Current Roles for Allogeneic Hematopoietic Cell Transplantation Following Nonmyeloablative or Reduced-Intensity Conditioning

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Abstract: Nonmyeloablative and reduced-intensity conditioning regimens followed by allogeneic hematopoietic cell transplantation (HCT) have been evaluated in patients with hematologic malignancies who were not considered candidates for conventional HCT because of age or medical comorbidities and in selected patients with metastatic renal cell carcinoma. The regimens have relied more on graft-versus-tumor effects than on chemoradiation therapy to facilitate engraftment and eradicate malignant cells. While nonmyeloablative HCT has been associated with reduced regimen-related toxicities and has been curative for a number of patients with hematologic malignancies, challenges have remained in regard to graft-versus-host disease, infections, and disease progression. In this article, we review data from a number of published phase I and II studies that describe the results of allogeneic HCT after nonmyeloablative conditioning.

Keywords
Hematopoietic cell transplantation, nonmyeloablative conditioning, lymphoma, leukemia, graft-versus-tumor effects.

Allogeneic hematopoietic cell transplantation (HCT) after a high-dose myeloablative conditioning regimen has been an effective treatment for many patients with hematologic malignancies.[1] Due to regimen-related toxicities, however, the use of ablative regimens has been restricted to younger and medically fit patients. This is unfortunate because the median age at diagnosis of patients with hematologic malignancies such as acute and chronic leukemias, lymphomas, myelodysplastic syndromes (MDS), and multiple myeloma (MM) ranges from 65 to 70 years.[2] It has been recognized for some time, however, that the curative potential of allogeneic HCT can be ascribed not only to the eradication of malignant cells by high-dose chemotherapy and total body irradiation (TBI) but also to immune-mediated graft-versus-tumor effects.[3-5] These observations led several investigators to explore the curative potential of donor lymphocyte infusions (DLI) in patients with hematologic malignancies who had relapsed after allogeneic HCT.[6-8] The induction of durable complete remissions by DLI in a number of patients demonstrated that graft-versus-tumor effects were capable of eradicating hematologic malignancies, even in the absence of chemotherapy.

In an attempt to extend the use of allogeneic HCT to include older patients and those with comorbid conditions, several groups of investigators have developed reduced-intensity[9-12] or truly nonmyeloablative conditioning regimens,[13-15] in which the burden of tumor eradication is shifted from high-dose chemoradiation therapy toward graft-versus-tumor effects.

Most of the reduced-intensity conditioning regimens do not meet the criteria of nonmyeloablative conditioning, which include: 1) no eradication of host hematopoiesis, 2) prompt hematologic recovery (<4 weeks) without HCT, and 3) presence of mixed chimerism (ie, coexistence of hematopoietic cells of host and donor origin) upon engraftment. Reduced intensity conditioning regimens have been aimed at both eliminating host-versus-graft reactions (graft rejections) and producing major antitumor effects. Conversely, nonmyeloablative conditioning regimens have relied on optimization of pre- and posttransplant immunosuppression to overcome host-versus-graft reactions, thereby allowing engraftment,[16,17] while eradication of tumors has depended nearly exclusively on the graft-versus-tumor effects.[18] A number of currently used reduced-intensity or truly nonmyeloablative conditioning regimens are shown in Table 1.

Both reduced-intensity and nonmyeloablative regimens are relatively well tolerated.[9-15] Two recent studies compared transplant-related toxicities after ablative and nonablative conditioning and found that even though nonablative recipients were older, more often had advanced disease, had more extensive prior therapies including failed ablative HCT, and had higher comorbidities at HCT, they experienced significantly less grade III–IV toxicities after HCT compared to concurrent patients given myeloablative conditioning.[19,20] In addition, multivariate analyses adjusting for pretransplant factors showed that the rate of 1-year nonrelapse mortality was lower in nonablative than in ablative recipients.

Graft-Versus-Host Disease and Graft-Versus-Tumor Effects after Nonmyeloablative Conditioning

Acute graft-versus-host-disease (GVHD), while less frequent than in conventionally transplanted patients,[25,26] has remained a significant complication of HCT following nonmyeloablative conditioning, and has been associated with nonrelapse mortality.[25-27] Some reduced-intensity conditioning regimens have used in vivo T-cell depletion of the grafts (with either antithymocyte globulin [ATG] or alemtuzumab [Campath, Berlex]) in order to decrease the incidence of acute and chronic GVHD. While these strategies achieved their goal, increased incidences of infection and disease relapse were observed.[28]

The biology of graft-versus-tumor effects remains poorly defined but is thought to involve reactions to polymorphic minor histocompatibility antigens expressed either specifically on hematopoietic cells or more widely on a number of tissue cells.[29] Several studies have demonstrated close relationships between GVHD and graft-versus-tumor responses after ablative HCT,[3-5,7,8,30] although achievement of complete remissions without GVHD has been observed in some patients given DLI as treatment of leukemic relapse after HCT.[7,8,31] Thus, even though graft-versus-tumor reactions were thought to be obligatory for eradication of underlying malignancies after nonmyeloablative conditioning, it seems that clinical manifestations of GVHD are not universally required for accomplishing remissions.

In order to address this question, we analyzed data from 322 patients given grafts from human leukocyte antigen (HLA)-matched related (n=192) or unrelated (n=130) donors after conditioning with 2 Gy TBI with or without fludarabine as well as postgrafting immunosuppression with mycophenolate mofetil (MMF) and cyclosporine (CSP).[18] Multivariate time dependent–regression Cox models were used to assess the impacts of either acute or chronic GVHD on HCT outcomes. Two hundred twenty-one patients had measurable malignant disease before HCT, and 98 of them achieved complete remission 27–963 days after HCT. Acute GVHD of any grade was not associated with an increased probability of achieving a complete remission, while extensive chronic GVHD was suggestively associated with a higher probability of achieving complete remission (P=.07). Grades II and III–IV acute GVHD had no significant impact on relapse/progression, but were associated with an increased risk of nonrelapse mortality, which resulted in decreased progression-free survival. In contrast, extensive chronic GVHD was associated with a decreased risk of relapse/progression (P=.006) and better progression-free survival (P=.003).

Results in Specific Diseases

Acute Myeloid Leukemia and Myelodysplastic Syndrome

The prognosis for acute myeloid leukemia (AML) in patients older than 55 years of age is known to be poor, with 2-year probabilities of overall survival of 18% and 13% for patients 56–64 years old and 65 and older, respectively.[32] This finding has led several groups of investigators to study the efficacy of nonmyeloablative HCT as treatment for AML in patients older than 55–60 years of age[12,33-36] (Figure 1).

Sayer and colleagues reported on data from 113 patients with AML who received HCT after various nonmyeloablative or reduced-intensity conditioning

Table 1. Examples of Reduced-Intensity or Nonmyeloablative Conditioning Regimens

Study Location	Preparative Regimens	Postgraft immuno-suppression	N (median age, yr)	Diseases/ Donors	GVHD		NRM*	Outcome
					Acute (grades II–IV)	Chron.		
Reduced-Intensity Regimens								
M. D. Anderson Cancer Center[21]	F, 25 mg/m^2/d (or Cl 12 mg/m^2) × 5 d M, 140–180 mg/m^2	FK506 + MTX	86 (52)	Hematologic malignancies/ MRD and URD	49%	68%	37% (at 100 days)	2-year OS: 28%; 2-year DFS: 23%
United Kingdom[22]	F, 30 mg/m^2/d × 5 d M, 140 mg/m^2 A, 20 mg/d × 5 d	CSP	88 (48)	Non-Hodgkin lymphoma/ MRD and URD	15%†	7%†	11‡–38%§ at 3 years	3-year OS: 55%
Jerusalem[23]	F, 30 mg/m^2/d × 6 d B (po), 4 mg/kg/d × 2 d ATG, 5–10 mg/kg/d × 4 d	CSP +/- MTX	24 (35)	Chronic myeloid leukemia in first chronic phase/MRD and URD	75%¶	55%	3 pts (days 116, 499 and 726)	4.7-year DFS 85%
Nonmyeloablative Regimens								
National Institutes of Health[15]	F, 25 mg/m^2/d × 5 d C, 60 mg/kg/d × 2 d	CSP	15 (50)	Hematologic + solid malignancies/MRD	10/15 pts, 1 after DLI	NR	2 pts (days 59 and 205)	For 8/15 pts, OS = 121–409 d (median, 200)
M. D. Anderson Cancer Center[24]	F, 25 mg/m^2/d × 5 d or F, 30 mg/m^2/d × 3 d C, 1g/m^2/d × 2 d or 750 mg/m^2/d × 3 d +/- R	FK506 + MTX	20 (51)	Indolent lymphomas/ MRD	20%	64%	2 (at day 45 and before 300 days)	2-year DFS: 84%
Seattle[18]	TBI 2 Gy +/- F, 30 mg/m^2/d × 3 d	CSP + MMF	322 (54)	Hematologic malignancies/MRD and URD	58%	56%#	22% (at 3 years)	3-year OS: 50%; 3-year PFS: 39%

* Days posttransplant.

† Before donor lymphocyte infusions given in 36 of 88 (41%) patients.

‡ In patients with low-grade NHL.

§ In patients with high-grade NHL.

¶ Grades I–IV.

Extensive chronic GVHD.

A = alemtuzumab; ATG = antithymocyte globulin; B = busulfan; C = cyclophosphamide; Cl = cladribine; CSP = cyclosporine; DFS = disease-free survival; DLI = donor lymphocyte infusions; F = fludarabine; FK506 = tacrolimus; GVHD = graft-versus-host disease; HLA = human leukocyte antigen; M = melphalan; MMF = mycophenolate mofetil; MRD = HLA-matched related donor; MTX = methotrexate; NHL = non-Hodgkin lymphoma; NR = not reported; NRM = nonrelapse mortality; OS = overall survival; PFS = progression-free survival; po = orally; R = rituximab; TBI = total body irradiation; URD = HLA-matched unrelated donor.

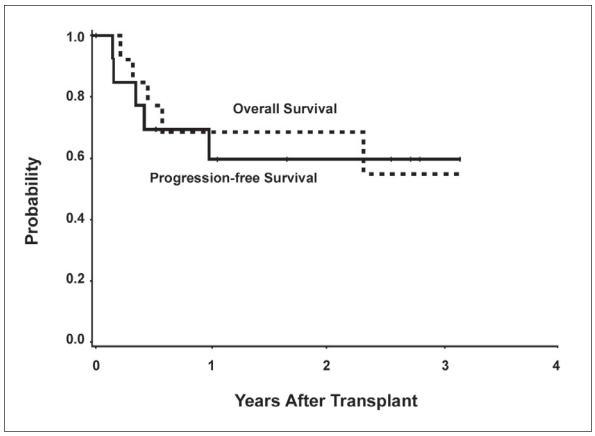

Figure 1. Overall and progression-free survival in patients 56–73 (median 60) years of age with de novo (n=9) or secondary (n=4) acute myeloid leukemia in first complete remission given allogeneic granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells from related donors after 2 Gy total body irradiation with (n=5) or without (n=8) fludarabine (90 mg/m^2).

Reprinted with permission from Feinstein LC, et al.[33]

regimens at multiple centers in Germany.[34] Thirty-seven percent of the patients were in first (22%), second (11%), or third or more (4%) complete remission at the time of HCT (Table 2). With a median follow-up of 12 months, the 2-year probabilities of overall and progression-free survival were 32% and 29%, respectively. In multivariate analysis, more than 5% blasts in the marrow at the time of HCT, alternative donors, and low Karnofsky performance scores were independent adverse prognostic factors for progression-free survival.

Hallemeier and coworkers studied 32 consecutive patients (median age 47 years) given unrelated marrow after 5.5 Gy TBI (given at 30 cGy/min) and cyclophosphamide (120 mg/kg) as treatment for AML in first (n=15), second (n=15), or third (n=2) complete remissions.[12] GVHD prophylaxis consisted of CSP, methotrexate and steroids. The 3-year probabilities of overall and progression-free survival were 55% and 57%, respectively, for patients in first complete remission versus 39% each for patients with more advanced disease (Table 2).

Niederwieser and associates reported data from 122 patients ineligible for conventional HCT given allogeneic HCT after conditioning with 2 Gy TBI with or without added fludarabine.[35] Postgrafting immunosuppression consisted of MMF and CSP. Disease status at HCT was first complete remission in 51 patients (42%), second complete remission in 39 (32%), and beyond second remission in 32 (26%). Two-year probabilities of overall survival were 45% for patients for patients transplanted in first complete remission, 51% for those transplanted in second remission, and 25% for those transplanted beyond second remission (Table 2). Low or standard cytogenetic risks predicted for better overall survival versus high cytogenetic risks (P=.009). The results have encouraged phase III studies investigating the role of low-intensity conditioning and allogeneic HCT as treatment for patients older than 55 years of age with AML in first complete remission.

Since allogeneic HCT has been the only curative treatment for MDS,[37] it is not surprising that several reports address the efficacy of nonablative HCT for MDS. Ho and associates reported results in 62 MDS patients (median age 56 years) given allografts from related (n=24) or unrelated (n=38) donors after reduced-intensity conditioning with fludarabine (150 mg/m^2), oral busulfan (8 mg/kg), and alemtuzumab (a humanized monoclonal antibody recognizing CD52 antigen expressed on T cells and B cells, given at 100 mg total dose).[38] Postgrafting immunosuppression consisted of CSP alone. Of the 62 patients, 16 had refractory anemia, 19 had refractory anemia with excess blasts, 23 had secondary AML, and 4 had chronic myelomonocytic leukemia. The 1-year probabilities of nonrelapse mortality, overall survival, and progression-free survival were 5%, 73%, and 61%, respectively, for patients given grafts from related donors, and 21%, 71%, and 59%, respectively, for patients given grafts from unrelated donors. Twenty-six patients required DLI, given 126–1323 days after HCT, for cytogenetic (n=4) or morphologic relapse (n=6), or for decreased donor marrow chimerism (n=16). All patients given DLI for cytogenetic relapse but no patients given DLI for morphologic relapse responded, while 14 of 16 patients given DLI for decreasing marrow chimerism achieved full donor-marrow chimerism. The 2-year cumulative incidences (including patients given DLI) of grade III–IV acute GVHD were 17% and 23% for patients given grafts from related or unrelated donors, respectively.

Kroger and colleagues[39] reported results from 37 MDS patients (median age 55 years) given grafts from related (n=19) or unrelated (n=18) donors after conditioning with fludarabine (120–180 mg/m^2), busulfan (8 mg/kg orally or 6.4 mg/kg intravenously), and ATG (n=25). GVHD prophylaxis combined CSP with methotrexate or MMF. Diagnoses at transplantation were refractory anemia (n=8), refractory anemia with excess blasts (n=6), refractory anemia with excess blasts in transformation (n=13), chronic myelomonocytic leukemia (n=3), and secondary AML (n=7). Grade II–IV acute GVHD was seen in 37% of patients, and chronic GVHD in 48%. Nonrelapse mortality was 12% in patients given grafts from related donors versus 45% in patients given grafts from unrelated

Table 2. Results After Nonmyeloablative HCT in Acute Myeloid Leukemia

	Niederwieser et al[35]	Hallemeier et al[12]	Sayer et al[34]
N	122	32	113
Median age, yr (range)	57.5 (17–74)	47 (32–60)	51 (16–67)
Disease status at HCT, n (%) CR#1 CR#2 >CR#2	 51 (42) 39 (32) 32 (26)	 15 (47) 15 (47) 2 (6)	 25 (22) 12 (11) 76 (67)
Conditioning regimens	2 Gy TBI +/- 90 mg/m² fludarabine	5.5 Gy TBI + cyclophosphamide (120 mg/kg)	Various
Postgrafting immunosuppression	CSP + MMF	CSP + MTX + steroids	Various
Donors, n (%) Related Unrelated	 58 (48) 64 (52)	 0 32 (100)	 51 (45) 62 (55)
Stem cells, n Marrow G-PBMC	 6 116	 32 0	 11 102
Grade II–IV acute GVHD, %	39	19	42
Chronic GVHD, %	42	76	33
NRM, %	19	28	53
OS	45% at 2 yr (CR#1) 51% at 2 yr (CR#2) 25% at 2 yr (>CR#2)	55% at 3 yr (CR#1) 39% at 3 yr (CR#2+)	32% at 2 yr (all pts)
DFS/PFS	36% at 2 yr (all pts)	57% at 3 yr (CR#1) 39% at 3 yr (>CR#2)	29% at 2 yr (all pts) 52% at 2 yr (CR#1)
Median follow-up, mo	23	26	12

CR#1 = first complete remission; CR#2 = second complete remission; >CR#2 = third or more complete remission; CSP = cyclosporine; DFS = disease-free survival; G-PBMC = granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; MMF = mycophenolate mofetil; MTX = methotrexate; NRM = nonrelapse mortality; OS = overall survival; PFS = progression-free survival; TBI = total body irradiation.

donors. The 3-year probabilities of overall and progression-free survival were 39% and 38%, respectively.

De Lima and coworkers compared HCT outcomes of 94 patients given allogeneic HCT after nonmyeloablative (fludarabine [120 mg/m^2], cytarabine [4 g/m^2], and idarubicin [36 mg/m^2]) or reduced-intensity (fludarabine [100–150 mg/m^2] and melphalan [140 or 180 mg/m^2]) conditioning.[36] The 3-year probabilities of overall survival were 30% in the nonablative group and 35% in the fludarabine/melphalan group (difference between groups not significant [NS]). The nonablative patients had fewer treatment-related complications, a lower incidence of grade III–IV acute GVHD (11% vs 19%, NS), a lower nonrelapse mortality (16% vs 39%, *P*=.036), and a higher risk of relapse (53% vs 26%, *P*=.029) than patients given fludarabine plus melphalan. However, these differences could not simply be explained by differences in the intensity of the conditioning, since nonablative recipients were mainly given bone marrow from related donors while fludarabine/melphalan patients mainly received granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells (G-PBMC) from unrelated donors, which could have impacted both the GVHD incidence and graft-versus-tumor effects. In addition, 20% of patients in the nonablative group experienced graft rejection, and most of the remainder had mixed chimerism, most likely accounting for the reduced graft-versus-tumor effects.[18,40]

Scott and associates recently compared the efficacy of HCT after myeloablative conditioning with busulfan (targeted 800–900 ng/mL; starting dose 1 mg/kg every 6 hours for 16 doses) and cyclophosphamide (120 mg/kg, n=132) or nonmyeloablative conditioning with 2 Gy TBI and fludarabine (90 mg/m^2, n=40) in MDS patients over 40 years of age.[41] The World Health Organization classification (highest at any time before HCT) was refractory anemia with or without ringed sideroblasts in 37% of the ablative and 22% of the nonablative recipients, refractory anemia with excess blasts in 29% of the ablative and 22% of the nonablative recipients, and transformed AML in 34% of the ablative and 55% of the nonablative recipients. The 3-year probabilities of progression-free survival were 42% in ablative recipients and 32% in nonablative recipients. In multivariate analyses, there were no significant differences in overall survival (hazard ratio [HR] 1.0, *P*=.89), progression-free survival (HR 0.7, *P*=.10), and relapse risk (HR 1.0, *P*=.95) between the groups, suggesting that graft-versus-tumor effects were more important than conditioning intensity in preventing relapse in patients with MDS.

Prospective randomized studies in younger patients with MDS are needed to determine the importance of conditioning intensity.

Acute Lymphoblastic Leukemia

Allogeneic HCT following myeloablative conditioning has been a valid treatment for adult patients with acute lymphoblastic leukemia (ALL);[42] however, several groups of investigators have recently assessed the efficacy of nonmyeloablative HCT in ALL patients ineligible for conventional HCT. Martino and associates summarized data from 27 patients (median age 50 years) included in 4 studies.[43] At HCT, 15 patients were in complete remissions, and 12 patients had refractory disease. Conditioning regimens consisted of fludarabine (90–150 mg/m^2), plus an alkylating agent (melphalan 140 mg/m^2 or thiotepa 10 mg/kg) or 2 Gy TBI. Grade II–IV acute GVHD was seen in 48% of patients, and chronic GVHD in 72%. The 2-year incidences of nonrelapse mortality and overall survival were 23% and 31%, respectively. Interestingly, GVHD (either acute or chronic) was associated with reduced risks of relapse (*P*=.05) in time-dependent analyses, demonstrating potent graft-versus-ALL effects, as has been previously observed in patients given grafts after myeloablative conditioning.[44]

Chronic Myeloid Leukemia

Despite promising results with imatinib mesylate (Gleevec, Novartis),[45] allogeneic HCT has remained the only proven curative therapy for chronic myeloid leukemia (CML).[46,47] Graft-versus-tumor effects have been well documented for CML, as evidenced by the ability of DLI to induce durable complete remissions in most patients who have relapsed after allogeneic HCT, making this disease an ideal candidate for HCT following nonablative or reduced-intensity conditioning.[31]

Sloand and coworkers described results in 12 patients (median age 43 years) given G-PBMC from HLA-identical siblings after conditioning with cyclophosphamide (120 mg/kg) and fludarabine (125 mg/m^2).[48] Postgrafting immunosuppression consisted of CSP with or without MMF. Seven patients were in first chronic phase and 5 in second chronic phase at HCT. No patient died of nonrelapse causes. Six patients developed grade II–IV acute GVHD, and chronic GVHD was seen in 6 patients. All 7 patients transplanted in first chronic phase achieved stable molecular remissions: 2 with no posttransplant intervention; 3 after DLI, imatinib, and interferon; and 2 after subsequent myeloablative HCT. Four of 5 patients transplanted in second chronic phase died in blast crisis and 1 survived in molecular remission. The authors speculated that the poor disease control might have been due to the high leukemic burden in these patients.

Or et al reported results of allogeneic HCT after reduced-intensity conditioning combining fludarabine, busulfan, and ATG in 24 relatively young patients (median age 35 years) with CML in first chronic phase.[23] Nineteen patients received grafts from HLA-matched family members, and 5 received grafts from HLA-matched unrelated donors. The 5-year probability of progression-free survival was 85%. The better results compared with those reported by Sloand and coworkers might have been due to a more intense conditioning regimen and younger patient ages.

Kerbauy and associates analyzed data from 24 patients (median age 58 years) with CML in first chronic phase (n=14) or beyond (n=10) given G-PBMC from HLA-matched related donors after conditioning with 2 Gy TBI with (n=16) or without (n=8) fludarabine (90 mg/m^2).[49] Postgrafting immunosuppression consisted of MMF and CSP. Reasons for nonmyeloablative HCT in patients younger than 50 years of age (n=7) were diabetes mellitus with end-organ damage (n=4), chronic hepatitis (n=2), and pulmonary aspergillosis with right-lobe resection (n=1). Grade II–IV acute GVHD occurred in 50% of patients, and extensive chronic GVHD was seen in 32% of patients. Four of 8 patients not given fludarabine experienced nonfatal graft rejection and recurrence of CML, while the 20 remaining patients had sustained engraftment. The 2-year overall survival rates for patients either transplanted in first chronic phase or with more advanced CML were 70% and 56%, respectively. Nine of 10 patients transplanted in first chronic phase after conditioning with 2 Gy TBI and fludarabine achieved molecular remissions 3–24 months after HCT.

We recently reported the data[50] from 21 patients with CML in either first chronic phase (n=12) or beyond first chronic phase (n=9) given either marrow (n=4) or G-PBMC (n=17) from HLA-matched unrelated donors after conditioning with 2 Gy TBI and fludarabine (90 mg/m^2), and postgrafting immunosuppression with MMF and CSP. The median patient age was 54 years. Reasons for nonmyeloablative HCT in patients younger than 50 years (n=4) were prior high-dose HCT (n=2), arteriovenous malformation (n=1), and morbid obesity (n=1). Sustained engraftment was achieved in 5 of 12 patients transplanted in first chronic phase, and 6 of 8 patients transplanted beyond first chronic phase, while 9 patients rejected their grafts 28–400 days after HCT. One patient transplanted in second blastic phase died before chimerism evaluation. Graft rejections were nonfatal in all cases and followed by autologous reconstitution with persistence/recurrence of CML. Seven of 11 patients with sustained engraftment, including all 5 patients in first chronic phase were alive in complete cytogenetic remissions 118–1,205 (median 867) days after HCT (Figure 2). Two of the remaining 4 patients with sustained engraftment died of nonrelapse causes in complete (n=1) or major (n=1) cytogenetic remissions, and 2 died of progressive disease.

A high rate of graft rejection among CML patients receiving grafts from unrelated donors after reduced-intensity conditioning has also been reported by other investigators. A graft failure rate of 44% (3 of 8 patients) was described after a regimen that combined fludarabine (150 mg/m^2), intravenous busulfan (6.6 mg/kg), and ATG.[51] Recently, Hallemeier observed graft failure in 5 of 22 evaluable patients given unrelated grafts after conditioning with 5.5 Gy TBI (given as a single dose at 30 cGy/min) and cyclophosphamide (120 mg/kg).[52] Further efforts for reducing the risk of graft rejection in CML patients given unrelated HCT are directed at increasing the degree of pretransplant immunosuppression.

Chronic Lymphocytic Leukemia

The median survival of relatively young patients (<56 years) with chronic lymphocytic leukemia (CLL) refractory to fludarabine has been reported to be 48 weeks,[53] with only 10–33% of patients responding to chemotherapy[53] or alemtuzumab.[54] Those patients are candidates for therapy with allogeneic HCT.

Dreger and coworkers reported results of 77 CLL patients given reduced-intensity (n=34) or nonmyeloablative conditioning (n=43) in European Group for Bone and Marrow Transplant (EBMT)-affiliated centers.[55] Median patient age was 54 years with a median of 3 previous chemotherapy regimens. Eight patients were in complete remission, 42 in partial remission, and 27 had refractory disease at transplant. The

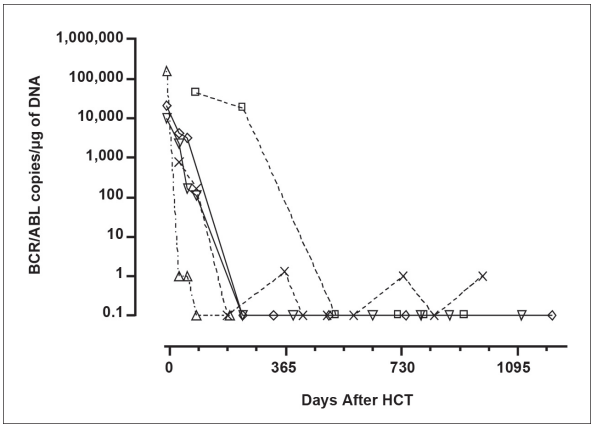

Figure 2. Evolution of BCR/ABL mRNA in 4 patients with first chronic phase chronic myeloid leukemia and 1 patient with accelerated phase chronic myeloid leukemia given unrelated grafts after 2 Gy total body irradiation and fludarabine. Molecular remissions were achieved 84–524 (median 230) days after hematopoietic cell transplantation.

1-year nonrelapse mortality was 18%, and the 2-year probabilities of overall and progression-free survival were 72% and 56%, respectively.

Schetelig and associates analyzed data from 30 CLL patients (median age 50 years) given grafts from related (n=15) or unrelated (n=15) donors after conditioning with fludarabine (180 mg/m^2), busulfan (8 mg/kg), and ATG.[56] GVHD prophylaxis consisted of CSP given alone (n=7), or in combination with MMF (n=12) or methotrexate (n=11) (Table 3). At HCT, 14 patients (46%) had chemorefractory disease, including 10 patients (33%) who were refractory to fludarabine. Twenty-five percent of patients achieved complete remission at 1 year and 66% at 2 years after HCT. The 2-year probabilities of nonrelapse mortality, overall survival, and progression-free survival were 15%, 72%, and 67%, respectively.

Khouri and associates reported data from 17 CLL patients (median age 54 years) given G-PBMC (n=16) or marrow (n=1) from HLA-matched related donors after conditioning with fludarabine (90 mg/m^2) and cyclophosphamide (2,250 mg/m^2), with subsequent incorporation of rituximab (Rituxan, Genentech) in the regimen to enhance tumor control after the initial 7 patients.[57] GVHD prophylaxis consisted of tacrolimus and methotrexate. All patients were either refractory to fludarabine or had relapsed following fludarabine therapy. Ten patients with persistent disease after HCT received DLI with or without rituximab after tacrolimus discontinuation in order to increase graft-versus-tumor effects. Sixteen patients ultimately achieved complete (n=12) or partial (n=4) remissions. The 2-year probabilities of nonrelapse mortality, overall survival, and

progression-free survival were 22%, 80%, and 60%, respectively (Table 3).

Sorror and colleagues described outcomes in 64 CLL patients (median age 56 years) who received HCT from HLA-matched related (n=44) or unrelated (n=20) donors after conditioning with 2 Gy TBI alone (n=11) or combined with fludarabine (90 mg/m^2, n=53).[58] Postgrafting immunosuppression consisted of MMF and CSP. Ninety-five percent of patients were refractory to at least 1 regimen, including 88% who were refractory to fludarabine. Three patients experienced graft rejection. One of the 3 died of aplasia and the 2 others were surviving with autologous marrow recovery and progressive disease. With a median follow-up of 24 months, the overall response rate was 67% (50% complete remission). Estimated 2-year rates of nonrelapse mortality, overall survival, and progression-free survival were 22%, 60%, and 52%, respectively (Table 3 and Figure 3).

Taken together, these results suggest that CLL is remarkably susceptible to graft-versus-tumor effects, and that HCT after nonmyeloablative or reduced-intensity conditioning should be explored in phase III studies in patients with fludarabine-refractory CLL.

Lymphoma

Conventional allogeneic HCT is a potential curative treatment for patients with non-Hodgkin lymphoma (NHL) in whom nontransplant therapies have failed.[59] The benefits of allogeneic HCT have been attributed to both the intensities of the conditioning regimens used and graft-versus-lymphoma effects.[60] However, the use of conventional allogeneic HCT has been associated with high nonrelapse mortalities (up to 40%) that are even higher (50–85%) in patients who had failed autologous HCT.[61] This high rate of mortality has led to the use of nonmyeloablative or reduced-intensity conditioning before HCT in patients with NHL who have failed lymphoma therapy and who are ineligible for conventional allogeneic HCT because of age and comorbid conditions.

Registry Data Study: Robinson and colleagues reported results in 188 patients with lymphoma (low-grade NHL [n=52], high-grade NHL [n=62], Hodgkin disease [n=52], and mantle-cell lymphoma [n=22]) given HCT after various reduced-intensity or nonmyeloablative conditioning regimens in EBMT-affiliated centers.[62] Median age was 40 years, and the median number of prior treatments was 3 courses. Forty-eight percent of patients had failed autologous transplantation, and 21% had chemoresistant disease. The overall 1-year probability of nonrelapse mortality was 26%, and that incidence was significantly higher in patients older than 50 years (39% vs 22% in younger patients, *P*=.03). Twenty-two patients received DLI with (n=8) or without (n=14) preceding chemotherapy for either disease progression or persistence after HCT. Ten of the 14 patients given DLI alone achieved complete (n=6) or partial (n=4) remissions. The 2-year overall and progression-free survival probabilities were 65% and 54%, respectively, for patients with low-grade NHL, 47% and 13%, respectively, for patients with high-grade NHL, 13% and 0%, respectively, for patients with mantle-cell lymphoma, and 56% and 42%, respectively, for patients with Hodgkin disease. In multivariate analyses, chemosensitive disease at HCT was associated with longer overall (relative risk [RR], 2.4; *P*=.002) and progression-free (RR, 2.3; *P*=.007) survival.

Low-grade NHL: Khouri and associates reported data from 20 patients with low-grade NHL given grafts from siblings after conditioning with fludarabine (90–125 mg/m^2) and cyclophosphamide (2,000–2,250 mg/m^2), with or without added rituximab.[24] Postgrafting immunosuppression consisted of tacrolimus and methotrexate. All patients had chemosensitive disease at HCT, including 12 patients (60%) who were in complete remission. Grade II–IV acute GVHD occurred in 20% of patients while extensive chronic GVHD was seen in 64% of patients. None have had relapse of disease after a median follow-up of 21 months. The 2-year probability of being alive in complete remission was 84%.

Morris and colleagues reported results of 41 patients with low-grade lymphoproliferative disorders given allogeneic HCT after conditioning with fludarabine (150 mg/m^2), melphalan (140 mg/m^2) and alemtuzumab (100 mg).[22] Forty patients (98%) had chemosensitive disease at HCT, including 11 patients (27%) who were in complete remission. The 3-year probability of relapse was 44% (some of the relapsing patients responded to discontinuation of immunosuppression or to DLI). The 3-year probabilities of overall survival were 78% for patients given grafts from related donors and 56% for those with grafts from unrelated donors.[63] The 2-year incidence of nonrelapse mortality was remarkably low (11%).

Mantle-Cell Lymphoma: Khouri and coworkers analyzed data from a total of 18 patients treated on 2 consecutive trials.[64] Five patients received HCT after conditioning with cisplatinum (100 mg/m^2), fludarabine (60 mg/m^2) and cytarabine (2 g/m^2), and 13 received HCT after conditioning with fludarabine (90 mg/m^2), cyclophosphamide (2,250 mg/m^2), and rituximab. Tacrolimus and methotrexate were used as postgrafting immunosuppression. Five patients had failed autologous HCT and 16 (89%) had chemosensitive disease including 8 patients who were in complete remission at HCT. Fourteen patients received grafts from related donors

Table 3. Results After Nonmyeloablative HCT in Chronic Lymphocytic Leukemia

	Schetelig et al[56]	Khouri et al[57]	Sorror et al[58]
N	30	17	64
Median age, yr (range)	50 (12–63)	54 (43–73)	56 (44–69)
Disease status at HCT, n (%) CR: Yes No Refractory to fludarabine	 NR NR 10 (33)	 0 17 (100) 9 (53)	 5 (8) 59 (92) 56 (88)
Conditioning regimens	Fludarabine (180 mg/m²), busulfan (8 mg/kg) and ATG	Fludarabine (90 mg/m²), cyclophosphamide (2250 mg/m²), +/-rituximab	2 Gy TBI +/- fludarabine (90 mg/m²)
Postgrafting immunosuppression	CSP +/- MMF or MTX	Tacrolimus + MTX	CSP + MMF
Donors, n (%) Related Unrelated	 15 (50) 15 (50)	 17 (100) 0	 44 (69) 20 (31)
Stem cells, n (%) Marrow G-PBMC	 3 (10) 27 (90)	 1 (6) 16 (94)	 0 64 (100)
Grade II–IV acute GVHD, %	56	29	55%
Chronic GVHD, %	75	60	50%
NRM	15% at 2 yr	22% at 2 yr	22% at 2 yr
Response rate	93% (40% CR)	94% (70% CR)	67% (50% CR)
OS	72% at 2 yr	80% at 2 yr	60% at 2 yr
DFS/PFS	67% at 2 yr	60% at 2 yr*	52% at 2 yr
Median follow-up, mo (range)	24 (7–43)	21 (11–84)	24 (3–63)

* Current PFS.

ATG = antithymocyte globulins; CR = complete remission; CSP = cyclosporine; DFS = disease-free survival; G-PBMC = granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells; GVHD = graft-versus-tumor disease; HCT = hematopoietic cell transplantation; NR = not reported; NRM = nonrelapse mortality; MMF = mycophenolate mofetil; MTX = methotrexate; OS = overall survival; PFS = progression-free survival; TBI = total body irradiation.

and 4 from unrelated donors. Grade II–IV acute GVHD occurred in 17% of patients and chronic GVHD in 36%. Complete remissions were maintained in the 8 patients transplanted in remission and accomplished in 9 of the 10 remaining patients. Three patients eventually relapsed, 1 of whom achieved complete remission after DLI. Three-year probabilities of overall and current progression-free survival were 86% and 82%, respectively.

Morris and colleagues reported results in 10 patients given grafts after fludarabine (150 mg/m²), melphalan (140 mg/m²), and alemtuzumab (100 mg).[22] The 3-year probabilities of relapse and overall survival were 50% and 60%, respectively.

Maris and associates reported a multi-institution study of 33 patients with relapsed or refractory mantle-cell lymphoma given allogeneic HCT after 2 Gy TBI and fludarabine (90 mg/m²).[65] Postgrafting immunosuppression consisted of MMF and CSP. Sixteen patients were given grafts from HLA-identical related donors and 17 from HLA-matched unrelated donors. Fourteen patients had failed autologous HCT and 13 had chemorefractory disease. Grade II–IV acute GVHD occurred in 57% of patients, and extensive chronic GVHD was seen in 64%. Complete remissions were maintained in the 13 patients transplanted in remission and accomplished in 14 of the 20 remaining patients. The 2-year probabilities of relapse, nonrelapse mortality, and overall and progression-free survival were 9%, 24%, 65%, and 60%, respectively (Figure 4).

High-grade NHL: A multicenter UK study using conditioning with fludarabine (150 mg/m²), melphalan

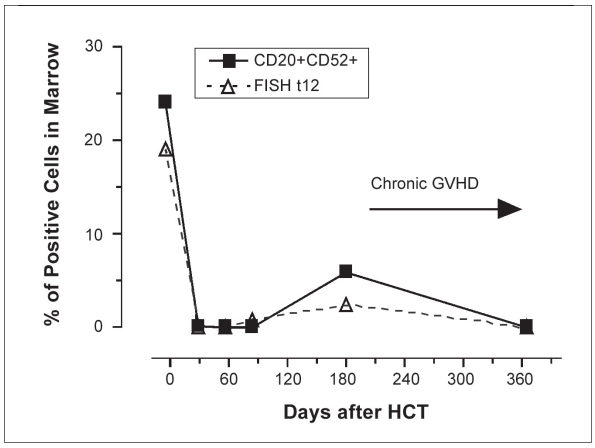

Figure 3. Evidence of graft-versus-tumor effects in a CLL patient with bone marrow involvement (CD20+, CD52+ cells with trisomy 12 on fluorescent in situ hybridization analysis) and axillary adenopathy at HCT, given G-PBMC from an HLA-matched unrelated donor after 2 Gy TBI and fludarabine (90 mg/m^2).[58] The patient achieved a complete remission on day 84, showed recurrent marrow disease on day 180, but then achieved a remission by day 365 (without treatment) after having had extensive chronic GVHD.

CLL = chronic lymphocyte leukemia; G-PBMC = granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; HLA = human leukocyte antigen; TBI = total body irradiation.

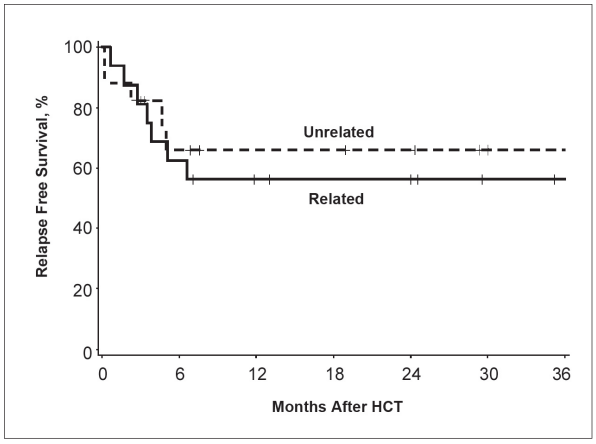

Figure 4. Kaplan-Meier estimates of progression-free survival among patients with mantle-cell lymphoma given grafts from related (n=16) or unrelated (n=17) donors after 2 Gy TBI with or without fludarabine (90 mg/m^2). Ten of 17 unrelated recipients and 4 of 16 sibling recipients had failed autologous HCT. Thirty-nine percent of the patients had disease which was refractory to salvage chemotherapy or autologous HCT.

Reprinted with permission from Maris MB et al.[65] © the American Society of Hematology.

HCT = hematopoietic cell transplantation; TBI = total body irradiation.

(140 mg/m^2), and alemtuzumab (100 mg) included 37 patients with high-grade NHL (including 22 with diffuse large B-cell lymphoma).[59] The 3-year probabilities of relapse, nonrelapse mortality, and overall and progression-free survival were 52%, 38%, 34%, and 34%, respectively. Only 1 of 8 patients transplanted with refractory disease remained alive without progression at 2.5 years after HCT.

Preliminary data from the Seattle consortium multicenter study were recently analyzed.[66] Forty-two patients with high-grade NHL were given grafts from related (n=29) or unrelated (n=13) donors after conditioning with 2 Gy TBI with or without fludarabine (90 mg/m^2). Twenty-four patients had failed autologous HCT. The 1-year probabilities of relapse, nonrelapse mortality, and overall and progression-free survivals were 36%, 15%, 63%, and 49%, respectively. Chemorefractory disease at HCT was associated with lower overall (HR 0.21, P=.0005) and progression-free (HR 0.21; P=.0003) survival rates, suggesting that tumor chemosensitivity should be a major consideration in the selection of patients who might benefit from HCT with nonablative conditioning.

Hodgkin Disease: Robinson et al[67] reported outcomes among 311 patients (median age 31 years) from EBMT-affiliated centers given allogeneic HCT from HLA-matched related (n=221), HLA-matched unrelated (n=61), or HLA-mismatched (n=17) donors after various reduced-intensity or nonmyeloablative conditioning regimens as treatment for Hodgkin disease. Forty-five percent of patients had failed autologous HCT, and 32% had chemoresistant disease. The 100-day and 1-year probabilities of nonrelapse mortality were 17% and 24%, respectively, and these rates were significantly higher in patients with chemoresistant disease at HCT. The 2-year probabilities of relapse, overall survival, and progression-free survival were 64%, 46%, and 26%, respectively. In multivariate analyses, chemoresistant disease at HCT was associated with decreased overall (P<.0001) and progression-free (P<.0001) survival.

Multiple Myeloma

Myeloablative allogeneic HCT is the only proven curative treatment for MM.[68] This efficacy has been attributed to ablation of myeloma cells both by the intense conditioning regimen and by graft-versus-myeloma effects, which have been directly demonstrated by the ability of DLI to induce remissions in some patients who relapsed after allografts.[69] However, the very high transplant-related mortality associated with standard allogeneic HCT (20–50% in the first 6 months, even in younger patients) has tempered enthusiasm for this approach,[70] and has led to the development of nonablative HCT for patients with MM.[71-73]

Table 4. Results After Nonmyeloablative HCT in Multiple Myeloma

	Badros et al[72]	Maloney et al[73]	Kroger et al[74]
N	31	54	120
Median age, yrs (range)	56 (38–69)	52 (29–71)	52 (31–65)
Disease status at HCT, n (%) CR or nCR Not in CR Refractory disease	 9 (29) 22 (71) 17 (55)	 6 (11) 48 (89) 19 (35)	 8 (7) 112 (93) 33 (28)
Conditioning regimens	Melphalan 100 mg/m² (n=25), melphalan 100 mg/m², 2.5 Gy TBI, fludarabine (60 mg/m²) (n=6)	Melphalan 200 mg (auto HCT) followed 40–229 days later by 2 Gy TBI (allo HCT)	Fludarabine, melphalan +/- ATG (various doses)
Tandem auto/allo HCT, n (%)	0	54 (100)	38 (32)
Postgrafting immunosuppression	CSP +/- steroids	CSP + MMF	Various
Donors, n (%) Related Unrelated	 25 (80) 6 (20)	 54 (100) 0	 85 (70) 35 (30)
Stem cells, n (%) Marrow G-PBMC	 3 (10) 28 (90)	 0 54 (100)	 8 (7) 112 (93)
Grade II–IV acute GVHD	52%	38%	46%
Chronic GVHD	33%	46%	47%
NRM	9/31 pts (29%)	9/54 pts (17%)	18% at 1 yr
Response rate	61% CR/nCR	83% (57% CR)	87% (49% CR)
OS	31% at 2 yr	78% at 2 yr	59% at 2 yr
DFS/PFS	31% at 2 yr	55% at 2 yr	39% at 2 yr
Median follow-up, mo (range)	6 (1.5–24)	20 (8–40)	16 (3–46)

allo = allogeneic; ATG = antithymocyte globulins; auto = autogeneic; CR = complete remission; CSP = cyclosporine; DFS = disease-free survival; G-PBMC = granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; MMF = mycophenolate mofetil; nCR = near complete remission; NRM = nonrelapse mortality; OS = overall survival; PFS = progression-free survival; TBI = total body irradiation.

Badros and associates treated 25 MM patients with intermediate dose melphalan (100 mg/m²) followed by HCT from HLA-matched siblings.[72] Six additional patients were given grafts from HLA-matched unrelated donors after melphalan (100 mg/m²), 2.5 Gy TBI, and fludarabine (60 mg/m²). All but 1 patient had failed autologous HCT, and 21 (68%) had a chromosome 13 abnormality. Nonrelapse mortality during the first 100 days was 10%. Overall, 61% of patients achieved complete or near-complete remissions. The 2-year probabilities of overall and progression-free survival were 31% each (Table 4).

Maloney and coworkers analyzed data from 54 MM patients who initially received autologous HCT after a cytoreductive dose of melphalan (200 mg/m²), followed 40–229 (median 62) days later by allogeneic HCT after 2 Gy TBI.[73] Patients were 29–71 (median 52) years old, and 48% had refractory (35%) or relapsed (13%) disease. The 100-day mortality rates after autologous and allogeneic HCT were 2% and 2%, respectively. With a median follow-up of 552 days after allografting, 57% of patients achieved complete remission and 26% partial remission. The estimated 2-year overall and progression-free survival were 78% and 55%, respectively (Table 4).

Kroger and colleagues recently analyzed data from 120 MM patients (median age 52 years) treated with melphalan/fludarabine followed by allogeneic HCT.[74] The 1-year incidence of nonrelapse mortality was 18%, while

Table 5. Potential Current Roles of HCT After Nonmyeloablative or Reduced-Intensity Conditioning

	Potential role	Comments
AML	Attractive in older patients in CR#1/CR#2.[35]	Phase III "randomized" trials ongoing in patients in CR#1.
ALL	Feasible in older patients with ALL in CR.[43,82]	Few published data.
CML	Particularly attractive in older patients with sibling donors.[23,49] Results are better in CP#1 than in more advanced stages.	Increase immunosuppression before HCT in order to assure consistent engraftment in patients given grafts from unrelated donors.[47]
CLL	Nonablative HCT efficacious. Very attractive for patients refractory to fludarabine.[55-58]	Phase III trials needed to compare nonablative HCT with alemtuzumab or chemotherapy.
Low-grade NHL	Nonablative HCT clearly efficacious.[62]	Phase III studies warranted to compare nonablative HCT with alternative treatment strategies.
MCL	Nonablative HCT clearly efficacious. Very attractive in patients relapsing after autologous HCT.[64,65]	Phase III studies warranted.
High-grade NHL/ Hodgkin disease	Efficacious in patients with low tumor burden. Increasingly used in patients failing autologous HCT.[62]	Better results in patients with chemosensitive diseases and in patients with low tumor burden. Consider debulking with autologous HCT (tandem auto/allo HCT).
Multiple myeloma	Nonablative HCT effective, particularly in patients with chemosensitive disease.[74] Promising results of tandem allogeneic and autologous HCT.[73]	Ongoing phase III studies assess the role of tandem autologous/allogeneic HCT.
Solid tumors	Graft-versus-RCC effect has been observed in selected patients.[76]	Ongoing phase II studies.

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; CP1 = first chronic phase; CR#1 = first complete remission; CR#2 = second complete remission; HCT = hematopoietic cell transplantation; MCL = mantle-cell lymphoma; NHL = non-Hodgkin lymphoma; RCC = renal cell carcinoma.

2-year probabilities of relapse, overall survival, and progression-free survival were 43%, 59%, and 39%, respectively. In multivariate analyses, relapse after autologous HCT was the most significant risk factor for nonrelapse mortality (HR 2.80; P=.02), relapse (HR 4.14; P<.001), failure of progression-free survival (HR 3.11; P<.001), and death (HR 2.69; P=.005). Relapse was diminished by chronic (but not acute) GVHD in a time-dependent Cox model (P=.02).

Metastatic Renal Cell Carcinoma

Childs and associates first demonstrated the efficacy of graft-versus-tumor effects in 1 patient with renal cell carcinoma (RCC) in 1999.[75] The authors next reported results in 19 patients with progressive metastatic RCC treated with cyclophosphamide and fludarabine followed by allogeneic HCT and posttransplant immunosuppression with CSP.[76] Ten patients (53%) achieved objective clinical responses, and 3 (16%) achieved sustained complete remissions. Subsequent reports from other centers confirmed that similar treatment protocols could induce objective regressions of metastatic RCC in 8–57% of patients studied,[77-80] and 1 study suggested that responses might be due to CD8(+) T cells recognizing minor histocompatibility antigens on tumor cells.[80] Based on these encouraging preliminary results, further exploration of nonablative HCT for RCC is warranted in the setting of clinical trials.

Summary and Possible Current Indications

Reduced-intensity and nonmyeloablative conditioning regimens have allowed for sustained engraftment of allogeneic hematopoietic cells and the development of therapeutic graft-versus-tumor effects. Achievement of complete remissions might require extended periods of time, with some patients achieving complete remissions more than 1 year after HCT. In patients with slowly progressing diseases such as CLL, low-grade NHL, or chronic-phase CML, or those with more aggres-

sive diseases in complete remission, nonmyeloablative conditioning might be sufficient to achieve cures of the underlying diseases (Table 5). In patients with aggressive diseases such as acute leukemias, MM, high-grade NHL, or Hodgkin disease who were not in complete remission, cytoreduction by preceding chemotherapy or autologous HCT might be required, and results have been worst in those patients with chemorefractory diseases. Remaining challenges include prevention of both severe GVHD and infections and increasing the efficacy of graft-versus-tumor effects. Further progress in adoptive transfer of T-cell populations with relative tumor specificity[81] and combinations of nonablative HCT with targeted therapies such as imatinib, rituximab, or radiolabeled monoclonal antibodies might make the use of nonmyeloablative allogeneic HCT effective even in patients with large disease burden.

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