Stem Cell Transplantation

Targeted marrow irradiation with radioactively labeled anti-CD66 monoclonal antibody prior to allogeneic stem cell transplantation for patients with leukemia: results of a phase I-II study

We treated 20 adult patients with a ^{188}Re-labeled anti-CD66 antibody (mean marrow dose 13.3 Gy) prior to allogeneic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia or advanced chronic myeloid leukemia. The intensified conditioning was not associated with increased non–relapse mortality. No reduction in the incidence of relapse was observed in the context of a T-cell depleted graft (4-year overall survival: 29%).

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Efforts to decrease the incidence of relapse after stem cell transplantation have focused on the use of intensified conditioning regimens by increasing the dose of total body irradiation or adding chemotherapy.[1] However, the intensification of conditioning is associated with greater regimen-related toxicity.[1] If radiation could be targeted directly and mainly to sites of hematopoiesis, the relapse rate might be reduced without increased organ toxicity. Investigators from Seattle and New York have pioneered this approach by using CD33 or CD45 antibodies labeled with iodine 131 (^{131}I).[2] We have used targeted marrow irradiation with a ^{188}Re labeled anti-CD66 antibody (Scintimun® Granulocyte) prior to allogeneic stem cell transplantation (3-6). In the current study we intensified the conditioning regimen in 20 patients with Philadelphia-chromosome positive acute lymphocytic leukemia (ALL) and chronic myeloid leukemia or advanced chronic myeloid leukemia (CML) beyond first chronic phase by using the ^{188}Re- labeled anti-CD66 antibody.

The patient population consisted of 16 males and 4 females with a median age of 43.5 years. Details on disease status, conditioning regimen and donor source are shown in Table 1. Renal shielding was used to reduce the radiation exposure of the kidneys from total body irradiation to 6 Gy. All patients received granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood progenitor cell grafts, which were T-cell depleted (Campath 1H in the bag (n=4), CD34$^+$ selection (CliniMACS)(n=16, mean CD3 cells/kg: 0.14×10^5). The median CD34 count/kg body weight was 7.5×10^6 (S.E.0.8). Cyclosporine (2×2.5 mg/kg) was given to six patients. In patients with mismatched family donors or a matched unrelated donor, antithymocyte globulin was added to prevent graft rejection.

Antibody labeling, dosimetry and radioimmunotherapy were performed as previously described.[3-8] The tracer dose consisted of 1 to 2 mg anti-CD66 antibody labeled with 1.2±0.6 GBq ^{188}Re. For therapy a mean of 9.5 (S.E.0.7) GBq was injected in 1 to 2 fractions. The mean red marrow absorbed dose was 13.3 Gy (S.E.1.1). The mean spleen, kidney and liver absorbed doses were 12.2Gy (S.E.1.8), 6.2 Gy (S.E. 0.6), and 4.4 Gy (S.E.0.4), respectively. The mean marrow/liver and marrow/kidney ratios were 3.3 (S.E.0.3) and 2.7 (S.E.0.4), respectively. The acute toxicity of the therapeutic antibody was very mild. The median time to achieve more than 0.5×10^9/L and 1×10^9/L neutrophils was 11.4 (9-15) and 12.4 (10-16) days. The median time to achieve more than 25×10^9/L and 50×10^9/L platelets was 16 (10-46) and 35 (11-209) days respectively. One patient had delayed graft rejection (Table 1). No patient developed severe acute graft-versus-host disease (GvHD)(grade III-IV) although clinically relevant grade 2 acute GvHD developed in two patients (10%). Extensive/limited chronic GvHD developed in two and six patients, respectively. Two patients devel-

Table 1. Characteristics and outcomes of patients treated with ^{188}Re labeled anti-CD66 antibody.

UPN	Age	Diagnosis	Disease status	Cond.	Donor	Outcome	Follow-up (day)	Course
921	41	ALL	1.CR	TBI, Cy	MFD	Sepsis,†	1020	Relapse and retransplantation
642	42	ALL	1.CR	TBI, Cy	MFD	Interstitial pneumonitis,†	350	
1054	42	ALL	1.CR	TBI, Cy	MFD	Relapse,†	522	Relapse and retransplantation
712	52	ALL	1.CR	TBI, Cy	MFD	TRM,†	487	
1112	27	ALL	PR	TBI, Cy	MFD	Relapse,†	637	Glivec (MRD), relapse and retransplantation
758	44	ALL	2.CR	TBI, Cy	MFD	Relapse,†	169	
683	45	ALL	1.CR	TBI, Cy	MUD	Relapse,†	151	
984	51	ALL	1.CR	TBI, Cy	MUD	Alive	1000	MRD negative
841	46	ALL	2.PR	TBI, Cy	MUD	Alive	1649	MRD negative
737	22	CML	AP	TBI, Cy, TT	Haplo	Alive	2037	Glivec for MRD & relapse, avascular bone necrosis, BMT-nephropathy, quant. PCR neg
945	49	CML	AP	TBI, Cy, TT	Haplo	MOF, VOD,†	13	
710	51	CML	2. cP	TBI, Cy, TT	Haplo	lost to follow-up,†	565	
1040	43	CML	2. cP	TBI, Cy, TT	Haplo	Relapse,†	322	Glivec for MRD
936	39	CML	AP	BU, Cy	MFD	Alive	1246	Glivec for MRD, MRD negative
703	56	CML	AP	TBI, Cy	MFD	Relapse,†	817	
806	32	CML	2. cP	TBI, Cy	MM, MUD	Alive	1736	BMT-nephropathy, avascular bone necrosis, MRD negative
750	39	CML	2. cP	TBI, Cy	MM, MUD	TTP,†	101	
964	46	CML	2. cP	BU, Cy	MUD	Alive	1104	MRD negative
684	19	CML	2. cP	TBI, Cy	MUD	Infection,†	891	Graft failure
628	49	CML	2. cP	TBI, Cy	MUD	Sepsis,†	208	

Cond.: conditioning; AP: accelerated phase; Bu: busulfan (12.8 mg/kg); cP: chronic phase; CR: complete remission; Cy: cyclophosphamide (120 mg/kg); MFD: matched family donor; MOF: multiorgan failure; MRD: minimal residual disease MUD: matched unrelated donor; MM: mismatch; PR: partial remission; TBI: total body irradiation (12Gy); TT: thiotepa (10mg/kg); TTP: thrombotic thrombocytopenic purpura; VOD: veno-occlusive disease.

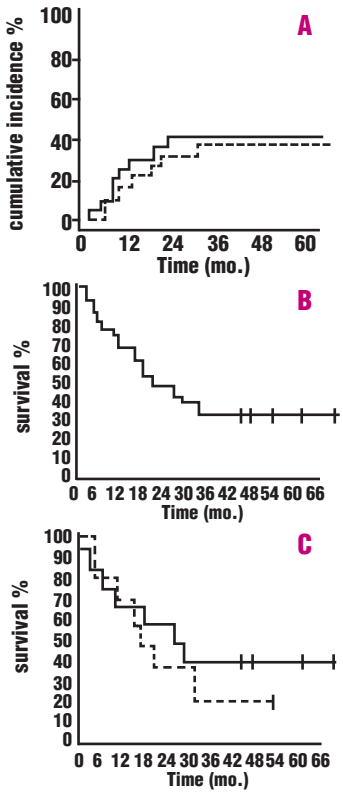

Figure 1. Outcome of patients treated with ^{188}Re labeled anti-CD66 antibody. **A.** Cumulative incidence of relapse (solid) and non-relapse mortality (NRM)(dotted) of all patients. **B.** Kaplan-Meier analysis of overall survival of all patients. **C.** Kaplan-Meier analysis of overall survival according to diagnosis (CML solid, ALL dotted).

oped late bone marrow radiation nephropathy. Non-relapse mortality at 100 days and one year was 5% (S.E. 5%) and 20% (S.E. 9%)(Figure 1). Overall, 7 of 20 patients have died of transplant-related causes and this risk was independent of the donor source (cumulative incidence of non-relapse mortality 35% (S.E.11%). With a median follow-up of 54 months (range 23-81) eight patients have relapsed (Figure 1) for a cumulative incidence of relapse of 40% (S.E.11%). There were five relapses among patients with ALL and three among patients with CML. Overall and disease-free survival rates after 4 years are 29% (95%-CI 14-58%) and 25% (95%-CI 12-53), respectively (Figure 1). The overall survival of patients with ALL and CML after 4 years is 17% and 36%, respectively, with a median survival of 17.1 and 26.1 months (Figure 1). Patients under the age of 40 (n=6) had a higher probability of surviving (50%) than had older patients (n=14) (p=0.18). Four-year overall survival for patients with a matched unrelated donor was 50% compared to 12.5% for those with a matched family donor and 25% for patients with haploidentical family donors.

The results extend the feasibility of our approach to patients with CML and Philadelphia-chromosome positive ALL.[4,6] Regimen-related organ toxicity was low and no higher than anticipated for this group of high-risk patients. Only one patient developed severe vaso-occlusive disease with multiorgan failure, and the observed day +100 mortality (5%) is considerably lower than expected from data reported by the International Bone Marrow Transplant Registries for similar patients, considering that we included patients with advanced disease and a high proportion of alternative donors.[9] As previously described chronic radiation nephropathy occurred in a fraction of our patients treated with radioimmunotherapy.[4] The intensified conditioning regimen has had no negative impact on other important variables of outcome after allogeneic stem cell transplantation such as the incidence of GvHD. Given the fact that only about one third of the patients had matched sibling donors, the incidence of acute and chronic GvHD is low due to the use of *in vivo/ex vivo* T-cell depletion. Although antileukemic efficacy was not the primary endpoint of this study, the relapse rate, especially in patients with Philadelphia positive ALL, was higher than in patients with high–risk acute myeloid leukemia/myelodysplastic syndrome (25%), despite the supplemental dose of radiation provided by the radioimmunoconjugate being similar in the two cohorts of patients (13 Gy vs. 15.3 Gy).[4,6] The main factor likely to be responsible for this is the lack of a graft-versus-leukemia effect because of the low incidence of GvHD. In our next study we will, therefore, use less intense T-cell depletion and attempt to achieve higher marrow doses by administering the more stable ^{90}Y-labeled anti-CD66 in patients in remission at the time of transplant. For patients not in remission we will dispense with T-cell depletion and try to achieve higher and more homogeneous marrow doses by using a ^{90}Y-labeled anti-CD45 antibody.

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