



Joanna Zjawinska. *Marie*. Oil on canvas, 34" × 46". Courtesy of the Hanson Gallery, New Orleans, Louisiana.

Additional disease-specific studies with clearly defined eligibility criteria are needed to determine the efficacy and toxicity of nonmyeloablative allogeneic stem-cell transplantation.

Nonmyeloablative Allogeneic Stem-Cell Transplantation for Hematologic Malignancies: A Systematic Review

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Background: Increasingly, clinicians advocate the use of nonmyeloablative allogeneic stem-cell transplants (NM-allo-SCTs, "mini-transplants") to manage hematologic malignancies. They hypothesize that NM-allo-SCT is equally efficacious to standard allo-SCT but produces less regimen-related toxicity.

Methods: To analyze available evidence on the benefits and harms of "mini-transplants," we identified 23 manuscripts, 1 abstract, and 1 letter that reported the outcome of mini-transplants in hematologic malignancies.

Results: Data were compiled on 603 treated patients, with 118 transplants using stem cells from matched unrelated donors. All studies were small prospective case series, and most lacked concurrent or historical controls. Outcomes of interest were not uniformly reported. The studies were heterogeneous and used different patient selection criteria, conditioning regimens, and timing of transplant with respect to disease status. The transplant-related mortality rate was 32%, the relapse rate was 15%, and toxicities included acute and chronic graft-vs-host disease and veno-occlusive disease. The aggregate rate of complete remission was 45%. Survival at 1 year or longer ranged from 30% to 60% at 1 to 5 years of follow-up. All studies reported successful chimerism.

Conclusions: Disease-specific studies with longer follow-up are needed to evaluate this potentially promising therapy.

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Introduction

Allogeneic Stem-Cell Transplantation

Allogeneic stem-cell transplantation (allo-SCT) utilizes hematopoietic stem cells from a nonidentical twin, another sibling or relative, or an unrelated donor to rescue patients from the myelotoxicity caused by high-dose chemotherapy (HDC).¹ Allo-SCT is one method of hematopoietic stem-cell transplantation (HSCT). Another approach to HSCT utilizes autologous stem cells (ie, cells harvested from the patient) for rescue after myeloablative therapy — HDC with autologous stem-cell support. This method produces no graft-vs-malignancy effect, and virtually all of the therapeutic efficacy results from the high-dose regimen. In general, HSCT takes advantage of a steep dose-response curve associated with chemotherapy, radiation therapy, or both. Otherwise, without a transplant, such high doses would cause severe myelosuppression.^{2,3}

An antitumor immunologic response (graft-vs-malignancy effect) may be associated with allo-SCT. Although there is strong evidence of a graft-vs-leukemia effect in allogeneic transplants for patients with chronic myeloid leukemia (CML), evidence is limited for comparable immunologic responses in patients with multi-

ple myeloma (MM), acute lymphocytic leukemia (ALL), acute myelocytic leukemia (AML), or other hematologic malignancies.

In standard allo-SCT, hematopoietic growth factors are usually given to stimulate engraftment and hematopoietic recovery after infusing the donor cells. Immunosuppressants are administered at the time of stem-cell infusion to reduce the incidence of graft-vs-host disease (GVHD), which is a major complication of allo-SCT. Matching donors with recipients according to class I and II HLAs affects the occurrence and severity of acute and chronic GVHD and thus affects the outcome of allo-SCT. Hematopoietic stem cells for allogeneic transplantation may be harvested from bone marrow or peripheral blood. Umbilical cord blood also may be used as a source of stem cells² but is not reviewed here.

Nonmyeloablative Conditioning With Allo-SCT

Myeloablative HDC/allo-SCT is associated with a high risk of treatment-related morbidity and mortality (TRM). Even in patients who are otherwise eligible for this procedure, myeloablative HDC/allo-SCT can be toxic. As shown in Table 1, TRM is high in patients with MM, non-Hodgkin's lymphoma (NHL), and Hodgkin's

Table 1. — Benefits and Harms of “Standard” Allo-SCT in Hematologic Malignancies: Data From the International Bone Marrow Transplant Registry

Disease	Benefits		Harms	
	5-Year Survival	Comments	100-Day Mortality	Comments
ALL	30–50%	Depending on the type of donor (HLA-identical sibling vs unrelated donor) and time of transplant (CR1, CR2+)	14–38%	Depending on timing of transplant (CR1, CR+, others)
AML	30–60%	Depending on the type of donor (HLA-identical sibling vs unrelated donor) and time of transplant (CR1, CR2+)	13–38%	Depending on timing of transplant (CR1, CR+, others); HLA-identical sibling, 1-year TRM for early leukemia: 21%; for intermediate: 24%; for advanced leukemia: 36%
CLL	38–46%	Depending on age at transplant (<45 yrs vs >45 yrs) (HLA-identical sibling only)		Currently not reported by/available from IBMTR
CML	37–67%	Depending on type of the donor and timing of transplant	15–29%	Depending on the phase of the disease (chronic, accelerated, blast crisis)
Hodgkin's disease		Currently not reported by/available from IBMTR		Currently not reported by/available from IBMTR
MDS	20–55%	Depending on the phase of the disease (RAEB/RAEB-t vs RA/RARS)	25%	
Myeloma	32% (at 4 years)	From Alyea and Anderson ⁴ ; currently not reported by/available from IBMTR	10–56%	From Alyea and Anderson ⁴ ; currently not reported by/available from IBMTR
NHL		Currently not reported by/available from IBMTR		Currently not reported by/available from IBMTR

CR = complete remission

disease (HD). In addition, many patients with malignancies that could potentially be treated with HDC/allo-SCT are not eligible for the procedure due to age (55 years of age is the most common upper limit for eligibility in clinical trials of allo-SCT) or due to coincident disease or poor organ function, which increases the risk for an adverse outcome as a result of treatment-related toxicity. Therefore, treatments are needed that would maintain the high efficacy of myeloablative HDC/allo-SCT with reduced toxicity. For these patients, a nonmyeloablative preparative regimen followed by allogeneic stem-cell transplant (NM-allo-SCT, also known as a “mini-transplant” or “transplant lite”) has been proposed to decrease the treatment-related morbidity associated with myeloablative chemotherapy while attempting to improve disease-free survival.

In recent years, the need for high-dose conditioning regimens has been challenged. Cures have been observed in patients with advanced malignancies, such as those in whom several courses of aggressive chemotherapy or standard allo-SCT have failed, with adoptive immunotherapy only (ie, using donor-lymphocyte infusion). This observation led to the hypothesis that the efficacy of allo-SCT may derive more from a “graft-vs-leukemia” effect than from the conditioning regimen. If so, long-term disease control might be feasible with less aggressive conditioning regimens. In turn, this might foster the development of safer allo-SCT that can be used for older patients and for those with preexisting organ dysfunction who are currently ineligible for standard HDC/allo-SCT.

Donor allogeneic stem cells can engraft in recipients with the use of less intensive but sufficiently immunosuppressive conditioning regimens to allow graft-host tolerance that yields stable mixed donor-host hematopoietic chimerism.⁵ After chimerism develops, donor-lymphocyte infusion can be given safely to eradicate malignant cells. Nonmyeloablative preparative regimens have been developed to enable mixed donor-host hematopoietic chimerism while minimizing the toxicity of standard, high-dose preparative regimens (Fig 1). These nonmyeloablative approaches can be divided in three categories⁶: (1) reduced-intensity allo-SCT, (2) pre-allo-SCT host immunosuppression with post-allo-SCT immunosup-

pression directed at host and donor immune cells, and (3) high-intensity auto-SCT followed by an immunosuppressive cytotoxic allo-BMT alone.

In all of these settings, NM-allo-SCT serves as the basis for subsequent adoptive immunotherapy of the underlying malignancies using donor-lymphocyte infusion. It is important to note that a consistent definition of “nonmyeloablative” regimens is lacking with respect to drug classes, doses, and durations. Multiple regimens have been described, ranging from low-dose total-body irradiation (2 Gy) plus immunosuppressive agents such as mycophenolate mofetil and cyclosporine⁷ to regimens using combinations of drugs in doses similar to standard allo-SCT.⁸ Thus, these regimens comprise a continuum that overlaps with standard myeloablative regimens.

Methods

Search Methods

We searched the MEDLINE computer database for reports from 1995 through June 2002 using the following search terms: (nonmyeloabl* OR “transplant lite” OR “mini-transplant” OR “mini-allograft*” OR graft-vs-host disease (mh)) AND explode hematologic neoplasms (mh) AND human. Similar terms were used to

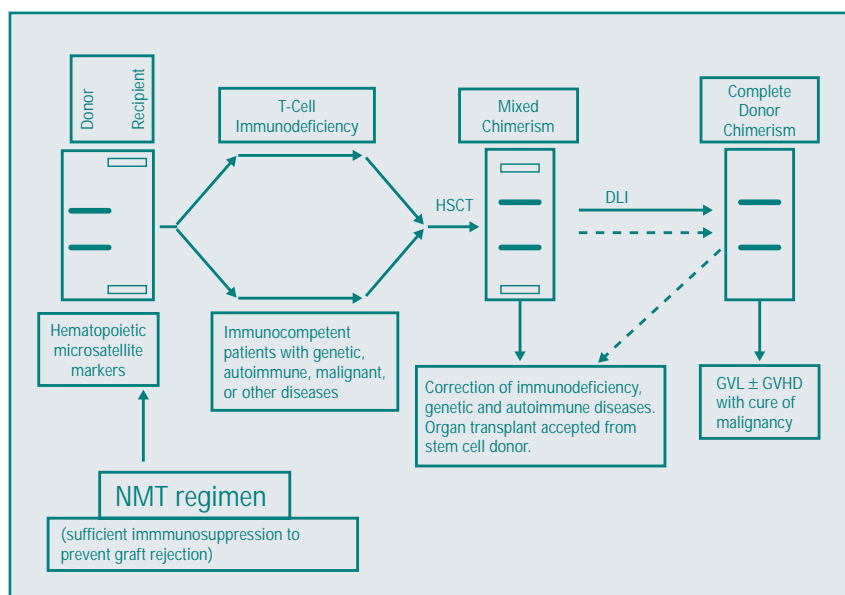


Fig 1. — Principle of nonmyeloablative allogeneic stem-cell transplantation. The goal of conditioning regimen (chemotherapy, radiation therapy or combination) is not to eradicate malignancy but to provide sufficient immunosuppression to prevent graft rejection and allow tolerance between donor and recipients (as measured by the existence of mixed chimerism). The purpose of donor T lymphocytes infusion (DLI) is to eradicate malignant clone. It is believed that mixed chimerism is sufficient to correct some nonmalignant disorders. Modified from McSweeney PM, Storb R. Establishing mixed chimerism with immunosuppressive, minimally myelosuppressive conditioning: preclinical and clinical studies. *Hematology*. Washington, DC: American Society of Hematology Education Program Book; 1999:396-405. American Society of Hematology, with permission.

search the EMBASE database. Computer searches were supplemented by manual reviews of bibliographies of selected references, reviews of meeting abstracts from key hematology/oncology meetings, and reviews of *Current Contents*, an electronic resource that provides access to bibliographic research information.

Study Selection

A flow diagram of our search results and selection process is shown in Fig 2. We initially identified 308 studies for potential retrieval. After further review, we excluded 283 studies, including review articles containing no primary data, abstracts that were later available as full reports, duplicate studies, reports on non-hematologic malignancies, studies on T-cell depletion and donor-lymphocyte infusion, reports on discussions at conferences about NM-*allo*-SCT, and reports involving fewer than 5 patients. Data were extracted from the remaining 25 studies, which included 23 published as full reports, one abstract, and one letter.

Objectives

Patient Indications

Patient disease was categorized by AML, ALL, HD, NHL, CML, or MM ineligible for HDC/*allo*-SCT. This category included patients older than 55 years of age and those with concurrent diseases or conditions that increased the risk of treatment-related toxicity. Each hematologic malignancy was considered as a separate indication.

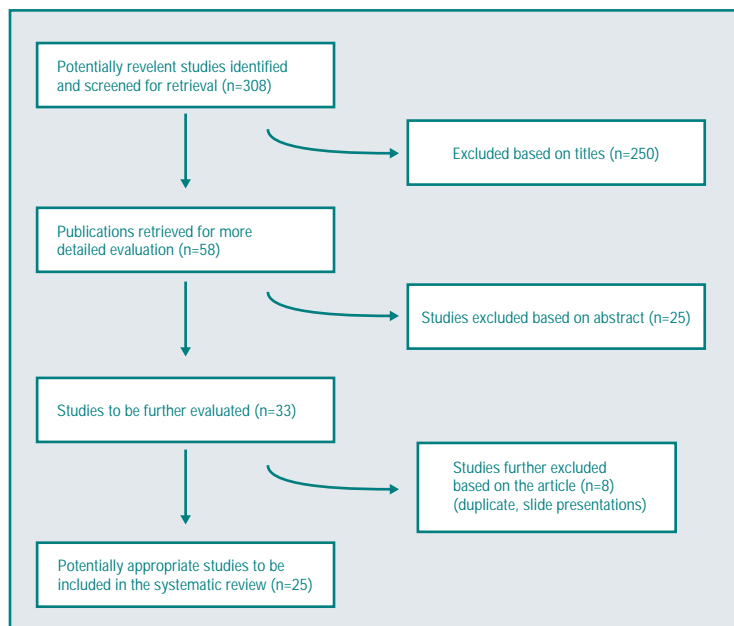


Fig 2. — Flow diagram showing identification of the papers for inclusion in the systematic review.

Comparison of Technologies

NM-*allo*-SCT entails administering reduced-intensity preparative regimens for *allo*-SCT that provide sufficient immunosuppression against host cells before transplants and against host and donor cells after transplants, with the net effect of establishing mutual graft-host tolerance to yield stable mixed donor-host hematopoietic chimerism. The goal of establishing chimerism is to allow the safe administration of donor-lymphocyte infusion to eradicate malignant cells. To date, NM-*allo*-SCT has been used predominantly in hematologic malignancies. Since so few studies reported using this technology in solid tumors, our systematic review focused on the safety and efficacy of NM-*allo*-SCT in hematologic malignancies.

Alternatives to NM-*allo*-SCT for patients with AML, ALL, HD, NHL, or MM ineligible for HDC/*allo*-SCT include HDC followed by autologous stem-cell transplantation (HDC/*auto*-SCT) and conventional-dose treatment. For patients with CML who are ineligible for HDC/*allo*-SCT, conventional-dose therapy (with imatinib mesylate [Gleevec]) is an alternative to NM-*allo*-SCT.

Health Outcomes

The goal of NM-*allo*-SCT is to improve the duration of survival either by directly altering the course of disease or by increasing the time to relapse or progression and thus forestalling the natural progression. Intermediate outcomes related to the effects of treatment on disease — complete remission, partial remission, and relapse rate — were also considered. Since NM-*allo*-SCT attempts to induce tolerance between the recipient and donor, data on mixed chimerism are also of interest. Adverse health outcomes of NM-*allo*-SCT are treatment-related morbidity and mortality, including the incidence or prevalence of acute and chronic GVHD, veno-occlusive disease, and grade III/IV toxicity according to the National Cancer Institute toxicity criteria.

Specific Questions

Does NM-*allo*-SCT improve the net health outcome of patients with AML, ALL, HD, NHL, CML, or MM who are ineligible for HDC/*allo*-SCT? Net health outcome includes an analysis of disease-free survival or overall survival balanced against treatment-associated toxicity, acute and chronic complications, and death. Results were compared with the natural history of each disease or the expected outcome of conventional treatment in patients with advanced hematologic malignancies.

Compared to treatment with the established alternatives, does NM-allo-SCT improve the net health outcome of patients with AML, ALL, HD, NHL, CML, or MM who otherwise are eligible for HDC/allo-SCT? Again, net health outcome includes an analysis of disease-free survival or overall survival balanced against treatment-related toxicity, complications, and death.

Results

Overview

Data were obtained from the 25 publications described. No prospective, randomized, controlled trials addressed the specific questions of this review. Only two studies^{9,10} reported retrospective comparisons with historical controls given standard allo-SCT, without matching in each comparison. All other studies reported case series, occasionally discussing their results in reference to outcomes of standard allo-SCT. Therefore, conclusions are limited from the overall body of evidence in this area.

Only four papers^{10,13} and one abstract¹⁴ reported results of NM-allo-SCT in a single malignancy. All other studies pooled the results from several diseases, which presented difficulties in data extraction. Additionally, many studies pooled results across varied conditioning regimens, which prevented comparison of outcomes as a function of the regimen. The sample size was small in most studies; only four included more than 10 patients with the same hematologic malignancy.^{11,13,15} The largest report included 86 patients and various hematologic malignancies.¹⁵ The largest study on a single malignancy included 31 patients with MM.¹⁰ Table 2 summa-

rizes the number of patients who received NM-allo-SCT in specific hematologic malignancies. The studies were heterogeneous, largely because they combined patients with several diseases in the same analysis and differed in patient selection criteria, conditioning regimens, and timing of NM-allo-SCT (after autologous transplant, in first or second remission, or after relapse).

Appendix 1A-C summarize the evidence from each of the 25 studies. The median age was approximately 51 years (range 1–72 years). The majority of patients were over 40 years of age. Multiple studies reported on patients older than age 50, who are rarely given standard allo-SCT. The International Bone Marrow Transplant Registry reports a category for patients over age 50 but does not provide details on the potential number of patients who might be older than age 50. Estimating the number of patients older than 50 years of age at the time of transplantation, as well as their outcomes, was difficult.

Of the 603 patients who received NM-allo-SCT, 158 were women, 266 were men, and 179 were not classified by gender. In four studies, patients with comorbid conditions were eligible for treatment; such patients routinely are excluded from standard allo-SCT. However, data on the specific comorbid conditions were scant. The number of patients who had undergone transplantation with special comorbid conditions was unclear. Appendix 2 provides data on eligibility criteria as reported in the studies included in this systematic review.

Various conditioning regimens were utilized (Appendix 3), but most studies used cyclophosphamide/fludarabine. In most studies, donors were HLA-compatible, but several studies used matched unrelated donors (MUDs) and/or donors with one or two mismatched antigens. In total, 118 patients underwent transplants from MUDs. It was not possible to extract data on TRM and other outcomes by HLA status.

Few studies reported data on overall survival and disease-free survival beyond 1 year.^{11,15,17} Kelemen et al¹¹ reported that 17 (89%) of 19 patients with CML were alive at 4 years, and 14 (83%) of the 17 were disease-free. Giralt et al¹⁵ reported a survival rate of 28% (95% confidence interval [CI], 20% to 39%) at 2 years for 86 patients with various hematologic malignancies. Disease-free survival for these patients was 23% (95% CI, 15% to 34%) at 2 years. Badros and colleagues¹⁰ recently reported a 68% overall survival rate for 31 patients with MM. This compared favorably with results from historical controls undergoing conventional allo-transplant who had a 1-year overall survival rate of 45% ($P=.08$). Elmaagacli and colleagues⁹ reported that cumulative estimates of survival after transplanta-

Table 2. — NM-Allo-SCT: Summary of Published Evidence*

Disease	No. of Patients
ALL	59
AML	105
CLL	27 †
CML	114
HD	37
NHL	124
MDS	32
MM	105 ‡
Total	603 ¶

* Data from 23 full papers, 1 abstract, and 1 letter. Note that most publications reported on more than one disease.
† Includes patients with PLL.
‡ Includes patients with plasma cell leukemia and extramedullary plasmacytoma (n=1). Assumed that the report by Michallet et al²⁰ included different patients than those described by Garban et al.²⁶
¶ Excludes 25 additional patients with unclassified acute leukemia, 2 with Waldenström's macroglobulinemia, and 1 with CMML.

tion in patients receiving reduced conditioning regimens compared to those receiving conventional BMT was 78% and 58% at 1 year and 77% and 74% at 2 years, respectively. Pawson et al¹⁸ reported the longest follow-up survival data for 14 patients who underwent NM-*allo*-SCT after previous conventional SCT failed. At 58 months, the actuarial survival rate was 60%, the disease-free survival rate was 26%, and no treatment-related deaths had occurred. Corradini and coworkers¹⁹ reported an overall survival rate of 53% in 45 patients at 24 months. Michallet et al²⁰ reported an overall survival rate of 31% at 2 years using NM-*allo*-SCT in several hematologic malignancies. Finally, Nagler and colleagues²¹ utilized MUD NM-*allo*-SCT in 16 patients and reported overall and disease-free survival rates of 75% and 60%, respectively, at 36 months.

Only six studies reported data on median survival or the range of survival.^{10-12,14,17,22} In these studies, survival ranged from approximately 2 months to longer than 24 months. No long-term survival outcomes are available at this time.

Complete remission rates were reported in 21 studies, which varied from 0% (0 of 2 patients with myelodysplastic syndrome (MDS) who underwent NM-*allo*-SCT) to 100% in a single case report. Most studies reported complete remissions in 40% to 70% of patients, but sample sizes were too small to permit meaningful conclusions. It is noted that chimerism,

another intermediate outcome, was achieved in nearly all patients. Data on relapse were inadequately reported. Although most reports focused on successful cases, relapse was reported in 6 (33%) of 18 patients in one of the few large series on patients with a single malignancy (CML).¹¹

Most studies reported data on TRM, which varied from none in a single case report to 3 (43%) of 7 patients.¹⁶ Causes of TRM included infection, GVHD, and organ failure. However, patient enrollment in each of these studies was insufficient to permit conclusions regarding TRM of NM-*allo*-SCT.

Graft-vs-host disease is a major complication of *allo*-SCT. Data are insufficient to permit conclusions, but it is hypothesized that inducing chimerism may reduce the incidence of GVHD. However, available data do not suggest that the incidence of acute GVHD (grade II-IV) was reduced; the incidence of acute GVHD varied from 0% in a single case report to 100% (5 of 5 patients) in a small series. The incidence of extensive chronic GVHD varied from 0% in a single case report to 66% (12 of 18 patients) in the largest series in a single disease.¹¹ Because most studies did not report the incidence of veno-occlusive disease, we could not determine if it did not occur or if it did occur but was not reported. Data on morbidity using grades III and IV toxicity according to the National Cancer Institute toxicity criteria suggest that NM-*allo*-SCT is more tolerable than standard *allo*-SCT. Most reports indicated that grades III and IV toxicity occurred in less than 15% of cases, although several single case studies reported toxic effects of NM-*allo*-SCT.

Table 3 presents an overview of aggregate data that were extractable from published reports. Due to considerable heterogeneity among studies, caution should be exercised when interpreting the summary of evidence presented in this table. Nevertheless, it is notable that TRM remains high (32%; 95% CI, 28% to 37%) in this heavily pretreated and generally older population with many comorbidities. Also, it is noted that this aggregated TRM pool included HLA-matched sibling donors as well as MUDs. Overall, there were 118 NM-*allo*-SCT with MUDs. We could not reliably compare TRM after transplants from MUDs with TRM after transplants from HLA-identical siblings.

Standard *allo*-SCT is likely associated with a greater risk of TRM (ranging from 10% to 56%) when compared with NM-*allo*-SCT (Table 1), even though this procedure is usually used in younger patients with no comorbid conditions. The incidence of acute GVHD following NM-*allo*-SCT was similar to that seen in standard *allo*-SCT, while the incidence of chronic GVHD was lower

Table 3. — NM-*Allo*-SCT:
Overview of Published Evidence in Hematologic Malignancies*

Benefits	
Survival**	75% at 1-4 yrs (n=18) ¹¹ 28% at 2 yrs (n=86, 95% CI, 20-39%) ¹⁵ 30% at 2 yrs (n=31) ¹⁰ 60% at 58 mos (n=14) ¹⁸ 53% at 24 mos (n=45) ¹⁹ 75% at 36 mos (n=16) ²¹ 31% at 2 yrs (n=76) ²⁰
Complete response	44% (215/486)
Harms	
Treatment-related mortality	32% (130/406)
Acute GVHD	51% (232/454)
Chronic GVHD	23% (99/435)
Veno-occlusive disease	0.8% (1/37)
Relapse	15% (50/330)
* The table represents a compilation of extractable data from 25 different studies that are heterogeneous with respect to population selection, pretransplant conditions, and conditioning regimens. Data should be interpreted with caution.	
** Data from individual studies reporting survival beyond 1 yr.	

than usually reported after standard allo-SCT. However, since direct comparative data were lacking, only tentative inferences are possible. The incidence of veno-occlusive disease after NM-allo-SCT also appeared to be less — 0.8% (95% CI, 0.02% to 4%) compared with 8.9% (95% CI, 7% to 11%) as reported in a prospective cohort study by the European Group for Blood and Marrow Transplantation.³⁵ Again, direct data are lacking for definitive conclusions. Table 3 also summarizes data on relapse, which occurred in approximately 15% of treated patients (95% CI, 11% to 19%). Data on long-term benefits are even more limited. Survival beyond 1 year was reported in few studies.^{10-12,17} Thus, it was not possible to combine data on disease-free survival and median survival at the time of this review. Across multiple reports, complete remission was reported in 215 (45%) of 482 patients with a variety of malignancies.

The current body of evidence regarding NM-allo-SCT is insufficient to permit definitive conclusions regarding potential advantages of this treatment compared with standard allo-SCT. Nevertheless, this treatment approach was largely studied in a population of patients generally deemed ineligible for standard allo-SCT. Unfortunately, most reports omitted the criteria to define “ineligibility” for standard allo-SCT. Clinical judgment, patient preference, or both likely influenced patient selection. For example, prior autologous stem-cell support has been a relative contraindication to standard allo-SCT in some studies.

Available data suggest that toxicity with NM-allo-SCT might be lower than that observed with standard

allo-SCT. Reports that some studies used NM-allo-SCT as an outpatient treatment support this possibility. For example, in a study by McSweeney et al,⁵ 53% of patients were treated entirely as outpatients with minimal toxicity and no alopecia, painful mucositis, severe nausea and vomiting, or toxicities to other vital organs. They also reported that only 23% of patients undergoing NM-allo-SCT received platelet transfusions compared with 100% of patients undergoing conventional allo-SCT.³⁶ Similarly, only 63% of patients treated with NM-allo-SCT received red blood cell transfusions compared with 96% of patients given conventional grafts. However, this study used the lowest-intensity conditioning regimen of all others reported; pancytopenia was minimal. Using a more intensive regimen (fludarabine, busulfan, and cyclophosphamide), Ruiz-Arguelles and colleagues³⁷ reported that outpatient transplants were feasible in 21 of 25 patients. Several reports noted that toxicity was minimal or acceptable, but in many cases details were not provided. Pancytopenia frequently occurred, indicating considerable myelosuppression after most NM-allo-SCT regimens. Currently, it is also unclear whether this potentially reduced toxicity will yield an overall net benefit in health outcome since data on benefits and harms are insufficient.

Evidence by Disease

Table 4 summarizes available data from the 25 selected publications according to malignancy. Note that this table aggregates and pools data from multiple references of considerable heterogeneity concerning

Table 4. — NM-allo-SCT: Overview of Published Evidence in Hematologic Malignancies According to Specific Diseases*

		AML	ALL	CML	MDS	NHL	HD	CLL	MM
Benefits	Survival**	NA at 4 yrs	NA	89% (17/19) at 1 yr	NA	100% (1/1) at 1 yr	NA	NA	33%
	CR	66% (41/62)	49% (27/55)	58% (42/72)	48% (10/21)	31% (32/103)	41% (16/39)	33% (9/27)	37% (38/103)
Harms	TRM	19% (10/52)	72% (29/40)	20% (13/64)	36% (5/14)	43% (32/75)	26% (9/35)	33% (8/24)	24% (24/98)
	Acute GVHD	36% (25/70)	36% (19/52)	60% (32/53)	54% (12/22)	50% (49/97)	57% (21/37)	68% (13/19)	59% (61/103)
	Chronic GVHD	23% (15/66)	24% (12/50)	29% (15/51)	31% (6/19)	12% (11/91)	41% (13/32)	32% (10/31)	18% (17/95)
	Veno-occlusive Disease	0% (0/6)	0% (0/2)	0% (0/27)	50% (1/2)	0% (0/38)	0% (0/10)	0% (0/2)	0% (0/50)
	Relapse	25% (13/52)	27% (11/40)	18% (12/65)	7% (1/15)	2% (1/41)	11% (3/27)	6.6% (1/15)	10% (8/76)

* This table represents a compilation of extractable data from 25 different studies; there is a considerable heterogeneity among studies reflected in population selection, pretransplant conditions, and variety of conditioning regimens. Caution is needed in interpreting these data since they likely do not reflect an accurate body of evidence in NM-allo-SCT.

** Data on survival from single reports.

differences in patient selection criteria, conditioning regimens, timing of NM-allo-SCT (after auto-SCT, in first or second remission, or after relapse), and comorbid conditions (age and exclusion criteria due to other organ dysfunction). Therefore, these data should be interpreted with caution.

No published reports have compared the effects of NM-allo-SCT with those of standard allo-SCT, either respectively or prospectively, in patients eligible for standard allo-SCT. Likewise, data are lacking to compare outcomes of NM-allo-SCT with those of standard treatment. Thus, definitive conclusions are not possible regarding net health outcomes in patients ineligible for standard allo-SCT. Overall, the available evidence on effects of NM-allo-SCT in specific hematologic malignancies is limited and of poor quality.

Conclusions

Firm recommendations regarding the net benefits of NM-allo-SCT in the management of hematologic malignancies are precluded by the lack of comparative data, the extreme heterogeneity of the studies, the short follow-up, and the relatively small number of patients studied to date. Initiation of disease-specific studies with clearly defined eligibility criteria are needed to further elucidate the safety and efficacy of NM-allo-SCT.

Table 1 was prepared with help from the Statistical Center of the International Bone Marrow Transplant Registry (Horowitz M, Nugent M, IBMTR, Milwaukee, Wisc, 2000).

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Appendix 1A — NM-Allo-SCT in Hematologic Malignancies: Demographics and Patient Characteristics

Study	Disease	No. of Patients	Sex	Median Age (range)	Comorbid Conditions	Regimen	Study Design	HLA Type	Comments
Giralt ¹⁷ , 1997 (updated 2001 ¹⁵)	AML/MDS	43	52 F, 34 M	52 (22-70) (56% older than 50 yrs)	NR	Flu/Ida or CDA/AraC or Flu/Mel 140 or 180	Prospective cohort/case series without historical control	HLA-compatible siblings (n=39) or 1-antigen mismatched siblings (n=7); HLA (6/6) MUD (n=40); not specified according to disease	All considered poor candidates for conventional allo-transplant; median of 3 previous treatments (range 0-8)
	CML	27							
	HD	4							
	NHL	9							
	ALL	3							
Carella ²⁴ , 1998	CML	2	1 F, 1 M	52 (50-55)	NR	Flu/Cy	Prospective cohort/case series without historical control	HLA-matched siblings	
	HD	4	2 F, 2 M	30 (22-36)					
	NHL	2	1 F, 1 M	33 (24-43)					
	MDS (RAEB)	1	1 F	57					
Kelemen ¹¹ , 1998	CML	19	NA	Not reported individually (21-51)	NR	DBM/AraC/Cy	Prospective cohort/case series, no historical control	HLA-identical siblings (n=19)	8 patients under age 30
	CLL	8	8 M	59 (51-71)	Yes	Flu/Cy/cisplatin/cytarabine	Prospective cohort/case series, no historical control	HLA-identical siblings	13 patients older than age 50, 2 had elevated ALT levels, 2 nd due to alcohol-induced liver toxicity, 1 had hepatitis C infections
Slavin ⁸ , 1998	NHL (4 patients with Richter's syndrome)	7	3 F, 4 M	52 (45-58)		Flu/Cy or cisplatin/Flu/cytarabine			
	ALL	2	2 M	49 (12-46)	NR	Flu/Bu/anti-T-lymphocyte globulin	Prospective cohort/case series without historical control	Matched related donors (n=2)	Included data on patients with nonhematologic malignancies but abstracted data only on those with hematologic malignancies
	AML	8	6 F, 2 M	26 (1-51)				Matched related donors (n=8)	
	CML	8	1 F, 7 M	37 (2-56)				Matched related donors (n=8)	
	NHL	2	2 M	49 (37-61)				Matched related donors (n=2)	
	MDS	1	1 M	41				Matched related donor	
	MM	1	1 M	51				Matched related donor	
Childs ²² , 1999	CML	4	1 F, 3 M	59 (28-68)	NR	Cy/Flu	Prospective cohort/case series without historical control	Not specified according to disease; HLA identical (n=14) or single HLA locus mismatched sibling (n=1)	Included data on patients with nonhematologic malignancies but abstracted data only on those with hematologic malignancies
	NHL	1	1 F	55l					
	MDS	2	2 M	59 (58-60)					
	MM (EMP)	1	1 F	34					
	MM	12	NR	53.5 (45-61)	PS<2	Bu/ATG/Flu	Prospective cohort/case series without control group	HLA-identical sibling	
Carban ²⁶ , 1999 abstract (updated 2001 ¹³)	MM	18	NR	50 (46-61)	NR	Flu/Mel	Prospective cohort/case series without control group	HLA-identical sibling (n=13); MUD (n=5)	
	NHL	5	NR	32 (20-51)	No	Cy/ATG/Flu	Prospective cohort/case series without historical control	Haploidentical-related donor sharing at least one HLA A, B or D allele on the mismatched haplotype	

Appendix 1A — NM-Allo-SCT in Hematologic Malignancies: Demographics and Patient Characteristics

Study	Disease	No. of Patients	Sex	Median Age (range)	Comorbid Conditions	Regimen	Study Design	HLA Type	Comments
Bornhauser ²⁹ 2000	ALL	1	1 F	52	Yes	Bu/Flu	Prospective cohort/case series with no control	HLA-matched sibling	
	AML	10	2 F, 8 M	53 (38-65)					
	CLL	3	1 F, 2 M	41 (33-46)					
	CML	4	1 F, 3 M	51 (25-61)					
	HD	2	2 M	36 (35-37)					
	NHL	1	1 F	59					
Gomez-Almaguer ²⁵ 2000 (updated Ruiz-Arguelles 2001 ³⁷)	AML	6	6 F, 9 M	43 (14-52)	NR	Bu/Cy/Flu	Prospective cohort/case series, no historical control	HLA-identical sibling	21 patients transplanted in outpatient setting, 1 with thalassemia (excluded from this analysis)
	MDS	1		39					
	CML	8		45 (24-61)					
	AML	11	4 F, 7 M	57 (36-63)	Yes	Low-dose TBI (n=44), 1 patient received Flu (30 mg/m ²) in addition to low-dose TBI (which is now the standard treatment and appeared to reduce incidence of the graft failure seen with low-dose TBI only)	Prospective cohort/case series without control group	HLA-identical sibling	53% transplanted as outpatients; general eligibility criteria included those with "relative contraindication to standard allo-SCT" such as age >50 years (>60 for CML); CLL/NHL had to fail at least frontline treatment and MM had to be resistant acute leukemia and aspergillosis (n=1) after induction chemotherapy
McSweeney ⁷ 1999 (updated 2001 ¹⁵)	CML	9	2 F, 7 M	(40-71)	No				
	CLL	8	1 F, 7 M	(46-67)	No				
	NHL	1	1 F	53	No				
	HD	4	2 F, 2 M	45 (31-61)	No				
	ALL	1	1 M	60	Yes				
	MM	8	4 F, 4 M	56 (46-63)	No				
	MDS	1	1 M	43 (36-72)	Yes				
	WF	2	2 M	55 (52-58)	No				
	NHL	19	4 F, 15 M	41 (13-62)	NR	Low-intensity Flu	Prospective cohort/case series, no historical control	HLA-matched sibling	
	HD	4	4 M	31 (17-53)					
Spitzer ²⁷ 2000	ALL	1	NE	40	NR	Cy/ATG/Flu	Prospective cohort/case series, no control group	HLA genotypic ally (n=20) or phenotypic ally (n=1) matched donor transplant	
	AML	3		38 (27-44)					
	HD	4		33 (27-55)					
	NHL	11		45 (22-62)					
	CLL	2		53 (50-55)					
Elmaagacli ¹⁹ 2001	ALL	2	3 F, 6 M	NE	Yes	Bu/Flu/ATG	Prospective cohort series with historical controls	HLA-matched genotypic ally (n=7); partially HLA identical (n=2)	Included data on myeloablative conditioning regimens but only data on nonmyeloablative regimens are included in this table; age and gender not reported separately by disease
	AML	1							
	CML	6							

Appendix 1A — NM-Allo-SCT in Hematologic Malignancies: Demographics and Patient Characteristics

Study	Disease	No. of Patients	Sex	Median Age (range)	Comorbid Conditions	Regimen	Study Design	HLA Type	Comments
Lee ³⁰ 2001	NHL	6	1 F, 5 M	31 (22-56)	Yes	Bu/Flu/ATG/ methylprednisone	Prospective cohort/case studies without historical controls	NR	
	HD	1	1 M	53					
Michallet ²⁰ 2001	ALL	25	NR	NR	Yes	Flu/Bu/ATG/Ida/ Flu/AraC OAT/LG	Retrospective case series analysis	All HLA-identical sibling; 1 HLA-identical unrelated donor but not reported according to disease category	Conditioning regimens and HLA types not reported separately by disease; 3 patients with solid tumors excluded from abstracting and analysis; data extracted on evaluable patients
	MDS	9							
	NHL	13							
	MM	11							
	HD	3							
	CLL	3							
	CML	12							
Mohy ³¹ 2001	NHL	3	1 F, 2 M	42 (26-47)	Yes	Bu/Flu	Prospective cohort/case studies without historical control	HLA-matched genotypic ally (n=10); partially HLA identical (n=1)	One each of NHL, HD and CLL also received ATG as part of conditioning regimen
	HD	1	1 M	40					
	CLL	1	1 M	49					
	MM	6	3 F, 3 M	54 (47-62)					
	MM	12	5 F, 7 M	47 (34-52)	Yes	CAMPATH1H/ Flu/Mel	Prospective cohort study without historical controls	Not specified according to disease; all patients had MUD transplant	Low- and high-grade lymphoma grouped as NHL
	NHL	15	5 F, 10 M	39 (18-56)					
	CML	5	2 F, 3 M	48 (36-53)					
Chakraverty ³³ 2002	AML	6	4 F, 2 M	49 (30-55)					
	ALL	2	1 F, 1 M	22 (18-27)					
	HD	5	3 F, 2 M	31 (22-38)					
	CLL (T-PLL)	1	1 F	50					
	CMMML	1	1 M	62					
	AML	5	17 F, 28 M	NE	Yes	Thiotepa/Cy/Flu	Prospective cohort study without historical controls	Not specified by disease: HLA- identical (n=42) or single HLA locus mismatched (n=3) sibling	Indolent and high-grade lymphoma grouped as NHL
	MDS	6							
Corradini ¹⁹ 2002	ALL	1							
	NHL	24							
	HD	4							
	MM	5							
	AML	9	3 F, 6 M	61 (30-64)	Yes	Flu/Cy/Ida/ etoposide	Prospective cohort study without historical control	All HLA-identical sibling (n=11)	
	ALL	1	1 M	57					
	CML	1	1 M	62					

Appendix 1A — NM-Allo-SCT in Hematologic Malignancies: Demographics and Patient Characteristics

Study	Disease	No. of Patients	Sex	Median Age (range)	Comorbid Conditions	Regimen	Study Design	HLA Type	Comments
Nagler ²¹ 2001	CML	7	1 F, 6 M	17 (12-48)	Yes	Flu/Bu/ATG	Prospective cohort study without historical controls	MUD (n=16)	
	AML	4	2 F, 2 M	21 (18-27)					
	ALL	4	4 M	10 (8-17)					
	NHL	1	1 M	13					
Pawson ¹⁸ 2001	AML	7	5 F, 2 M	32 (24-48)	Yes	FLAG (n=2) FLAG-Ida (n=4) FLAG-X (n=1)	Prospective cohort/case series with no historical control	Full HLA-matched (n=13), 1-antigen-mismatched (n=1)	
	ALL	5	5 M	18 (9-31)		FLAG-Ida (n=4) FLAG-X (n=1)			
	MDS/(RAEB-t)	2	2 F	40 (38-42)		FLAG-Ida			
Badros ¹⁰ 2002	MM	31	13 F, 18 M	56 (38-69)	Yes	Mel/TBI/Flu	Prospective cohort/case studies with historical controls	HLA-matched sibling (n=25); MUD (n=6)	Conditioning regimen for HLA-matched transplant differed from MUD transplant
	ALL	1	1 M	25	No	Flu/TBI	Prospective cohort/case studies with no historical control	MUD, identical	Patients eligible for NM-allo-SCT if older than age 55 (n=4), had concurrent medical conditions (n=0), failed previous autograft (n=4), or had multiple factors (n=3); 2 with RCC excluded from abstraction; MUD or not heavily pretreated patients received TBI/Flu; Flu/Cyused if previously given ≥12 Gy TBI
Baron ²² 2002	ALL	1	1 M	25	No	Flu/TBI	Prospective cohort/case studies with no historical control	MUD, identical	
	AML	1	1 F	57		TBI		HLA-matched sibling	
	CLL	1	1 F	61		TBI		HLA-matched sibling	
	CML	2	1 F, 1 M	60 (58-62)		TBI (n=1) Flu/TBI (n=1)		HLA-matched sibling	
	HD	1	1 M	22		TBI		HLA-matched sibling	

Table Abbreviations

ALL = acute lymphocytic leukemia
 AML = acute myelocytic leukemia
 AraC = cytarabine
 ATG = antithymocyte globulin
 Bu = busulfan
 BW = body weight
 CDA = chloradenosine
 CLL = chronic lymphocytic leukemia
 CMVL = chronic myelogenous leukemia
 CMML = chronic myelomonocytic leukemia
 CMV = cytomegalovirus
 CR = complete remission
 Cy = cyclophosphamide
 d = days
 DBM = dibromomannitol
 DFS = disease-free survival

EMP = extramedullary plasmacytoma
 FLAG = Flu/AraC/G-CSF
 FLAG-Ida = FLAG with Ida
 FLAG-X = FLAG with daunorubicin
 Flu = fludarabine
 GVHD = graft-vs-host disease
 HD = Hodgkin's disease
 Ida = idarubicin
 LCL = large-cell lymphoma
 MDS = myelodysplastic syndrome
 Mel = melphalan
 MM = multiple myeloma
 MUD = matched unrelated donor
 NE = not extractable
 NHL = non-Hodgkin's lymphoma
 NR = not reported

NS = not stated
 OAT/LG = other regimens with ATG or ALG
 PFS = progression-free survival
 PR = partial remission
 PS = performance status
 RAEB = refractory anemia with excess blasts
 RAEB-t = RAEB in transformation
 RCC = renal cell carcinoma
 TBI = total body irradiation
 TI = thymic irradiation
 T-PLL = T-cell prolymphocytic leukemia
 TRM = treatment-related mortality
 WM = Waldenström macroglobulinemia
 yr = year

Appendix 1B — NM-Allo-SCT in Hematologic Malignancies: Benefits

Reference	Disease	Overall Survival at 1-5 Yrs	Disease-Free Survival at 1-5 Yrs	Median or Survival Range	Complete Response	Partial Response	Mixed Chimerism	Full Chimerism	Comments
Giralt ¹⁷ , 1997 (updated 2001 ¹⁵)	AML	30% at 400 d	32% at 400 d	NE	NE	NR	Yes	Yes	2-yr survival for all patients was 28% (95% CI, 20-39); 2-yr disease-free survival for all patients was 23% (95% CI, 15-34)
	MDS	30% at 400 d	32% at 400 d		NE				
	CML	40% at 400 d	40% at 400 d		70% (19/27)				
	HD	20% at 400 d	20% at 400 d		25% (1/4)				
	NHL	20% at 400 d	20% at 400 d		22% (2/9)				
	ALL	20% at 400 d	20% at 400 d		33% (1/3)				
Carella ²⁴ 1998	CML	NE	NE	4 mos (2-10)	50% (1/2)	0% (0/2)	Yes	Yes	No patients required sterile room or red cell/platelet transfusion
	HD			NE	50% (2/4)	25% (1/4)			
	NHL			4 mos (2-10)	50% (1/2)	50% (1/2)			
	MDS			4 mos (2-10)	100% (1/1)	0% (0/1)			
Kelemen ¹¹ 1998	CML	89% at 4 yrs (17/19)	82% at 4 yrs (14/17)	NE	NR	NR	Yes	Yes	Chimerism investigated at 6 mos in 16 patients
	CLL	NE	NE	NE	38% (3/8)	25% (2/8)	Yes	Yes	
Khoury ¹⁶ 1998	NHL/LCL				71% (5/7)	14% (1/7)			50% probability of survival at 1 yr for the whole group based on median follow-up of 180 days (range 90 to 767 days)
Slavin ⁸ 1998	ALL	NE	NE	NE	NR	NR	Yes	Yes	No procedure-related deaths reported: survival for whole group at >1 yr was 85% (22/26); 21% disease free; included patients with nonmalignant hematologic disease
	AML								
	CML								
	NHL								
	MDS								
	MM								
Childs ²² 1999	CML	NE	NE	206 d (106-379)	75% (3/4)	NE	Yes	Yes	
	NHL			220 d	100% (1/1)				
	MDS			226 d (205-248)	0% (0/2)				
	MM			121 d	0% (0/1)				
Garban ²⁶ 1999 (updated 2001 ¹³)	MM	NE	NE	>6->15 mos	33% (4/12)	58% (7/12)	Yes	Yes	
	MM	33% at 1 yr	30% at 1 yr	194 d (0-582)	47% (8/18)	NE	Yes	Yes	
Giralt ¹⁴ 1999	NHL	0% at 1 yr (1/5)	NE	20% (1/5)	20% (1/5)	20% (1/5)	Yes	Yes	

Appendix 1B — NM-Allo-SCT in Hematologic Malignancies: Benefits

Reference	Disease	Overall Survival at 1-5 Yrs	Disease-Free Survival at 1-5 Yrs	Median or Survival Range	Complete Response	Partial Response	Mixed Chimerism	Full Chimerism	Comments
Bornhauser ²⁹ 2000	ALL	NE	NE	NE	100% (1/1)	0% (0/1)	Yes	Yes	100-day survival was 95% for the whole group
	AML				80% (8/10)	NE			
	CLL				67% (2/3)	33% (1/3)			
	CML				100% (4/4)	0% (0/4)			
	HD				NE	50% (1/2)			
	NHL				NE	NE			
Gomez-Almaguer ²⁵ (updated Ruiz-Arguelles, 2001 ³⁷)	AML	NE	NE	60-360 d (4/6 alive)	60% (4/6)	NR	Yes	Yes	Median survival for all patients was 249 days; 1 graft failure reported
	MDS			90 d (1 died)	NR				
	CML			60-360 d (4/8 alive)	50% (4/8)				
	ALL			30-300 d (5/10 alive)	50% (5/10)				
	AML			2 ->15 mos	64% (7/11)	0% (0/11)	Yes	Yes	
	CML			6 ->12 mos	56% (5/9)	0% (0/9)			
McSweeney ⁷ 1999 (updated 2001 ⁵)	CLL			4 ->12 mos	38% (3/8)	38% (3/8)			Median follow-up for whole group was 417 days (320-769 days); overall survival for all patients was 67% (30/45); 20% (9/44) rejected graft between 2 and 4 mos; no fatal rejections; overall TRM was 7% (3/45); relapse-related mortality was 27%; full chimerism in 21 patients by day 56
	NHL			2 mos (died)	100% (1/1)	NA			
	HD			4 ->10 mos	50% (2/4)	0% (0/4)			
	ALL			11 mos	100% (1/1)	NA			
	MM			2 ->24 mos	50% (4/8)	38% (3/8)			
	MDS			6 mos (died)	0% (0/1)	0% (0/1)			
	WM			11 ->12 mos	0% (0/2)	0% (0/2)			
	NHL	NE	NE	NE	NE	NE	Yes	Yes	
	HD								
	ALL	NE	NE	NE	0% (0/1)	0% (0/1)	Yes	Yes	
	Spitzer ²⁷ 2000	AML				33% (1/3)	33% (1/3)		
HD					50% (2/4)	25% (1/4)			
NHL					36% (4/11)	27% (3/11)			
CLL					50% (1/2)	50% (1/2)			
Elmagaci ¹⁸ 2001	ALL	NE	NE	NE	NE	NE	Yes	Yes	Survival/DFS/CR/PR not reported by disease: Survival at 1 and 2 yrs in the group receiving reduced conditioning regimen compared to conventional BMT was 77% and 74%, respectively
	AML								
	CML								

Appendix 1B — NM-Allo-SCT in Hematologic Malignancies: Benefits

Reference	Disease	Overall Survival at 1-5 Yrs	Disease-Free Survival at 1-5 Yrs	Median or Survival Range	Complete Response	Partial Response	Mixed Chimerism	Full Chimerism	Comments
Lee ³⁰ 2001	NHL	NR	NR	NR	33% (2/6)	0% (0/6)	Yes	No	Survival not reported according to disease group
	HD				0% (0/1)	100% (1/1)			
Michallet ²⁰ 2001	ALL	NE	NR	NE	36% (9/25)	16% (4/25)	Yes	Yes	Survival not reported by disease; overall survival was 38% at 1 yr and 31% at 2 yrs
	MDS				22% (2/9)	11% (1/9)			
	NHL				8% (1/13)	85% (11/13)			
	MM				0% (0/11)	54% (6/11)			
	HD				42% (5/12)	0% (0/12)			
	CLL				0% (0/3)	33% (1/3)			
	CML				0% (0/3)	67% (2/3)			
Mohy ²¹ 2001	NHL	NR	NR	NR	33% (1/3)	33% (1/3)	Yes	Yes	
	HD				100% (1/1)	0% (0/1)			
	CLL				0% (0/1)	0% (0/1)			
	MM				33% (2/6)	0% (0/6)			
Chakraverty ³³ 2002	MM	NE	NE	NE	0% (0/12)	45% (5/12)	Yes	Yes	Survival or DFS not reported by disease; at 1 yr, overall was 76% and PFS was 62%
	NHL				47% (7/15)	7% (1/15)			
	CML				100% (5/5)	0% (0/5)			
	AML				67% (4/6)	0% (0/6)			
	ALL				50% (1/2)	0% (0/2)			
	HD				40% (2/5)	0% (0/5)			
	CLL (T-PLL)				0% (0/1)	0% (0/1)			
	CMMML				100% (1/1)	0% (0/1)			
Corradini ¹⁹ 2002	AML	NE	NE	NE	60% (3/5)	0% (0/5)	Yes	Yes	Survival not reported by disease; overall survival at 2 yrs was 63%; progression-free survival at 20 mos was 57%
	MDS				83% (5/6)	0% (0/6)			
	ALL				100% (1/1)	0% (0/1)			
	NHL				67% (16/24)	25% (6/24)			
	HD				25% (1/4)	0% (0/4)			
	MM				20% (1/5)	60% (3/5)			
Schlenk ³⁴ 2002	AML	NR	NR	NR	67% (6/9)	0% (0/9)	Yes	No	Survival not reported by disease; overall survival at 22 mos was 44%
	ALL				100% (1/1)	0% (0/1)			
	CML				0% (0/1)	0% (0/1)			

Appendix 1B — NM-Allo-SCT in Hematologic Malignancies: Benefits

Reference	Disease	Overall Survival at 1-5 Yrs	Disease-Free Survival at 1-5 Yrs	Median or Survival Range	Complete Response	Partial Response	Mixed Chimerism	Full Chimerism	Comments
Nagler ²¹ 2001	CML	NE	NE	NE	0% (0/7)	14% (1/7)	Yes	Yes	Survival/DFS not reported by disease; actuarial survival and DFS at 36 mos were 75% and 60% respectively; alive and continuously disease-free were considered CR in this analysis; alive and well were considered PR
	AML				25% (1/4)	50% (2/4)			
	ALL				25% (1/4)	50% (2/4)			
	NHL				0% (0/1)	100% (1/1)			
	AML				25% (1/4)	50% (2/4)			
Pawson ¹⁸ 2001	AML	NE	NE	NE	86% (6/7)	14% (1/7)	Yes	Yes	Survival and DFS not reported by disease; overall survival was 75% at 1 yr and 62% at 2, 3, 4, and 5 yrs; DFS was 63% at 1 yr, 38% at 2 yrs, and 26% at 3, 4, and 5 yrs
	ALL				100% (5/5)	0% (0/5)			
		MDS (RAEB-t)				100% (2/2)	0% (0/2)		
Badros ¹⁰ 2002	MM	1 yr: 68% 2 yrs: 30%	NR	NE	61% (19/31)	10% (3/31)	Yes	Yes	Median survival was 15 mos; projected actuarial survival at 1 yr was 71% and 31% at 2 yrs; survival at 1 yr posttransplant was 71% for mini allograft compared to 45% for historical controls with conventional allo-SCT
Baron ²² 2002	NHL	NE	NE	NE	100% (5/5)	0% (0/5)	Yes	Yes	Survival not reported by disease; overall survival at 1 yr was 69%
	CML				50% (1/2)	0% (0/2)			
	CLL				0% (0/1)	100% (1/1)			
	AML				100% (1/1)	0% (0/1)			
	ALL				100% (1/1)	0% (0/1)			

Appendix 1C — NM-Allo-SCT in Hematologic Malignancies: Harms

Reference	Disease	Transplant-Related Mortality	Acute GVHD	Chronic GVHD	Veno-Occlusive Disease	Relapse	Other Toxicity (Grade III-IV) and Comments
Giralt ¹⁷ 1997 (updated 2001 ¹⁵)	AML	43% (16/43)	49% (95% CI 38-60)	68% ± 9% (21/46)	NR	27% (23/86)	Nonrelapse mortality at 2 yrs was ~45%
	MDS		60% (34/76)	NE		NE	
	CML	25% (7/27)	NE				
	HD	75% (3/4)					
	NHL	78% (7/9)					
	ALL	67% (2/3)					
Carella ⁴ 1998	CML	0% (0/2)	50% (1/2)	NR	NR	NR	No severe procedure-related toxicity
	HD	25% (1/4)	50% (2/4)				
	NHL	0% (0/2)	0% (0/2)				
	MDS (RAEB)	0% (0/1)	0% (0/1)				
Kelemen ¹¹ 1998	CML	11% (2/19)	11% (2/18)	67% (12/18)	0% (0/18)	33% (6/18)	6% (1/18); not explicitly stated but estimated from Table 1 and comments in the text
Khouril ¹⁶ 1998	CLL	38% (3/8)	NE	13% (1/8)	NR	NE	Toxicity NE; acute GVHD occurred after initial transplantation in 5 patients; not specified according to disease
	NHL	43% (3/7)	14% (1/7)				
Slavin ⁸ 1998	ALL	0% (0/2)	NE	50% (1/2)	NE	50% (1/2)	Differences noted in reporting on GVHD between text and Table 3; data extracted from Table 3
	AML	25% (2/8)	38% (3/8)	13% (1/8)		13% (1/8)	
	CML	25% (2/8)	50% (4/8)	13% (1/8)		0% (0/8)	
	NHL	0% (0/2)	NE	50% (1/2)		0% (0/2)	
	MDS	0% (0/1)	NE	NS		0% (0/1)	
	MM	0% (0/1)	NE	NS		0% (0/1)	
Childs ²² 1999	CML	NE	50% (2/4)	25% (1/4)	0% (0/4)	0% (0/4)	2 patients died of transplant-related causes (1 had melanoma)
	NHL		100% (1/1)	0% (0/1)	0% (0/1)	0% (0/1)	
	MDS		50% (1/2)	0% (1/2)	50% (1/2)	0% (0/2)	
	MM		0% (0/1)	0% (0/1)	0% (0/1)	100% (1/1)	
Garban ²⁶ 1999 (updated 2001 ¹³)	MM	17% (2/12)	50% (6/12)	58% (7/12) (2 extensive)	NR	8% (1/12)	5 of 11 patients developed CMV infection (1 died of CMV encephalitis)
Giralt ¹⁴ 1999	MM	47% (8/17)	52% (9/17)	18% (3/17)	NR	NR	
Sykes ¹² 1999	NHL	40% (2/5)	100% (5/5)	0% (1/5)	NR	20% (1/5)	

Appendix 1C — NM-Allo-SCT in Hematologic Malignancies: Harms

Reference	Disease	Transplant-Related Mortality	Acute GVHD	Chronic GVHD	Veno-Occlusive Disease	Relapse	Other Toxicity (Grade III-IV) and Comments
Bornhauser ²⁹ 2000	ALL	NE	100% (1/1)	0% (0/1)	NE	NE	100% (1/1)
	AML	10% (1/10)	40% (4/10)	50% (5/10)		30% (3/10)	10% (1/10)
	CLL	NE	67% (2/3)	33% (1/3)		0% (0/3)	33% (1/3)
	CML		75% (3/4)	25% (1/4)		50% (2/4)	0% (0/4)
	HD		50% (1/2)	0% (0/2)		100% (2/2)	50% (1/2)
	NHL		100% (1/1)	0% (0/1)		NE	0% (0/1)
Gomez-Almaguer ²⁶ 2000 (updated Ruiz-Arguelles, 2001 ³⁷)	ALL	NE	30% (3/10)	29% (2/7)	NE	60% (3/5)	TRM was 12% (3/25) for all patients; each died of acute GVHD
	AML		0% (0/6)	0% (0/5)		50% (2/4)	
	CML		62% (5/8)	63% (5/8)		75% (3/4)	
	MDS		100% (1/1)	100% (1/1)		0% (0/1)	
	AML	0% (0/11)	36% (4/11)	45% (5/11)		% (1/11)	Toxicity was mild: none experienced mucositis, severe nausea and vomiting, pulmonary toxicity, cardiac toxicity, hemorrhagic cystitis, or new-onset alopecia; 3 of 45 patients (7%) died
	CML	0% (0/9)	67% (6/9)	44% (4/9)	NR	0% (0/9)	
McSweeney ⁷ 2000 (updated 2001 ⁵)	CLL	13% (1/8)	63% (5/8)	75% (6/8)		0% (0/8)	
	NHL	100% (1/1)	100% (1/1)	NR		0% (0/1)	
	ALL	0% (0/1)	100% (1/1)	0% (0/1)		0% (0/1)	
	MM	13% (1/8)	50% (4/8)	17% (1/6)		13% (1/8)	
	HD	0% (0/4)	75% (3/4)	50% (2/4)		0% (0/4)	
	MDS	0% (0/1)	0% (0/1)	NR		0% (0/1)	
	WM	0% (0/2)	50% (1/2)	100% (2/2) 1 extensive		0% (0/2) stable disease	
	NHL	NE	NE	NE	0% (0/19)	NE	7 patients died (4 of grade III-IV GVHD and severe infections, 2 of bacterial sepsis, 1 of pulmonary failure)
	HD				0% (0/4)		NE
	Spitzer ³⁷ 2000	ALL	0% (0/1)	0% (0/1)	NE	NE	NE
AML		33% (1/3)	67% (2/3)				
CLL		0% (0/2)	100% (2/2)				
HD		0% (0/4)	100% (4/4)				
Elmaagacli ⁹ 2001	NHL	9% (1/11)	36% (4/11)	9% (1/11)			
	ALL	NE	NE	NE	NE	NE	NE
	AML						
	CML						

Appendix 1C — NM-Allo-SCT in Hematologic Malignancies: Harms

Reference	Disease	Transplant-Related Mortality	Acute GVHD	Chronic GVHD	Veno-Occlusive Disease	Relapse	Other Toxicity (Grade III-IV) and Comments
Lee ³⁰ 2001	NHL	100% (6/6)	50% (3/6)	17% (1/6)	NR	NE	NR
	HD	100% (1/1)	100% (1/1)	100% (1/1)			
Michallet ²⁰ 2001	ALL	96% (24/25)	24% (6/25)	24% (6/25)	NR	16% (4/25)	NE
	MDS	44% (4/9)	44% (4/9)	22% (2/9)		11% (1/9)	
	NHL	54% (7/13)	62% (8/13)	8% (1/13)		0% (0/13)	
	MM	55% (6/11)	72% (8/11)	27% (3/11)		37% (4/11)	
	HD	17% (2/12)	42% (5/12)	42% (5/12)		0% (0/12)	
	CLL	67% (2/3)	67% (2/3)	0% (0/3)		0% (0/3)	
	CML	0% (0/3)	33% (1/3)	33% (1/3)		0% (0/3)	
	NHL	67% (2/3)	0% (0/3)	NR	0% (0/3)	NR	All patients survived beyond day 30 and maintained good oral intake throughout the procedure
Morty ³¹ 2001	HD	100% (1/1)	100% (1/1)		0% (0/1)		
	CLL	100% (1/1)	100% (1/1)		0% (0/1)		
Chakraverty ³³ 2002	MM	33% (2/6)	100% (6/6)		0% (0/6)		
	MM	17% (2/12)	50% (6/12)	0% (0/12)	0% (0/12)	8% (1/12)	NR
	NHL	47% (6/15)	27% (4/15)	0% (0/15)	0% (0/15)	0% (0/15)	
	CML	0% (0/5)	60% (3/5)	20% (1/5)	0% (0/5)	0% (0/5)	
	AML	17% (1/6)	33% (2/6)	17% (1/6)	0% (0/6)	17% (1/6)	
	ALL	50% (1/2)	0% (0/2)	0% (0/2)	0% (0/2)	0% (0/2)	
	HD	20% (1/5)	40% (2/5)	20% (1/5)	0% (0/5)	20% (1/5)	
	T-PLL (CLL)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	100% (1/1)	
Corradini ¹⁹ 2002	CMMML	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	NR
	AML	NE	40% (2/5)	40% (2/5)	NR	NE	
Schlenk ²⁴ 2002	MDS		83% (5/6)	17% (1/6)			
	ALL		100% (1/1)	0% (0/1)			
	NHL		75% (18/24)	42% (10/24)			
	HD		50% (2/4)	75% (3/4)			
	MM		80% (4/5)	40% (2/5)			
Schlenk ²⁴ 2002	AML	4% (4/9)	22% (2/9)	0% (0/9)	NR	44% (4/9)	11% (1/9)
	ALL	0% (0/1)	0% (0/1)	0% (0/1)		100% (1/1)	0% (0/1)
	CML	100% (1/1)	100% (1/1)	100% (1/1)		100% (1/1)	0% (0/1)

Appendix 1C — NM-Allo-SCT in Hematologic Malignancies: Harms

Reference	Disease	Transplant-Related Mortality	Acute GVHD	Chronic GVHD	Veno-Occlusive Disease	Relapse	Other Toxicity (Grade III-IV) and Comments
Nagler ²¹ 2001	CML	67% (2/7)	86% (6/7)	0% (0/7)	NR	0% (0/7)	14% (1/7)
	AML	25% (1/4)	100% (4/4)	0% (0/4)		25% (1/4)	25% (1/4)
	ALL	25% (1/4)	100% (4/4)	0% (0/4)		50% (2/4)	0% (0/4)
	NHL	0% (0/1)	100% (1/1)	0% (0/1)		0% (0/1)	0% (0/1)
Pawson ¹⁸ 2001	AML	NE	29% (2/7)	0% (0/7)	NR	NE	Relapse not reported by disease but 10 of 14 patients relapsed
	ALL		60% (3/5)	60% (3/5)			
	MDS (RAEB-t)		50% (1/2)	50% (1/2)			
Badros ¹⁰ 2002	MM	10% (3/31)	58% (18/31)	32% (10/31)	0% (0/31)	0% (0/31)	TRM in mini-allograft group was 10% (3/31) vs 29% (27/93) in standard allo-SCT group
Baron ³² 2002	NHL	20% (1/5)	60% (3/5)	80% (4/5)	NR	NR	NR
	CML	50% (1/2)	0% (0/2)	0% (0/2)			
	CLL	100% (1/1)	100% (1/1)	0% (0/1)			
	AML	0% (0/1)	0% (0/1)	00% (1/1)			
	ALL	100% (1/1)	0% (0/1)	0% (0/1)			

Appendix 2 — Overview of Published Evidence in Hematologic Malignancies According to Specific Diseases: Indications for Nonmyeloablative Allogeneic Transplant, HLA Status, and Engraftment Outcomes

Author	Comorbid Condition	Reasons for Consideration of NM-allo-SCT vs Standard	HLA	MUD	Graft Failure	Comments
Giralt ¹⁷ 1997 (update 2001 ¹⁵)	Concurrent medical conditions were also eligible	Patients considered poor candidates for conventional allotransplant because of age (>50 yrs) or concurrent medical conditions	HLA-compatible siblings 6/6 (n=39); one-antigen-mismatched siblings 5/6 (n=7)	n=40 (6/6)	n=1 (autologous reconstitution)	All 17 patients who entered remission had 100% donor cells at 1 yr
Carella ²⁴ 1998	NS (no general contraindication to stem cells transplantation)	First- and second-line therapy without success (HD=4; NHL=2); CML in accelerated phase (n=1); CML in myeloblastic transformation with 70% marrow blasts (n=1); refractory anemia with excess blasts (n=1)	HLA-matched siblings (n=9)	n=0	n=0	Evidence of 100% donor cell engraftment in 6 patients
Kelemen ¹¹ 1998	NS	NS	HLA-identical siblings (n=19)	n=0	n=0	
Khouri ¹⁶ 1998	Patients were eligible if >50 yrs or had other medical problems that would preclude the administration of high dose; elevated ALT secondary to alcohol-induced liver toxicity (n=2); history of active hepatitis C (n=1); performance status of 3 (n=4)	Patients ineligible for high-dose ablative preoperative regimens due to age >50 yrs (n=13) or comorbidities	HLA-identical siblings (n=15)	n=0	n=0	
Slavin ⁸ 1998	NS	26 patients with standard indications for allogeneic BMT; NS	HLA-matched related donors (n=22)	n=0	n=0	
Childs ²² 1999	NS	Eligibility criteria for hematologic malignancies included disease with a probability of slow progression or in remission in patients >85 yrs	HLA-identical siblings (n=8)	n=0	n=0	One patient rejected transplant with subsequent recovery of autologous hematopoiesis
Garban ²⁶ 1999 (update 2001 ¹³)	NS	Poor candidates to conventional allogeneic transplantation with high-risk or relapsing myeloma patients	HLA-identical siblings (n=12)	n=0	n=0	
Giralt ¹⁴ 1999	NS	Patients having failed prior auto SCT (n=7)	HLA-identical siblings (n=13)	n=5	n=0	8 patients were <30 yrs of age
Sykes ¹² 1999	Eligibility criteria: chemotherapy-refractory NHL, performance status 2 or less, age 65 yrs or younger, and adequate organ function	Chemotherapy-refractory NHL performance status 2 or less; age 65 yrs or less, and adequate organ function	Haploidentical-related donor sharing at least 1 HLA A, B, or D allele on the mismatch haplotype	n=0	n=0	
Bornhauser ²⁹ 2000	NS according to patients and disease	Patients with reduced performance status or major infectious complications not eligible for standard transplant procedure	HLA-matched siblings (n=21)	n=0	n=0	
Gomez-Almaguer ²⁵ 2000 (update Ruiz-Arguelles 2001 ¹⁷)	NS	NS	HLA-identical siblings in all instances 6/6 (n=25)	n=0	n=1	Full chimerism (defined as more than 90% of donor cells on day 30 and afterwards) was seen in 17 patients, outpatients n=21
McSweeney 1999 ⁷ (update 2001 ³)	Preexisting liver cirrhosis (n=1), coronary artery disease, pulmonary aspergillosis, number of patients not specified	Patients ineligible for conventional HCT because of age or medical contraindications CLL and lymphomas had failed at least front-line therapy (n=NS); resistant acute leukemia (n=3); preexisting liver cirrhosis (n=1) aspergillosis (n=1)	HLA-identical siblings in all instances 6/6 (n=45)	n=0	n=9	53% of eligible patients had entirely outpatient transplants; 9 patients subsequently rejected their grafts (between 2-4 mos); none of these patients died

Appendix 2 — Overview of Published Evidence in Hematologic Malignancies According to Specific Diseases: Indications for Nonmyeloablative Allogeneic Transplant, HLA Status, and Engraftment Outcomes

Author	Comorbid Condition	Reasons for Consideration of NM-allo-SCT vs Standard	HLA	MUD	Graft Failure	Comments
Nagler ²⁸ 2000	NS	All patients were very high risk and heavily treated; of the 23 patients, 12 had resistant disease (primary refractory or resistant relapse) and 11 were in third partial relapse at treatment	HLA-matched siblings (n=22)	n=1	n=0	
Spitzer ²⁷ 2000	NS	Chemotherapy-refractory hematologic malignancies	HLA genotypic ally (n=20) or phenotypic ally (n=1) matched-donor transplant	n=0	n=0	
Elmaagacli ⁹ 2001	NS	To assess the efficacy of NM-allo-SCT vs BMT	HLA sibling (n=7); HLA partially matched family (n=2)	n=0	n=0	
Lee ³⁰ 2001	NS according to patients and disease	To investigate the effectiveness of nonmyeloablative stem-cell transplantation for patients with heavily pretreated refractory lymphoma	NR	NR	NE	HLA type not reported in this study
Michelle ²⁰ 2001	NS according to treatment and disease	To assess the impact of pre- and post-transplantation factors on the outcome after nonmyeloablative preparative regimens	HLA-identical sibling (n=78)	n=0	NR	
Moh ²¹ 2001	NS	NS	HLA-identical sibling (n=11)	n=0	n=0	
Chakraborty ²³ 2002	NS	To investigate the effectiveness of reduced-intensity conditioning regimen in patients undergoing transplant from matched unrelated donor	n=0	n=47	NE	
Corradini ¹⁹ 2002	NS according to disease	To investigate the effectiveness of reduced-intensity conditioning regimen in patients considered as poor candidates for conventional myeloablative regimens	HLA-identical (n=42) or single HLA locus-mismatched (n=3) siblings	n=0	NE	
Schlenk ²⁴ 2002	NS according to patients and disease	Assess toxicity and feasibility of achieving engraftment of allogeneic blood progenitor cells following nonmyeloablative conditioning	HLA-identical sibling (n=11)	n=0	NR	
Nagler ²¹ 2001	NS	To investigate the feasibility of low intensity conditioning for BMT from matched unrelated donors	n=0	n=16	n=0	
Pawson ¹⁸ 2001	NS	To test the use of reduced intensity conditioning regimens to lessen transplant-related morbidity and mortality	Full HLA match (n=13); one-antigen-mismatch (n=1)	n=0	n=0	
Badros ¹⁰ 2002	NS	To investigate the feasibility of low-intensity melphalan-based conditioning regimen	HLA-identical siblings (n=25)	n=6	n=0	
Baron ³² 2002	NS	Patients were not eligible for standard SCT	HLA siblings (n=7); HLA sibling one-mismatch (n=2)	n=2	NR	

Appendix 3 — Conditioning Regimens Used in Studies of Nonmyeloablative Allo-SCT

Study	Conditioning Regimen Doses										Comments
	Flu	Bu	CY	ATG	TBI	Ti	Mel	Other			
Giralt ¹⁷ 1997	30 mg/m ² IV × 4 days							Either Ara-C 2 g/m ² or 12 mg/m ² × 3 days (IV)	1 patient received melphalan 140 mg/m ² once at the end of chemotherapy. 2/15 had grade III/IV toxicity		
	30 mg/m ² IV × 4 days							Ara-C 1 g/m ² × 5 days and 2-CDA 12 mg/m ² (IV)	7 patients		
Carella ²⁴ 1998	30 mg/m ² × 3 days		300 mg/m ² × 3 days						No procedure-related deaths		
Kelemen ¹¹ 1998			150 mg/kg IV on days -4, -3, -2					DBM 120 mg/kg p.o. × 3 days, Ara-C IV 60 mg/kg × 3 days	Remarkable reduction in certain transplant-related complication		
Khouri ¹⁶ 1998	30 mg/m ² IV × 3 days		300 mg/m ² IV × 3 days						5 CLL patients		
	30 mg/m ² IV × 5 days		1000 mg/m ² IV × 2 days						4 patients		
	30 mg/m ² IV × 2 days							Cisplatin 25 mg/m ² IV × 2 days, cytarabine 500 mg/m ² × 2 days	4 patients with Richter's syndrome		
Slavin ⁸ 1998	30 mg/m ² IV × 6 days	Oral 4 mg/kg × 2 days		10 mg/kg × 4 days					No procedure-related deaths reported		
Childs ²² 1999	25 mg/m ² IV × 5 days		60 mg/kg IV × 2 days								
Garban ²⁶ 1999 abstract	25 mg/m ² × 5 days	2 mg/kg × 2 days		2.5 mg/kg × 5 days					Well-tolerated protocol, no mucositis; duration of aplasia < 7 days		
Giralt ¹⁴ abstract 1999						140 or 180			Flu/mel 140 or 180 was well tolerated with only 1 toxic death from tumor lysis and multiorgan failure		
Sykes ¹² 1999			50 mg/kg	30 mg/kg		7 Gy on day -1			TRM was 12.5%		
Bornhauser ²³ 2000	30 mg/m ² IV × 5 days	3.3 mg/kg IV × 3 days									
Gomez-Almaguer ²⁵ 2000 (update Ruiz-Arguelles 2001 ¹⁷)	30 mg/m ² IV × 3 days	Oral 4 mg/kg × 2 days	350 mg/m ² IV × 3 days						Showed that allogeneic stem cell transplantation can be performed safely on outpatient basis		
McSweeney 2000 ⁷ (update 2001 ⁵)					Low-dose TBI 2 Gy single fractional day -4				Toxicity was mild, no mucositis, and no nausea; almost no myelosuppression noted		
Nagler ²⁸ 2000	Low-intensity regimen								7 patients died (4 of grade III-IV GVHD and severe infections, 2 of bacterial sepsis, 1 pulmonary failure)		
Spitzer ²⁷ 2000			50 mg/kg IV on day -6 or -5 through -3	30 mg/kg × 2 days		7 Gy on day -1					

Appendix 3 — Conditioning Regimens Used in Studies of Nonmyeloablative Allo-SCT

Study	Conditioning Regimen Doses										Comments			
	Flu	Bu	CY	ATG	TBI	TI	Mel	Other						
Elmaagacli ⁹ 2001	30 mg/m ² IV × 4 days	1 mg/kg BW p.o. every 6 hrs over 2 days		10 mg/kg BW for 4 days										
Lee ³⁰ 2001	30 mg/m ² /d IV on days -7 to -2	4 mg/kg/d p.o. on days -7 and -6		20 mg/kg/d IV on days -5 to -2								Methylprednisolone 2 mg/kg/d IV on days -5 to -2		
Michallet ²⁰ 2001	Dose varying from 25-30 mg/m ² /d for 5 or 6 days	2 to 4 mg/kg/d for 2 days		2.5 mg/kg/d for 3, 4 or 5 days	ALG 5 mg/kg/d for 4 or 5 days combined with TBI in 5 patients							Ida 21 mg/m ² /d for 2 days, cytarabine 2 g/m ² /d for 4 days	3 different types of conditioning regimens were considered: FBI v IFA v ATG/ALG or regimens containing or not containing ATG/ALG; with ATG/ALG (FBI + ATG/ALG) and without ATG/ALG (IFA)	
Mohty ³¹ 2001	25 mg/m ² IV × 5 days	2 mg/kg BW p.o. over 2 days		2.5 mg/kg/d IV for 4 days									ATG was administered to 3 patients only (NHL, HD, and CLL)	
Chakraverty ³³ 2002	30 mg/m ² /d IV on days -7 and -3								140 mg/m ² IV 30 min on day -2			CAMPATH-1H 20 mg/d IV on days -8 to -4		
Corradini ¹⁹ 2002	30 mg/m ² /d IV on days -4 and -3, 4 hrs after cyclophosphamide administration		30 mg/kg days on -4 and -3									Thiotepa 15 or 10 mg/kg (38 patients); thiotepa 5 mg/kg (7 patients)	Conditioning regimen was generally well tolerated in terms of mucosal or organ toxicity	
Schlenk ²⁴ 2002	25 mg/m ² /d on days -7 to -3		200 mg/m ² /d on days -7 to -3									Ida 12 mg/m ² /d on days -7 to -5; etoposide 250 mg/m ² /d on days -4 to -3	1/11 patients developed grade IV mucositis; 3/11 developed fever >38.5°C	
Nagle ²¹ 2001	30 mg/m ² /d IV for 6 days from day 10 to 5	4 mg/kg/d orally for 2 days on days 6 and 5		10 mg/kg/d IV for 4 days from day 4 to 1										Low median age of the patients (17.5 yrs) might have contributed to low toxicity
Pawson ¹⁸ 2001														Dose for the FLAG regimen not reported; 10 patients received FLAG-Ida, 2 FLAG, and 2 FLAG + liposomal daunorubicin 80 mg/m ² /d on days 1-3
Badros ¹⁰ 2002	30 mg/m ² /d IV on days -2 and -1				2.5 Gy in 2 fractions on day -2									Flu and TBI were used only in MUD cases