disease progression was 27% at 1 year. With a median follow-up of 19 months, 18 (35%) patients were alive and 25% of these were in remission. The authors concluded that NMA transplantation from HLA-matched or mismatched unrelated donors can be performed in patients who are ineligible for conventional MA transplantation (Niederwieser et al., 2003).

Diaconescu et al. (2004) performed a retrospective analysis of morbidity and mortality with NMA transplantation compared with MA transplantation from HLA-matched related donors ( $n=73$  in NMA group;  $n=73$  in MA group). NMA patients were at higher risk than MA patients due to greater age, longer time from diagnosis to HSCT, more frequent preceding MA transplantation, and higher pretransplantation Charlson comorbidity scores. The incidence of severe (grades III to IV) toxicities was significantly lower ( $P\leq 0.05$ ) among NMA patients compared with MA patients within 8 of 12 categories studied, including neutropenia, thrombocytopenia, gastrointestinal, hemorrhage, hepatic, infection, metabolic, and pulmonary. Day-100 and 1-year nonrelapse mortalities were 23% and 30% for MA patients compared with 3% and 16% for NMA patients, respectively ( $P=10^{-4}$  and  $P=0.04$ , respectively). Most deaths among MA patients occurred during the first 3 months following HSCT, whereas most deaths among NMA patients occurred between 3 and 6 months. Overall, 12 NMA and 22 MA patients died within the first year from infections with or without preceding GVHD ( $n=24$ ), sinusoidal obstruction syndrome ( $n=5$ ), acute lung injury ( $n=2$ ), and central nervous system (CNS) complications ( $n=3$ ) ( $P=0.04$ ). In multivariate analysis, the strongest factor predicting lessened regimen related toxicities and nonrelapse mortality was NMA conditioning, whereas high pretransplantation comorbidity scores predicted higher nonrelapse mortality. The authors concluded that NMA transplantation had lower regimen related toxicities and nonrelapse mortality than MA transplantation (Diaconescu et al., 2004).

Sorrer et al. (2004) conducted a retrospective study to compare morbidity and mortality of HLA-matched unrelated donor NMA transplantation and MA transplantation (n=60 in NMA group; n=74 in MA group).

Although the NMA patients had significantly higher pretransplantation comorbidity scores ( $P<0.0001$ ), were older ( $P<0.0001$ ), and had more often failed preceding MA transplantations and cytotoxic therapies ( $P<0.0001$ ), they experienced fewer grades III to IV toxicities than MA patients. Lower mean numbers of hematologic ( $P<0.0001$ ), gastrointestinal ( $P<0.0001$ ), hepatic ( $P=0.005$ ), infection-related ( $P=0.02$ ), and hemorrhagic ( $P=0.02$ ) adverse events were seen in NMA compared with MA patients; cardiovascular, metabolic, pulmonary, and renal toxicities were comparable between the two groups. The incidence of grades II to IV acute GVHD was significantly lower in NMA than MA patients (77% versus 91%;  $P=0.03$ ), in part, due to fewer instances of grades III to IV GVHD (17% versus 35%;  $P=0.01$ ). Both patient groups had comparable 1-year probabilities of chronic GVHD. Although MA patients had higher incidences of overall grade IV toxicities ( $P<0.0001$ ), the differences in nonrelapse mortality at day 100 (12% for NMA group, 18% for MA group;  $P=0.07$ ) and 1 year (20% for NMA group, 32% for MA group;  $P=0.04$ ) were not statistically significant between the two groups. The causes of 1-year nonrelapse mortality were GVHD and infections, 5% for NMA group and 9% for MA group; GVHD complications, 5% and 7%; infections, 3% and 9%; other causes, 7% and 7%, respectively. Multivariate analyses showed higher pretransplantation comorbidity scores to result in increased toxicity and mortality in both groups.

In summary, this study demonstrated that recipients of NMA transplantation, despite older age, more advanced diseases, greater number of pretransplantation chemotherapy regimens, more frequent prior high-dose HSCT, and higher pretransplantation Charlson Comorbidity Index scores had lower rates of 1-year morbidity and nonrelapse mortality compared with concurrent recipients of MA transplantation (Sorrer et al., 2004).

Alyea et al. (2005) performed a retrospective analysis to compare outcome of allogeneic NMA transplantation and MA transplantation for patients aged > 50 years (n=71 in NMA group; n=81 in MA group)

NMA transplantation patients were more likely to have unrelated donors (58% versus 36%;  $P=0.009$ ), a prior transplant (25% versus 4%;  $P\leq 0.0001$ ), and active disease at transplantation (85% versus 59%;  $P\leq 0.001$ ). The incidence of grades II to IV acute GVHD was similar in patients undergoing NMA and MA transplantation, 29% versus 27%, respectively. The 100-day TRM was significantly lower for patients receiving NMA transplantation than for recipients of MA transplantation (6% versus 30%). The cumulative incidence of nonrelapse mortality was 32% for patients receiving NMA conditioning compared with 50% for patients receiving MA conditioning ( $P=0.01$ ). Estimated overall survival was improved in the NMA group at 1 year (51% versus 38%) and 2 years (39% versus 29%;  $P=0.056$ ). There was no significant difference in progression-free survival (2 years, 27% versus 25%;  $P=0.24$ ). Disease relapse was the primary cause of treatment failure for patients receiving NMA transplantation. The cumulative incidence of relapse was 46% for patients receiving NMA transplantation and 30% for patients receiving MA transplantation ( $P=0.052$ ). The nonrelapse mortality rate was lower for NMA patients than MA patients (32% versus 50%;  $P=0.01$ ). The authors

of this study concluded that, in patients aged > 50 years, NMA transplantation leads to an overall outcome at least as good as that following MA transplantation (Alyea et al., 2005).

Baron et al. (2005c) conducted a retrospective analysis of GVT effects following allogeneic NMA transplantation from both related and unrelated donors (n=322) utilizing two different conditioning regimens.

Graft rejection occurred in 21 patients; durable donor engraftment, as assessed by genetic markers, occurred in 301 patients. Grades I, II, III, and IV acute GVHD were seen in 8.1%, 43.8%, 10.6%, and 3.4% of patients, respectively. Chronic extensive GVHD was seen in 56.2% of patients, and, of these patients, 19.9% had de novo chronic extensive GVHD. The 3-year probability of overall survival was 49.7%. The 3-year probability of progression-free survival was 38.5% (48.6%, 34.2%, and 5.9%, respectively, for patients with standard-, high-, and very-high-risk disease). In multivariate analysis, the factors that significantly influenced progression-free survival included disease risk ( $P<0.0001$ ), Charlson comorbidity score ( $P<0.0001$ ), and tandem autologous and allogeneic HSCT ( $P=0.0008$ ). Of 221 patients with measurable disease at NMA transplantation, 98 (44%) patients achieved complete remission 27 to 963 days (median, 176) following HSCT, and 28 (13%) were in partial remission at the time of analysis. In multivariate analysis, there was a higher probability trend of achieving complete remission in patients with chronic extensive GVHD ( $P=0.07$ ). At the time of analysis, 108 (34%) patients relapsed or progressed. In multivariate analysis, achievement of full donor chimerism was associated with a decreased risk of relapse or progression ( $P=0.002$ ). Grades II to IV acute GVHD had no significant impact on the risk of relapse or progression but were associated with increased risk of nonrelapse mortality and decreased probability of progression-free survival. Conversely, chronic extensive GVHD was associated with decreased risk of relapse or progression ( $P=0.006$ ) and increased probability of progression-free survival ( $P=0.003$ ).

The authors concluded that new approaches aimed at reducing the incidence of grades II to IV acute GVHD might improve survival following allogeneic NMA transplantation (Baron et al., 2005c).

Baron et al. (2005b) performed a retrospective analysis evaluating whether the individual cell subsets (such as high doses of transplanted CD34+ cells) in unrelated, unmanipulated hematopoietic grafts affected outcomes among patients given NMA transplantation (n=130).

Higher numbers of grafted CD14+ ( $P=0.0008$ ), CD3+ ( $P=0.0007$ ), CD4+ ( $P=0.001$ ), CD8+ ( $P=0.004$ ), CD3-CD56+ ( $P=0.003$ ), and CD34+ ( $P=0.0001$ ) cells were associated with higher levels of day-28 donor T-cell chimerism. Higher numbers of CD14+ ( $P=0.01$ ) and CD34+ ( $P=0.0003$ ) cells were associated with rapid achievement of complete donor Tcell chimerism, while high numbers of CD8+ ( $P=0.005$ ) and CD34+ ( $P=0.01$ ) cells were associated with low probabilities of graft rejection. In 6 of 14 marrow recipients and 8 of 116 granulocyte-peripheral blood mononuclear cell (GPBMC;  $P=0.001$ ) recipients, the grafts were rejected. Of the patients that rejected their graft, 4 patients did so before day 28. In the remaining 122 patients who were studied, day-28 donor T-cell chimerism levels were predictive of the subsequent risk of graft rejection

( $P < 0.0001$ ). Grades II, III, and IV acute GVHD occurred in 64 (55.2%), 16 (13.8%), and 2 (1.7%) patients, respectively. Chronic GVHD that required systemic therapy was seen in 70 patients.

In total, 42 of 116 (36%) patients relapsed/progressed following NMA transplantation; 19 (16%) patients died of nonrelapse causes. The probabilities of progression-free survival at 1, 2, and 3 years were 49, 43, and 33%, respectively. The probabilities of overall survival at 1, 2, and 3 years were 62%, 52%, and 43%, respectively. When analyses were restricted to G-PBMC recipients, higher numbers of grafted CD34+ cells were associated with higher levels of day-28 donor T-cell chimerism ( $P = 0.01$ ), rapid achievement of complete donor T-cell chimerism ( $P = 0.02$ ), and a trend toward lower risk for graft rejection ( $P = 0.14$ ). There were no associations between any cell subsets and acute or chronic GVHD or relapse/progression.

The authors concluded that the data suggest more rapid engraftment of donor T cells, and reduced rejection rates could be achieved by increasing the doses of CD34+ cells in unrelated grafts that are administered following NMA conditioning (Baron et al., 2005b).

### ***Evidence from NMA Transplantation for Specific Hematological Disease Diagnoses***

Several studies examined NMA transplantation in patients with specific hematological malignancies. Most studies were retrospective analyses.

#### ***Acute Lymphocytic Leukemia (ALL)***

Arnold et al. (2002) conducted a retrospective study ( $n = 22$ ) that evaluated the efficacy of NMA transplantation in adults with high risk ALL. Multiple conditioning regimens were used. All patients had unmanipulated transplants. Peripheral blood stem cells served as a stem cell source in 18 patients and bone marrow in 4 patients. Following NMA transplantation, 18 (82%) patients engrafted, 3 patients had refractory ALL, and 1 patient had a graft failure. Of 16 patients with active disease at the time of HSCT, 13 (81%) patients reached complete remission. GVHD developed in 15 (68%) patients; 6 of 8 patients following unrelated and 9 of 14 patients following related transplant. Seven patients received donor leukocyte infusion. At the time of analysis, 4 (18%) patients were alive and in complete remission; 8 (36%) patients died from leukemia; 9 (41%) patients died from GVHD and infections; and 1 patient died following graft failure.

Following first NMA transplantation 10 of 11 (91%) patients engrafted; 6 of 7 patients with active disease reached complete remission. Following donor lymphocyte infusions and termination of immunosuppression or imatinib, 3 of 5 relapsing patients reached subsequent complete remission. At 5 to 30 months following HSCT, 3 of 11 (27%) patients were alive in complete remission; 8 patients died (3 from leukemia and 5 from transplant-related causes). Following salvage HSCT, 8 of 11 (73%) patients engrafted; 7 of 9 patients with active disease reached complete remission. At 19 months following HSCT, 1 of 11 patients was alive; 5 patients died from leukemia, 1 died following graft failure, and 4 died from transplant-related causes.

The authors concluded that NMA transplantation is feasible in adults with high risk ALL. However, TRM remains high, and only patients transplanted in complete remission seem to have long-term disease-free survival (DFS) (Arnold et al., 2002).

#### ***Chronic Lymphocytic Leukemia (CLL):***

Schetelig et al. (2003) evaluated evidence of a GVT effect following allogeneic NMA transplantation in patients with advanced CLL. Donors were siblings (n=13), non-HLA-identical family members (n=2), and matched unrelated volunteers (n=15). After a median follow-up of 2 years, 23 patients were alive. Neutrophil and platelet engraftment occurred after a median of 17.5 and 15 days, respectively. Evidence of initial mixed chimerism was not confirmed for all patients. Grades II to IV acute GVHD was observed in 17 (56%) patients, and chronic GVHD was observed in 21 (75%) patients. Complete remission was achieved in 12 (40%) patients, and 16 (53%) achieved a partial remission. Late complete remission occurred up to 2 years following transplantation. Minimal residual disease was monitored in 8 patients with complete remission. All patients achieved a molecular complete remission. At last follow-up, 6 patients were in ongoing molecular complete remission. Causes of death were treatment-related complications in 4 patients and progressive disease in 3 patients. The probability of overall survival (OS), progression-free survival (PFS), and nonrelapse mortality at 2 years was 72%, 67%, and 15%, respectively.

The authors concluded that TRM following reduced-intensity transplantation was low, and that the procedure induced molecular remissions in patients with advanced CLL (Schetelig et al., 2003).

Khouri et al. (2004) investigated the GVT effect of allogeneic NMA transplantation as treatment for patients with CLL (n=17).

The patients received unfractionated peripheral blood progenitor cells (n=16) or bone marrow (n=1) from HLA-matched sibling donors. The median time from diagnosis to transplant was 67 months (range, 22 to 168). Platelet transfusions were not necessary for 11 (65%) patients; transfusions were needed mainly in patients who were cytopenic at study entry. All patients had donor-cell engraftment. Immunomanipulation, including immunosuppression withdrawal and donor lymphocyte infusion with or without rituximab treatment, was performed in 10 patients due to early progression or persistent disease. Of 10 patients, 7 had a complete response and 2 had a partial response; 8 of 9 responders had received rituximab with their immunomanipulation process. Ultimately 12 patients achieved complete remission and 4 achieved partial remissions, considering the effect of the primary transplant and subsequent immune manipulation. The final response rate was 94%, including 70.5% complete remission. None of the patients who achieved complete remission relapsed. At the time of this analysis, the median time of the durable complete remission was 10.6 months. With a median follow-up time of 21 months, the estimated survival rate at 2 years was 80%. PFS at 2 years was estimated to be 60%. TRM was 0% at 100 days, with an estimated 1-year and 2-year TRM of 6% and 22%, respectively. The incidence of grades II to IV acute GVHD and III to IV GVHD was 29% and 12%, respectively. The incidence of chronic GVHD was 60%; 4 patients died of chronic GVHD, and 1 patient died of infection with GVHD. One patient, who had no response to transplantation, died of progressive disease. The patients who received rituximab with their conditioning regimen had a significantly improved survival compared with the group who received fludarabine/cyclophosphamide alone. The characteristics of these groups of patients were comparable, but their survival rates were 100% versus 14%, respectively ( $P=0.03$ ). A trend for a better current PFS at 2 years, also favoring the rituximab-containing conditioning regimen, was also observed (71% versus

43%, respectively). The patients in the overall NMA group compared with the patients in a historical MA conditioning regimen group had comparable survival, PFS, and chronic GVHD. The risk of grades II to IV GVHD was twofold higher in the MA group compared with the NMA group.

The authors concluded that a pronounced GVT effect occurs following allogeneic NMA transplantation for advanced CLL, and that this activity might be augmented by rituximab (Khoury et al., 2004).

Sorrer et al. (2005) analyzed the outcome of patients with advanced CLL when treated with NMA transplantation. HSCT was from related (n=44) or unrelated (n=20) HLA-matched donors. Sustained engraftment was achieved by 61 patients; 3 patients experienced graft rejection. The incidences of grades II, III, and IV acute GVHD were 42%, 17%, and 2% of patients, respectively. At 2 years, 50% of patients had developed chronic extensive GVHD (46% for related and 69% for unrelated recipients, respectively;  $P=0.56$ ). The median times for onset of acute and chronic GVHD were 1.4 and 4.5 months, respectively. Three patients who underwent transplantation in complete remission remained in complete remission. The overall response rate among 61 patients with measurable disease was 67% (50% complete remission, 17% partial remission), whereas 5% had stable disease. Related recipients had lower complete remission rates (42%) than unrelated recipients (78%;  $P=0.005$ ). This difference remained significant after adjusting for pretransplantation disease burden characteristics ( $P=0.03$ ). All of the patients with morphologic complete remission who were tested by polymerase chain reaction (n=11) achieved negative molecular results, and 1 patient subsequently experienced disease relapse. The 2-year incidence of relapse/progression was 26% (34% for related and 5% for unrelated recipients;  $P=0.08$ ). The 2-year rate of relapse related mortality was 18% (22% for related and 5% for unrelated recipients;  $P=0.16$ ). At a median follow-up of 24 months (range, 3 to 63 months), 39 patients were living: 25 in complete remission, 5 in partial remission, 2 with stable disease, and 7 with relapse / progressive disease. Rates of day 100 and 2-year nonrelapse mortalities were 11% and 22%, respectively, with no significant differences between related and unrelated recipients. Rates of 2- year overall and disease-free survivals were 60% and 52%, respectively. In this study, unrelated HSCT resulted in higher complete remission and lower relapse rates than related HSCT, suggesting more effective graft-versus leukemia activity.

The authors concluded that CLL is susceptible to graft-versus-leukemia effects, and allogeneic NMA transplantation might prolong the median survival for patients with advanced CLL (Sorrer et al., 2005).

#### *Acute Myelogenous Leukemia (AML) and/or Myelodysplastic Syndrome (MDS) and AML:*

Hegenbart et al. (2006) assessed outcomes for patients with AML in different stages of their disease, who were not considered candidates for conventional MA transplantation due to age and/or other known risk factors and were given NMA transplantation from related (n=58) or unrelated (n=64) donors. Two conditioning protocols were used. Platelet transfusions were not required in 71% of related and 42% of unrelated recipients. RBC transfusions were not given to 50% of related and 16% of unrelated recipients.

Among the remaining 121 patients (1 died on day 8), 115 (95%) had sustained engraftment; and 6 rejected their grafts. Grades II to IV acute GVHD developed in 48 patients. All 6 patients with grade IV and 1 patient with grade III acute GVHD died. Chronic GVHD, which required therapy, occurred in 44 patients, and an additional 16 patients experienced limited chronic GVHD, which did not require therapy. The cumulative probability of chronic extensive GVHD at 2 years for all patients was 36%. No differences in acute and chronic GVHD incidences were observed between patients with related and unrelated donors. With a median follow-up of 44 months, 51 patients were alive, of whom 48 were in complete remission. Cumulative nonrelapse mortalities were 10% and 22%, and cumulative mortalities from disease progression were 47% and 33% at 2 years for related and unrelated recipients, respectively. Overall, 2-year survival was 48%, and DFS was 44%, with no statistically significant differences between related and unrelated, as well as younger (< 60 years) and older (> 60 years) recipients. The patients who received transplantation in first complete remission had 2-year OS of 44% following related and 63% following unrelated HSCT, respectively. A total of 48 patients died following relapse, 27 following related and 21 patients following unrelated HSCT. Of 122 patients, 23 died from nonrelapse causes, all but one of whom were in complete remission. Nonrelapse mortality among all patients was 19%. Major causes of death included complications from GVHD (9%) and infections (7%).

The authors concluded that NMA transplantation from related and unrelated donors is a promising treatment for elderly patients with AML (Hegenbart et al., 2006).

Scott et al. (2006) conducted a retrospective analysis that compared outcomes among concurrent patients with AML or patients with MDS that transformed into acute myeloid leukemia (tAML) who were prepared for allogeneic NMA transplantation or MA transplantation. A total of 38 patients received NMA regimens. A total of 112 patients received a MA regimen. The NMA patients were older (median age 62 versus 52 years;  $P < 0.001$ ), more frequently had progressed to tAML (53 versus 31%;  $P = 0.06$ ), had higher-risk disease by the International Prognostic Scoring System (53% versus 30%;  $P = 0.004$ ), had higher transplant-specific comorbidity indices (68% versus 42%;  $P = 0.01$ ) and more frequently had durable complete responses to induction chemotherapy (58% versus 14%). Among 112 MA patients, 5 died before day 28 without evidence of GVHD and were not evaluable for engraftment; 1 MA patient developed graft rejection on day 266 following HSCT. Among 38 NMA patients, 4 died before day 28 without evidence of GVHD and were not evaluable for engraftment; 1 NMA patient rejected his graft on day 84 following HSCT. The incidence of grades II to IV acute GVHD was lower in patients who received a NMA regimen (54%) compared with patients who received a MA regimen (78%). There was no difference between NMA and MA transplantation for grades III to IV acute GVHD (22% versus 21%). The 2-year incidence of clinically chronic extensive GVHD was 55% in the NMA group and 64% in the MA group. Disease progression was the most common cause of death among both MA and NMA patients. Of MA patients, 26 progressed a median 147 days (range, 29 to 1441) following HSCT, and 22 patients died secondary to progression. Of NMA patients, 11 progressed a median 82 days (range, 28 to 523) following HSCT, and 10 patients died secondary to disease progression. Overall, 23% of MA and 31% of NMA patients had disease

progression at 3 years ( $P=0.43$ ). Among MA patients, 36 (32%) died from nonrelapse causes, and, among NMA patients, 15 (39%) died from nonrelapse causes ( $P=0.94$ ). Three-year OS (27% for NMA versus 48%, for MA;  $P=0.56$ ), PFS (28% versus 44%;  $P=0.60$ ), and nonrelapse mortality (41% versus 34%;  $P=0.94$ ) did not differ significantly between NMA and MA transplantation. Overall ( $P=0.84$ ) and progression-free survivals ( $P=0.93$ ) were similar for patients with chemotherapy-induced remissions irrespective of conditioning intensity.

The authors concluded that graft-versus-leukemia effects may be more important than conditioning intensity in preventing progression in patients in chemotherapy-induced remissions at the time of transplantation (Scott et al., 2006).

#### *Chronic Myelogenous Leukemia (CML):*

Or et al. (2003) retrospectively evaluated NMA transplantation in patients with CML in first chronic phase ( $n=24$ ). In 19 patients, allografts were from fully HLA-matched family members (sibling/parent); 5 patients received allografts from fully HLA-matched unrelated donors. Patients were free to leave the hospital between treatment schedules, and 9 were treated partially on an outpatient basis. All of the patients displayed evidence of engraftment. Evidence of initial mixed chimerism was not confirmed for all patients. No platelet transfusions were required for 6 patients. Mortality at day 100 was 0. At a median follow-up of 37 months following transplantation, both OS and DSF were  $85\% \pm 8\%$ , with no patients relapsing during this period. Acute GVHD ( $\geq$  grade I) occurred in 13 (54%) patients while on cyclosporine. The early withdrawal of cyclosporine in 7 patients resulted in 6 additional cases of acute GVHD. In 11 patients, acute GVHD progressed to chronic GVHD. Three patients died as a consequence of GVHD. At a median follow-up of 42 months, 21 patients remained alive and disease free. The Kaplan-Meier probability of survival and DFS at 5 years was  $85\% \pm 8\%$ . The authors concluded that NMA transplantation may successfully replace MA transplantation, providing a safer, well-tolerated therapeutic option for all patients with CML in first chronic phase with a matched donor. However, the authors noted that their conclusion must be tested in a prospective randomized clinical trial (Or et al., 2003).

Baron et al. (2005d) conducted a retrospective analysis of patients ( $n=21$ ) with CML who were ineligible for MA transplantation and underwent HLA-matched, unrelated donor NMA transplantation. Data from consecutive patients in first chronic phase ( $n=12$ ), accelerated phase ( $n=5$ ), second chronic phase ( $n=3$ ), and blast crisis ( $n=1$ ) were analyzed. The median numbers of RBC and platelet transfusions were 8 (range, 0 to 32) and 0 (range, 0 to 10), respectively. The patient who underwent transplantation in blast crisis died on day 21 (too early to be evaluated for engraftment) from progressive disease. Sustained engraftment was achieved in 5 of 12 patients who underwent transplantation in second chronic phase, 4 of 5 patients who underwent transplantation in accelerated phase, and 2 of 3 patients who underwent transplantation in second chronic phase, whereas 9 patients rejected their grafts between 28 and 400 days following HSCT. Specifically, 1 of 4 marrow recipients and 10 of 17 G-PBMC recipients achieved sustained engraftment. Grades II and III acute GVHD occurred in 6 (55%) and 3 (27%) patients with sustained engraftment, respectively; no grade IV acute GVHD was observed. Chronic extensive GVHD was seen in 8 patients. Graft rejections were nonfatal in all cases and were

followed by autologous reconstitution with persistence or recurrence of CML. Of 11 patients with sustained engraftment, 7 were alive in complete cytogenetic remissions a median 867 days (range, 118 to 1205) following HSCT. Two of the remaining 4 patients died of nonrelapse causes, and 2 died of progressive disease.

The authors concluded that unrelated donor NMA transplantation is feasible, with relatively low nonrelapse mortality, and they suggest that the risk of rejection may be reduced by exclusive use of GPBMC and by increasing the degree of pretransplantation immunosuppression (Baron et al., 2005d).

Kerbaux et al. (2005) evaluated the outcomes for patients with CML who were treated with NMA transplantation from HLA-identical sibling donors. All patients initially engrafted. However, 4 of 8 patients who were not given fludarabine experienced nonfatal rejection, while all others had sustained engraftment. The patients at the European sites (n=9) had scheduled hospital admissions for HSCT. Among patients who were eligible for outpatient transplantation (n=15) in the other institutions, 6 patients did not require hospitalization during the first 60 days following HSCT. The remaining 9 patients were hospitalized for a median of 1 day (range, 0 to 56). The transfusion requirements were low; 1 (4%) patient received platelet and 5 (21%) received RBC transfusions. With a median follow up of 36 months (range, 4-49), 13 of 24 (54%) patients were alive and in complete remission. There were 5 (21%) patient deaths from nonrelapse mortality, 1 (4%) during the first 100 days following transplant. The proportions of grades II, III, and IV acute GVHD were 38%, 4%, and 8%, respectively; 9 (38%) patients developed chronic GVHD. The 2-year estimate of chronic GVHD was 32%. The 2-year survival estimates for patients in first chronic phase (n=14) and beyond first chronic phase (n=10) were 70% and 56%, respectively. Infections were the most common toxicity affecting 42% of patients.

The authors concluded that patients with CML, who were not eligible for MA transplantation, may benefit and may achieve complete remissions from NMA transplantation (Kerbaux et al., 2005).

#### *Non-Hodgkin's Lymphoma (NHL):*

Khouri et al. (2001) investigated the use of allogeneic NMA transplantation to decrease toxicity, achieve engraftment, and allow a GVT effect to occur in patients with follicular (n=18) or small cell lymphocytic lymphoma (n=2) following relapse from a prior response to conventional chemotherapy. Of 20 patients, 12 were in complete remission at transplantation. All patients achieved engraftment of donor cells. The median number of days with severe neutropenia was 6 (range, 6 to 14). Only 2 patients required platelet transfusion on more than one occasion prior to hematologic recovery. The median number of RBC units transfused within the same period of time was 1 (range, 0 to 9). Hematologic recovery was sustained, and no patient developed graft failure. The cumulative incidence of grades II to IV acute GVHD was 20%. Only 1 patient developed grade III acute GVHD. The cumulative incidence of chronic GVHD was 64%. All patients achieved complete remission. With a median follow-up of 21 months (range, 5 to 46), 17 (85%) patients remained alive and 0 relapsed. The actuarial probability of being alive and in remission at 2 years was 84%.

The authors concluded that NMA transplantation is a promising therapy for indolent lymphoma with minimal toxicity and myelosuppression (Khouri et al., 2001).

Khouri et al. (2003) also evaluated allogeneic NMA transplantation for advanced/recurrent mantle cell lymphoma (n=18). The patients were treated in one of two sequential phase II trials. Prior autologous transplantation failed in 5 (28%) patients, and 16 (89%) had chemosensitive disease. Donor cell engraftment occurred in all patients. No platelet or RBC transfusions were required in 8 (44%) patients. Grade II acute GVHD developed in 3 patients; none developed acute GVHD of grades III or higher. The incidence of chronic extensive GVHD was 36%. Complete remission occurred in 17 patients; 3 had recurrent disease at 2, 3, and 12 months, respectively. Of these patients, 1 was reinduced into continuous complete remission with donor lymphocyte infusion. Death occurred in 3 patients, 1 from infection, 1 of progressive disease, and 1 unrelated to therapy. The day-100 mortality was 0%. With a median follow-up of 26 months (range, 11 to 47), the estimated 3-year survival and current PFS rates were 85.5% and 82%, respectively.

The authors concluded that allogeneic NMA transplantation is a safe and potentially effective strategy for patients with relapsed and chemosensitive mantle cell lymphoma (Khouri et al., 2003).

Escalón et al. (2004) investigated the safety and efficacy of NMA transplantation in patients with NHL who experience a recurrence following an autologous transplantation (NOTE: Some of these same patients were also evaluated in the Khouri et al., 2001 and Khouri et al., 2003 reports.) The patients were treated in two sequential trials. Prior autologous transplantation failed one time in 19 patients, and 1 had disease that recurred following 2 previous transplantations. The median time of progression following the autologous transplantation was 15.5 months (range, 1 to 70), and the median time from autologous transplantation to allogeneic NMA transplantation was 24 months (range, 6 to 117). All of the patients experienced engraftment of donor cells. No platelet transfusions were required for 7 patients. Grade II acute GVHD developed in 1 patient; no patients developed acute GVHD of grades III or higher. The incidence of extensive and limited chronic GVHD was 50%. All of the patients achieved complete remission (10 patients had no evidence of disease at transplantation, the remaining 10 achieved complete remission following allogeneic transplantation). One patient experienced disease progression at 115 days post-transplantation and responded to donor lymphocyte infusion and achieved complete remission at day 220. The remaining patients remained disease free. One patient died at 10.5 months from a fungal infection. With a median follow-up of 25 months (range, 12 to 52), the estimated 3-year current PFS rate was 95%.

The authors concluded that allogeneic NMA transplantation is an effective option in lymphoma patients with chemosensitive or stable disease who experience disease recurrence following autologous transplantation (Escalón et al., 2004).

Maris et al. (2004) evaluated allogeneic NMA transplantation with related and unrelated donors for patients with relapsed and refractory mantle cell lymphoma (n=33). The median time from disease diagnosis to HSCT was 2.8 years (range, 0.4 to 9.5). The median number of treatment regimens was 4 (range, 1 to 10); 14 (42%) patients had

failed previous high dose autologous HSCT. Of 33 patients studied, 31 had stable engraftment, whereas 2 experienced nonfatal graft rejections. The incidences of grades II, III, and IV acute GVHD were 27%, 17%, and 13%, respectively. Chronic extensive GVHD occurred in 18 of 28 (64%) patients who were evaluable beyond day 100. Complications from acute and chronic GVHD were responsible for the deaths of 4 (12%) patients. The overall response rate in the 20 patients with measurable disease at the time of HSCT was 85% (n=17; 75% complete remissions and 10% partial remissions), whereas 3 had progressive disease. Only 1 of 17 patients who responded and 0 of 13 who received transplants and were in complete remission had disease relapse with a median follow-up of 24.6 months. Of 11 patients who died, 3 (9%) died of disease progression and 8 (24%) died of nonrelapse causes. The Kaplan-Meier probabilities of overall and disease-free survivals at 2 years were 65% and 60%, respectively. The authors concluded that allogeneic NMA transplantation is a promising salvage strategy for patients with relapsed and refractory mantle cell lymphoma (Maris et al., 2004).

*Multiple Myeloma (MM):*

Badros et al. (2001) evaluated an allogeneic NMA transplantation from HLA-matched or mismatched siblings in patients with refractory and poor risk MM (n=16).

On day 0, mobilized unmanipulated allogeneic peripheral blood stem cell grafts from their HLA-matched siblings. All of the patients had received 1 (n=9) or 2 (n=7) prior autologous transplants. At the time of allograft, 10 patients had refractory relapse, 4 responsive relapse, and 2 were in near complete remission with poor-prognosis disease. The median number of RBC transfusions was 9 (range, 2 to 29); the median number of platelet transfusions was 8 (range, 0 to 70). Five patients did not require any platelet support. The median duration of hospitalization was 14 days (range, 12 to 67). Grades I to III acute GVHD developed in 10 patients; 1 had fatal grade IV GVHD. Chronic GVHD developed in 7 patients, limited in 3 and extensive in 4. Donor lymphocyte infusions were given to 14 patients with no clinical evidence of GVHD, either to attain full donor chimerism (n=4) or to eradicate residual disease (n=10). Of 16 patients, 15 showed myeloid engraftment, and 12 patients were full donor chimeras at day 21. No TRM was observed during the first 100 days. At a median follow-up of 1 year, 5 patients achieved and sustained complete remission, 3 near complete remission, and 4 partial remissions. Of 4 patients progressing following transplantation, 3 achieved a remission following further chemotherapy and donor lymphocyte infusions. Overall, 3 (18%) patients died of late transplant-related (GVHD) complications and 2 patients died of progressive disease.

The authors concluded that that allogeneic NMA transplantation is a promising strategy for patients with refractory and poor-risk MM (Badros et al., 2001).

Badros et al. (2002) furthered the previous study, evaluating allogeneic NMA transplantation from HLA-matched siblings and unrelated donors in patients with high-risk MM (n=31). NOTE: Some patients in this study overlap with patients in the Badros et al. (2001) study. In total, 25 patients received allografts from HLA matched siblings, 6 patients received them from unrelated donors. At the time of allograft, 17 patients had progressive disease and 14 had responsive disease. All but 1 patient had received one

(n=13) or  $\geq$  two (n=17) prior autologous transplantations. The chromosome 13 abnormality was found in 21 patients. Two patients were hemodialysis dependent. Blood and bone marrow grafts were administered to 28 and 3 patients, respectively. Donor lymphocyte infusions were given to 18 patients either to attain full donor chimerism (n=6) or to eradicate residual disease (n=12). By day 100, 25 of 28 (89%) patients were full donor chimeras, 1 was a mixed chimera, and 2 had autologous reconstitution. Acute GVHD developed in 18 (58%) patients, and 10 progressed to chronic GVHD (limited in 6 and extensive in 4). At a median follow-up of 6 months, 19 of 31 (61%) patients achieved complete/near complete remission. Death occurred in 12 (39%) patients. TRM in the first 100 days was 3 (10%); later, 3 patients died of progressive disease, and 6 of late complications, which were secondary to immunosuppressive therapy for GVHD. Median OS was 15 months. At 1 year, there was a significantly longer event-free survival (EFS) (86% versus 31%;  $P=0.01$ ) and OS (86% versus 48%;  $P=0.04$ ) when NMA transplantation was performed following one versus two or more prior autologous transplantations, respectively. When compared with historical MM controls (n=93) receiving conventional MA transplantation, early TRM was significantly lower (10% versus 29%;  $P=0.03$ ), and OS at 1 year was better (71% versus 45%;  $P=0.08$ ) in the NMA transplantation patients.

The authors concluded that allogeneic NMA transplantation induced excellent disease control for patients with high-risk MM, although NMA transplantation is still associated with significant GVHD (Badros et al., 2002).

Maloney et al. (2003) conducted a trial (n=54) that combined autologous MA transplantation with subsequent allogeneic NMA transplantation to maintain the benefits of both approaches with acceptable toxicity for patients with previously treated stage II or III MM. The patients were given NMA transplantation from HLA-identical siblings. Following autologous MA transplantation, the regimen-related toxicities were moderate, with a median of 6 days of neutropenia, 7 days of hospitalization, and 1 death from infection. Following allogeneic NMA transplantation from HLA-identical siblings, the patients (n=52) experienced medians of 0 days of hospitalization, neutropenia, and thrombocytopenia. The median numbers of platelet and RBC transfusions within the first 60 days were 0 (range, 0 to 40) and 0 (range, 0 to 140), respectively. All 52 patients had sustained engraftment. Grades II to IV acute GVHD developed in 20 (38.5%) patients at a median of 58 days (range, 10 to 107). Chronic extensive GVHD that required therapy developed in 23 (46%) patients. Of 48 patients who were not in complete remission at study entry, 25 (52%) achieved complete remission and 14 (29%) achieved partial remission, with an overall response rate of 81% at a median follow-up of 550 days (range, 194 to 1114) following allografting. Of 6 patients who were in complete remission at the start of the trial, 1 relapsed and 2 died from infection or GVHD. With a median followup of 552 days following allografting, OS was 42 (78%) patients. At the time of analysis, 12 patients had died; one patient from pneumonia following autologous HSCT and 11 following allogeneic HSCT. The 100-day mortalities following autologous and allogeneic HSCT were 2% (n=1) and 2% (n=1), respectively, with the one allogeneic recipient dying of disease progression.

The authors concluded that, despite being evaluated in elderly patients with MM, this two step approach reduced the acute toxicities of allogeneic MA transplantation, while achieving potent antitumor activities (Maloney et al., 2003).

Gerull et al. (2005) conducted a retrospective analysis (n=52) of examining the outcome of allogeneic NMA transplantation in patients with high-risk MM. In all, 32 patients had related donors, of whom 26 were fully HLA-matched (others had one mismatch). A total of 20 patients had HLA-matched unrelated donors. The cell source was bone marrow (n=5), and the remaining patients received unmanipulated peripheral blood stem cells. Of 48 patients evaluable on day +56, 42 (90%) patients had > 90% donor chimerism; 4 (8%) had < 90% donor chimerism, and 1 experienced primary graft failure. On day 100, the chimerism data remained unchanged. There were no cases of late graft failure. The median of transfused RBC and platelet units until day 60 was 0. Excluding the patient with graft failure, grades II to IV acute GVHD occurred in 37% of patients, and 24% had grades III to IV severe GVHD. In patients with a related donor, 19% experienced severe GVHD compared with 30% of those with an unrelated donor. Four patients died as a result of severe GVHD. Of 46 patients who were evaluable beyond day-100 posttransplant, 70% developed chronic GVHD. In all, 71% of patients with a related donor and 67% of those with an unrelated donor experienced chronic GVHD. The median follow-up was 567 days, and, at the time of analysis, 24 patients remained alive. Of those who were alive, 9 patients were in complete remission, 7 in partial remission, and 2 had achieved minor response. Estimated PFS and OS at 18 months was 29.4% and 41.1%, respectively. In total, disease progression occurred in 29 (56%) patients. Transplant-related mortality was 17%, in total. The patients with chronic GVHD had a significantly higher PFS ( $P=0.01$ ). The authors concluded that, in this highly pretreated patient group, disease control from allogeneic NMA transplantation was unsatisfactory (Gerull et al., 2005).

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