A comparison between low intensity and reduced intensity conditioning in allogeneic hematopoietic stem cell transplantation for solid tumors

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The online version of this article contains a supplemental appendix.

ABSTRACT

Background
Following different types of conditioning, allogeneic hematopoietic stem cell transplantation produces a graft-versus-tumor effect in patients with solid tumors. We performed a non-randomized study comparing low intensity conditioning with reduced intensity conditioning after stem cell transplantation to demonstrate the graft-versus-tumor effect.

Design and Methods
Allogeneic stem cell transplantation was performed in 48 patients with metastatic renal cell cancer (n=17), colo-rectal cancer (n=15), non-metastatic advanced primary liver cancer after orthotopic liver transplantation (n=11), and other solid tumors (n=5). Tumor response was determined based on the international response evaluation criteria for solid tumors (RECIST).

Results
No significant difference in the incidence of graft rejection was found between the low intensity conditioning and reduced intensity conditioning groups. Engraftment occurred earlier in the low intensity conditioning group than in the reduced intensity conditioning group (median 0 *vs.* 16 days, respectively; $p<0.001$). Complete donor chimerism in B cells occurred earlier after low intensity conditioning than after reduced intensity conditioning (median 28 *vs.* 97 days, respectively; $p<0.001$). No significant difference in the incidence of tumor response was found between groups receving the different types of the conditioning. The most favorable tumor response rate was found in patients who received donor lymphocyte infusions and de-veloped chronic graft-versus-host disease (75% *vs.* 34%, $p=0.003$). The best graft-versus-tumor effect was demonstrated in patients with advanced primary liver cancer who had previously undergone liver transplantation ($p=0.018$). Patients receiving reduced intensity conditioning had a tendency to better overall survival compared to the low intensity conditioning group (30% *vs.* 17%, $p=0.005$).

Conclusions
Adjuvant cell therapy with donor lymphocyte infusion may augment the graft-versus-tumor effect of cronic graft-versus-host disease. Patients with limited tumor load are indicated for allogeneic stem cell transplantation and reduced intensity conditioning may be favorable compared to low intensity conditioning.

Key words: allogeneic hematopoietic stem cell transplantation, liver transplantation, reduced intensity conditioning, graft-versus-tumor effect, solid tumor.

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Introduction

Allogeneic hematopoietic stem cell transplantation (SCT) using low intensity or reduced intensity conditioning (RIC) has been shown to be an effective treatment in patients older than 50 years with hematologic malignancies. This treatment is particularly helpful in patients who otherwise could not tolerate a transplant due to organ impairment.[1] Tumors may be eradicated by a graft-versus-leukemia/graft-versus-tumor effect mediated by donor T cells[2] and donor lymphocyte infusions (DLI).[3] Low intensity conditioning, using only 2 Gy total body irradiation, reduces the toxicity associated with conventional SCT.[4]

Today, several hundred patients with various solid tumors such as renal cell,[5-10] colorectal,[8,11,12] advanced primary liver,[8,13] prostate,[9] breast,[6,8,9,14] ovarian,[9,15] and pancreas cancer[16,17] have undergone allogeneic hematopoietic SCT. Initially, we applied low intensity conditioning with 2 Gy total body irradiation and fludarabine together with cyclosporine A and mycophenolate mofetil for patients with solid tumors. However, the high risk of graft rejection prompted us to switch to slightly stronger conditioning (RIC) using fludarabine and cyclophosphamide.[8,18]

In this non-randomized study we compared low intensity conditioning with RIC in patients undergoing allogeneic hematopoietic SCT for solid tumors.

Design and Methods

Patients and donors

Forty-eight patients with solid tumors were treated with low intensity conditioning or RIC and allogeneic hematopoietic SCT at Karolinska University Hospital, Huddinge between August 1999 and November 2004. As one patient with renal cell cancer was grafted twice due to initial rejection, a total of 49 procedures were performed. With the exception of two patients, each patient had undergone debulking of the primary tumor before SCT.

Patients with advanced primary liver cancer were treated with orthotopic liver transplantation.[13] The debulking procedure occurred a median of 8 weeks (range, 2-19) before allogeneic hematopoietic SCT. In hepatocellular cancer the isolated central tumors were > 10 cm large or multiple tumors. Patients with cholangiocarcinoma had tumors of any size making resection impossible. Both tumor types were still confined to the liver, according to radiological investigations.

Peripheral blood stem cells were collected from the donor after stimulation with granulocyte colony-stimulating factor (G-CSF) (Neupogen®, Amgen, Stockholm, Sweden).[19] Before August 2001, G-CSF was also given from day +10 after SCT until neutrophil engraftment.

The characteristics of the patients and donors in the groups receiving the two different conditioning regimens are presented in Table 1.

Typing of the human leukocyte antigens (HLA) was performed in patients and donors using polymerase chain reaction (PCR) amplification with sequence-specific primers for HLA classes I and II with allele level resolution.[20] All donors were HLA-A, -B, and DRB1 compatible with the recipient. A graft from an HLA-identical sibling donor was preferred; if this was unavailable, a graft from an HLA-matched unrelated donor was used (Table 1).

The Research Ethics Committee at Karolinska University Hospital, Huddinge approved the two study protocols. All patients gave written informed consent. Some of the patients with solid tumors, have been reported previously.[8,10,13,18,21]

Conditioning

Low intensity conditioning consisted of fludarabine 30 mg/m^2/day for 3 days in sibling transplants and for 5 days in grafts from HLA-matched unrelated donors, followed by 2 Gy total body irradiation.[8,22] After May 2001, total body irradiation was replaced by cyclophosphamide 60 mg/kg/day for 2 days in the RIC group.[18] Recipients of grafts from HLA-matched unrelated donors were given 2 mg/kg/day of antithymocyte globulin (Thymoglobuline, Genzyme, Cambridge, MA, USA) for 2 days (Table 1).[8]

Graft-versus-host disease prophylaxis

Graft-versus-host disease (GvHD) prophylaxis consisted of cyclosporine A (Novartis Pharma AG, Basel, Switzerland) for up to 3 months combined with mycophenolate mofetil (Hoffmann-La Roche, Basel, Switzerland) in the low intensity conditioning regimen or methotrexate in the RIC regimen. The cyclosporine A doses ranged between 3-12.5 mg/kg/day to achieve a trough level of 100 ng/mL in patients with a sibling donor, or 250 to 300 ng/mL in patients with a HLA-matched unrelated donor.[23,24] Mycophenolate mofetil was administered at the dose of 15 mg/kg twice a day for 35 days if the donor was a sibling and for 45 days if the donor was unrelated.[4,8,22] Methotrexate was administered at the dose of 15 mg/m^2 on day 1 and at the dose of 10 mg/m^2 on days 3, 6, and 11.[25,26]

Patients who underwent combined orthotopic liver transplantation and SCT continued to receive immunosuppression to protect against rejection of the liver graft. This immunosuppression consisted of either cyclosporine A (n=3) or tacrolimus (n=8) (Astellas Pharma, Munich, Germany) in combination with steroids. The tacrolimus doses ranged between 0.05-0.1 mg/kg/day orally to achieve a trough level between 10 and 15 ng/mL.[13] After SCT, cyclosporine A or tacrolimus was combined with mycophenolate mofetil or methotrexate (Table 1).

Rejection, engraftment, and graft-versus-host disease

Acute liver graft rejection was defined using histopatological evaluation of liver biopsies.[27] Rejection of stem cells was defined as less than 1% donor CD3$^+$ cells in peripheral blood samples.

The day of engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count

>0.5×10⁹/L. The diagnosis and treatment of acute and chronic GvHD have been described elsewhere.[23,28,29]

Chimerism

Chimerism using PCR amplification of a variable number of tandem repeats (until 2003) and short tandem repeats was analyzed in peripheral blood from the donor and recipient before transplantation, and from the recipient on days +14, +21, and +28, and every other week for 3 months, and monthly thereafter until complete donor chimerism was achieved. To evaluate lineage-specific chimerism, CD3⁺, CD19⁺, and CD45⁺ cells were selected from peripheral blood using immunomagnetic beads (Dynal, Oslo, Norway), as previously described.[21,30] Complete donor chimerism was defined as 100% donor cells, whereas mixed chimerism was defined as 1-99% donor cells.

Infections

Bacteremia was defined by the finding of a positive blood culture related to a febrile episode (≥ 38.5°C).

Cytomegalovirus infection was defined as isolation of the cytomegalovirus or detection of viral proteins or nucleic acid in any body fluid or tissue specimen,[31] which was achived by semi-quantitative PCR in the earlier part of the study[32] and later by real-time TaqMan PCR.[33] Cytomegalovirus disease was defined as symptomatic organ involvement such as pneumonia, hepatitis, colitis, and retinitis and detection of virus in the affected organ.[31] Invasive fungal infection was defined as a positive blood culture and/or positive cultures for *Candida* or *Aspergillus* species from at least two sterile body fluid or tissue samples. The supportive therapies against bacterial, viral, and fungal infections were those used according to the SCT protocol of the Center.[23]

Adjuvant cell infusions

Donor lymphocyte infusions were given every 4 weeks in escalating doses, starting with 0.5 or 1×10⁶, followed by 5 or 10×10⁶, and then 100×10⁶ CD3⁺ cells/kg recipient body weight. Infusions of donor-derived *ex vivo* long-term expanded mixed natural killer (NK) cells and natural killer T (NKT) cells with or without interleukin-2 were given according to an experimental phase I study.[34] The NK/NKT cell infusions were given every 4 weeks in escalating doses, starting with 1×10⁶, followed by 10×10⁶, and then 100×10⁶ CD3⁺ cells/kg recipient body weight. Donor lymphocyte and NK/NKT cell infusions were given without immunosuppressive therapy. Indications for both cell infusions were tumor progression and/or mixed chimerism in the absence of GvHD.

Evaluation of tumor response

The tumor load was examined by computer tomography of the thorax and abdomen before SCT and every third month after SCT. The tumor response was evaluated on the international response evaluation criteria in solid tumors (RECIST).[35] A complete response was defined as complete disappearance of all evidence of disease and no new lesions or disease-related symptoms for more than 1 month. A partial response was defined as at least a 30% decrease in the sum of the longest diameters of metastatic lesions compared with tumor load before SCT. Progressive disease was indicated by at least a 20% increase in the same metastatic lesions or the appearance of one or more new lesions. Stable disease was defined as neither sufficient decrease to qualify for partial response nor sufficient increase to qualify for progressive disease.

RECIST was not applicable in patients with advanced primary liver cancer because of the lack of pre-transplant metastases. Therefore, these patients were evaluated using clinical parameters based on either the results of

Table 1. Characteristics of the patients and donors.

Characteristic	*LIC n (%)*	*RIC n (%)*	*p*
Patients	23	25	
Age, median (range) years	57 (38-77)	55 (28-67)	n.s.
Sex (male/female)	14/9	19/6	
Donors			
Age, median (range) years	47 (28-71)	39 (23-63)	.02
Sex (male/female)	16/7	19/6	
Sibling	14 (61)	11 (44)	n.s.
Matched unrelated donor	9 (39)	14 (56)	n.s.
Diagnoses			
Renal cell cancer	11 (48)	6* (24)	n.s.
Colorectal cancer	6 (26)	9 (36)	n.s.
Advanced primary liver cancer**	4 (17)	7 (28)	n.s.
Prostate cancer	0 (0)	2 (8)	
Breast cancer	1 (4)	0 (0)	
Klatskin tumor	1 (4)	0 (0)	
Sarcoma in the kidney	0 (0)	1 (4)	
Conditioning			
Fludarabine + TBI	23	0	
Fludarabine + Cy	0	25	
GvHD prophylaxis			
CsA + MMF	19 (83)	0 (0)	
CsA + MTX	1 (4)	20 (80)	
Tacrolimus + MMF	3 (13)	0 (0)	
Tacrolimus + MTX	0 (0)	5 (20)	
Antithymocyte globulin			
Thymoglobulin	9 (39)	14 (56)	n.s.
OKT-3	0 (0)	1 (4)	
G-CSF post-SCT	22 (96)	3 (12)	<.001
Graft source			
Peripheral blood stem cells	22 (96)	24 (96)	n.s.
Bone marrow	1 (4)	1 (4)	n.s.
Graft cell dose, median (range)			
ANC×10⁸	11.0 (4.1-25.3)	11.1 (2.7-18.7)	n.s.
CD34+ cells×10⁶	7.2 (2.4-28.0)	8.6 (1.5-20.0)	n.s.
Engraftment, median (range) dys	0 (0-28)	16 (11-22)	<.001
Donor lymphocyte infusion			
No. of patients	12 (52)	19 (76)	n.s.
No. of DLI, median (range)	2 (1-11)	3 (1-8)***	n.s.
Day of first DLI, median (range)	137 (44-354)	96 (49-313)	n.s.

*ANC indicates absolute neutrophil count; CsA: cyclosporine A; Cy: cyclophosphamide; G-CSF: granulocyte colony-stimulating factor; GvHD: graft-versus-host disease; LIC: low intensity conditioning; MMF: mycophenolate mofetil; MTX: methotrexate; OKT-3, anti CD3 monoclonal antibody; RIC, reduced intensity conditioning; Sibling, HLA-identical sibling; TBI, total body irradiation. *6 patients but 7 grafts.**patients with advanced primary liver cancer underwent orthotopic liver transplantation before stem cell transplantation.*** including infusions of ex vivo expanded mixed donor natural killer/natural killer T cells in four patients.*

computer tomography (thorax and abdomen), bone scans, and magnetic resonance imaging of liver, bile ducts, and pancreas, performed according to the same time schedule after SCT as for the other solid tumor patients, or autopsy examinations. A patient with non-metastatic advanced primary liver cancer after orthotopic liver transplantation and SCT was evaluated as having a complete response.

All patients with a complete response, partial response, or stable disease were considered to have had a graft-versus-tumor effect after SCT.

Statistical analysis

The probability of overall survival was calculated according to the Kaplan and Meier method. Times to transplant-related death, response, acute GvHD, and chronic GvHD were estimated using a non-parametric estimator of cumulative incidence curves. Competing events for transplant-related mortality were death in progressive disease for response, death without response, and death without GvHD. Patients were evaluated for tumor response and chronic GvHD if they survived more than 90 days. The differences between numbers of days to complete donor chimerism in T and B cells were compared using the Mann-Whitney U test. Analyses were performed using the cmprsk package (developed by Gray, June 2001), Splus 6.2 software, and Statistica software (Statsoft Inc, Tulsa, OK, USA). A p-value <0.05 was considered statistically significant.

Results

The median age of the donors was 47 (28-71) years in the low intensity conditioning group and 39 (23-63) years in the RIC group (p=0.02) (Table 1).

Rejection and engraftment

One patient with advanced primary liver cancer was diagnosed as having acute liver graft rejection after SCT, but was successfully treated with steroids. Rejection of stem cells occurred at a median of 69 (33-166) days in the low intensity conditioning group and 48 (26-69) days after SCT in patients who had received RIC (p=n.s.). No significant difference in the number of patients suffering from stem cell rejection was observed between the two groups (Table 2). The median time of neutrophil engraftment was 0 (range, 0-28) days in patients given low intensity conditioning and 16 (11-22) days in those given RIC (p<0.001) (Table 1). The number of G-CSF-treated patients was higher in the low intensity conditioning group than in the RIC group (96% *vs.* 12%, p<0.001) (Table 1).

Chimerism

Complete donor chimerism of T cells developed in 13 (57%) patients after low intensity conditioning at a median of 60 (13-234) days and in 19 (76%) patients after RIC at a median of 76 (15-180) days after SCT (p=n.s.) (Figure 1A). Complete donor chimerism in B cells developed in 18 (78%) patients who had received low intensity conditioning at a median of 28 (12-74) days and in 16 (64%) patients given RIC at a median of 97 (15-283) days after SCT (p<0.001) (Figure 1B).

Graft-versus-host disease

No significant differences in the cumulative incidences of acute GvHD grades II-IV (45% *vs.* 38%; p=n.s.) or chronic GvHD (30% *vs.* 22%; p=n.s.) were seen between the low intensity conditioning and RIC groups.

Infections

Likewise, no significant differences were found in the incidences of bacteremia (Table 2) or cytomegalovirus infection or cytomegalovirus disease between the two groups. All patients with cytomegalovirus disease suffered from acute GvHD-associated inflammation of the gastrointestinal tract. No fungemia was diagnosed.

Adjuvant cell infusions

The number of DLI and the number of patients who received DLI were equal in the two groups (Table 1). *Ex vivo* long-term expanded NK/NKT cells were infused start-

Table 2. Results on stem cell rejection, graft-versus-host disease, infections and outcome.

Characteristic	*LIC n (%)*	*RIC n (%)*	*p*
Rejection	6 (26)	3 (12)	n.s.
Acute GvHD*			
Grade 0	8 (35)	10 (40)	
Grade I	6 (26)	6 (24)	
Grade II	8 (35)	8 (32)	
Grade III-IV	1 (4)	1 (4)	
Chronic GvHD			
Limited	3 (16)	0 (0)	
Acute GvHD post-DLI			
Grade 0	9 (75)	9 (47)	
Grade I	1 (8)	1 (5)	
Grade II	0 (0)	6 (32)	
Grade III-IV	2 (17)	3 (16)	
Chronic GvHD post-DLI			
Limited	3 (25)	5 (26)	
Bacteremia	5 (22)	11 (44)	n.s.
Viral infections			
CMV infection	21 (91)	19 (76)	n.s.
CMV disease	1 (4)	2 (8)	n.s.
Outcome			
Alive	0 (0)	7 (28)	
Alive > 1 year post-SCT			
Renal cell cancer	4 (36)	2 (33)	
Colorectal cancer	1 (17)	6 (67)	
Advanced primary liver cancer	1 (25)	5 (71)	
Dead	23 (100)	18 (72)	
Transplant-related cause	8 (35)	5 (20)	
Progressive disease	15 (65)	13 (52)	n.s.

*CMV: cytomegalovirus; DLI: donor lymphocyte infusion; GvHD: graft-versus-host disease; LIC: low intensity conditioning; RIC: reduced intensity conditioning; SCT: stem cell transplantation; *the maximum grade of GvHD before DLI.*

ing at a median of 407 (352-856) days after SCT and were given to four patients with RIC without development of acute GvHD (Table 1). No significant difference in the incidence of acute GvHD grades II-IV after DLI was found between the two groups (Table 2).

Tumor response

Tumor response was evaluated excluding patients who died within 3 months after SCT (two with renal cell cancer, one with advanced primary liver cancer, and one with primary liver cancer who did not undergo orthotopic liver transplantation) (Table 3). All patients who rejected their stem cell grafts were included in the tumor evaluation. No significant difference in the incidence of tumor response was found between the two conditioning groups (Figure 2A). Furthermore, no significant difference in the incidence of tumor response for all tumor types except advanced primary liver cancer was found between the two groups (*Figure S1, online supplement*). The most favorable tumor response was found in patients with advanced primary liver cancer (70% *vs.* 32% for all other tumor types p=0.018) (*Figure S2, online supplement*). No significant difference in the incidence of tumor response for advanced primary liver cancer was found between the two groups (*Figure S3, online supplement*). Tumor response was, however, more common in patients receiving adjuvant cell

Table 3. Tumor response according to RECIST in patients with solid tumors.

Tumor type	Tumor response, n (%)			
	CR	PR	SD	PD
Renal cell cancer, n=15	0 (0)	1 (7)	2 (13)	12 (80)
Colorectal cancer, n=15	0 (0)	0 (0)	6 (40)	9 (60)
Prostate cancer, n=2	0 (0)	0 (0)	2 (100)	0 (0)
Breast cancer, n=1	0 (0)	0 (0)	0 (0)	1 (100)
Sarcoma, n=1	0 (0)	0 (0)	0 (0)	1 (100)
Advanced primary [liver cancer, n=10*	6 (60)	0 (0)	1 (10)	3 (30)

*CR: complete response; PD: progressive disease; PR: partial response; RECIST: response evaluation criteria in solid tumors; SD: stable disease. *patients with advanced primary liver cancer not evaluated according to RECIST.*

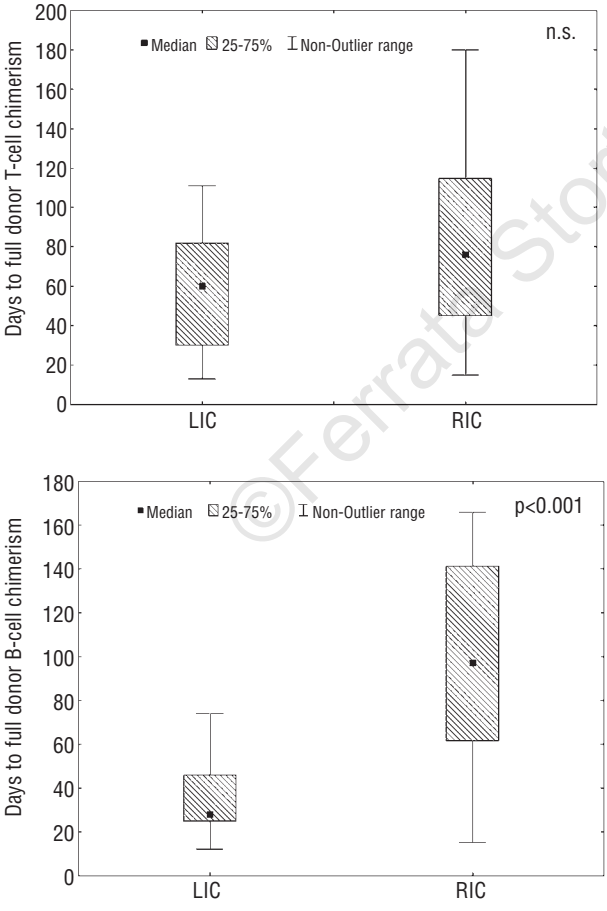

Figure 1. Days to complete donor chimerism in patients with solid tumors after allogeneic hematopoietic stem cell transplantation. The boxplots show the range of days to complete donor chimerism after low intensity conditioning (LIC, n=23) and reduced intensity conditioning (RIC, n=25) in: A) T cells (LIC, median 60 (13-234) days; RIC, median 76 (15-180) days), and B) B cells (LIC, median 28 (12-74) days; RIC, median 97 (15-283) days).

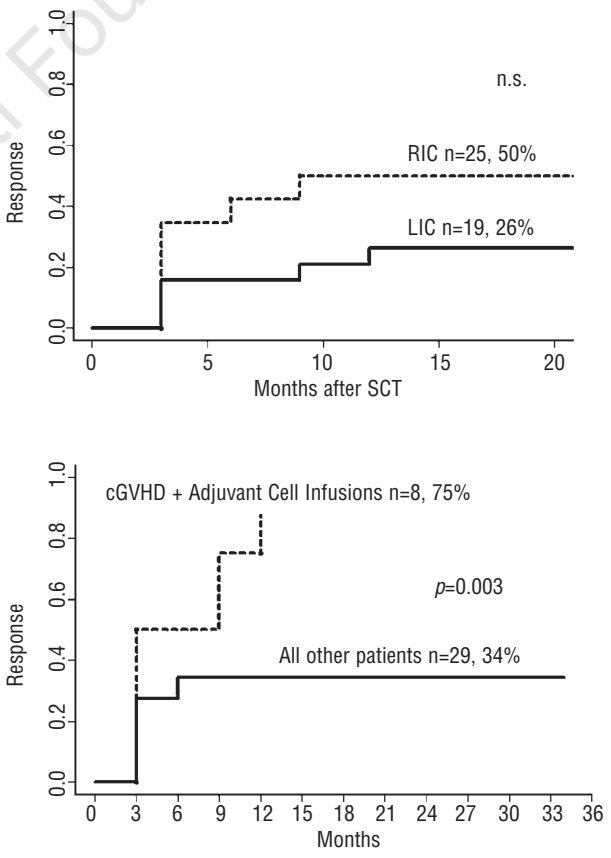

Figure 2. Tumor response in patients with solid tumors after allogeneic hematopoietic stem cell transplantation. The cumulative incidence of tumor response is shown in: A) patients who were treated with low intensity conditioning (LIC, n=19, 26%) or reduced intensity conditioning (RIC, n=25, 50%), and B) patients who were received adjuvant cell infusions and who developed chronic graft-versus-host disease (cGvHD) (cGvHD+Adjuvant Cell Infusions, n=8, 75%) compared to all other patients (n=29, 34%).

infusions and who developed chronicGvHD either before or after the cell infusions (75% *vs.* 34% of all other patients p= 0.003) (Figure 2B).

Transplant-related mortality

No significant differences in the incidences of transplant-related mortality and progressive disease were found with respect to the type of conditioning (Table 2).

Overall survival

Seven patients, all receiving RIC, were alive as of November 2005 with a median follow-up of 32 (12-36) months after SCT. Prolonged survival beyond 1-year after SCT for the tumor types and the two groups are presented in Table 2. The probability of overall survival according to the type of conditioning is presented in Figure 3 (17% *vs.* 30% at 2-years, p=0.05).

Discussion

In this study, we examined the factors that influenced the outcome of allogeneic hematopoietic SCT based on 6 years of experience with solid tumor patients using either low intensity conditioning or RIC. Changing low intensity conditioning to RIC resulted in a longer neutropenic phase and development of T-cell before B-cell chimerism. In the low intensity conditioning group, patients were treated with G-CSF after SCT. This may partly explain the shorter time for neutrophil engraftment[36-38] and fewer bacterial infections. A stronger effect of cyclophosphamide and prolonged fludarabine treatment used in RIC may have caused more effective suppression of the patient's immunocompetent cells (T cells and antigen-presenting cells) as compared to low intensity conditioning, leading to an increased risk of early bacterial infections.

The significantly lower number of G-CSF-treated patients in the RIC group was expected, given our previous findings of a higher incidence of acute GvHD grades II-IV in patients with hematologic malignancies treated with low intensity conditioning, a result that prompted us to discontinue G-CSF treatment in RIC.[36,39] In the present study, we did not find an increased risk of acute GvHD in G-CSF-treated patients. Neither did we find a correlation between the risk of acute GvHD, one of the main causes of early transplant-related mortality, using the two conditioning treatments. There was no significant difference between the two conditioning regimens concerning the incidence of graft rejection. We used chimerism analysis of $CD3^+$ cells to define rejection. To better predict rejection, NK cells may also be included in the chimerism analysis. Less than 50% of donor T and NK cells on day 14 after SCT has indicated an increased risk for rejection in patients given low intensity conditioning.[40]

The age of the donors was lower for patients transplanted with RIC was lower, which could be explained by a larger proportion of unrelated donors for this group. However, the stem cell dose was comparable between the patients in the two conditioning groups.

There was no significant difference between the conditioning groups in the incidence of the graft-versus-tumor effect. In the absence of an association with the type of conditioning, the graft-versus-tumor effect was strengthened by adjuvant cell infusions together with chronic GvHD, which was also demonstrated in a larger series of patients with renal cell cancer.[10] The effect of DLI and GvHD seems to support the allogeneic graft-versus-tumor effect, which has been shown to be associated with $CD8^+$ T cells in renal cell cancer patients.[41,42] One might postulate that T- and NK-cell functions of DLI trigger the development of chronic GvHD. This would induce a pro-inflammatory cytokine and chemokine environment, supporting the migration of the lymphocytes of donor origin towards tumor cells. Thus, infusion of donor's NK/NKT-cells could be a valuable alternative to DLI. None of the patients who received NK/NKT cell infusions developed acute GvHD. In the present study, no difference was found in the incidence of severe acute GvHD grades III-IV after DLI between the groups given the two conditioning regimens. However, 32% of patients with RIC developed acute GvHD grade II after DLI, whereas none of those receiving low intensity conditioning did so. This may imply that acute GvHD grade II is desirable for the graft-versus-tumor effect in solid tumor patients, reflecting the tendency towards prolonged survival in patients given RIC. That overall survival was longest for patients with advanced primary liver cancer might be due to the fact that these patients are younger (median 48 years) than patients with renal cell and colorectal cancer (median ages of 58 and 60 years, respectively). The overall survival for renal cell and colorectal cancer patients was also longer than that achieved with even the most modern combinations of oncological treatments for metastatic disease. Indeed,

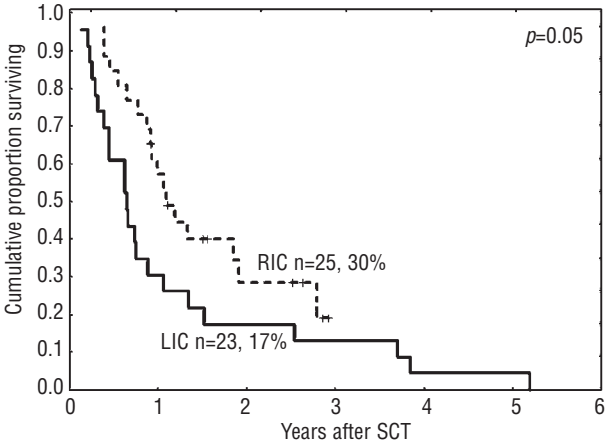

Figure 3. Overall survival for patients with solid tumors after allogeneic hematopoietic stem cell transplantation. The cumulative incidence of overall survival is shown for patients who were treated with low intensity conditioning (LIC, n=23, 17%) or reduced intensity conditioning (RIC, n=25, 30%).

patients should have an expected survival of at least 1 year before allogeneic SCT is undertaken, even using low intensity conditioning or RIC.

Although progress has been made, with a tendency for survival to be longer in the present series following the change from low intensity conditioning to more intense conditioning, the majority of patients (irrespective of tumor type) died in progressive disease. In our study, the mortality rate from progressive disease was 65% in the low intensity conditioning group and 52% in the group given RIC, reflecting the clinical practice of using SCT for patients with a lower metastatic load. Published results on progressive disease vary between 17-40% in patients with renal cell,[7,10,43] breast[6,9,14] and ovarian cancer.[15] However, in most studies only sibling donors were considered, so the conditioning regimens did not include antithymocyte globulin and caused less immunological imbalance.

The results could potentially be improved by a better selection of patients. Allogeneic SCT could be given only to patients with stable disease at the time of the transplantation, preferably after a few months of follow-up of the tumor status. Furthermore, suppression of the tumor and its progression may be undertaken before and after SCT combined with adjuvant cell therapies, as donor-derived immune cells allow the allogeneic graft-versus-tumor effect. Stereotactic irradiation, radiofrequency ablation, and surgery of metastases in combination with new drugs, such as antibodies against vascular endothelial growth factor and epidermal growth factor, may act in synergy, together with allogeneic SCT, against tumors.[44,45]

Authorship and Disclosures

RC designed the study in co-operation with the other authors and collected the clinical data. LB is in charge of the solid tumor program at our center and took clinical responsibility for the study. KC evaluated tumor responses according to the international RECIST. MR was responsible for the statistical analyses. LB, OR, and MR were in charge of the study design, critical analysis of the results and preparation of the manuscript. The results and manuscript draft were completed by RC. All co-authors actively participated in the preparation of the manuscript. The authors reported no potential conflicts of interest.

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