Netherlands
The Journal of Medicine

Reduced-intensity conditioning regimens in malignant haematological diseases

T.E. Buffart, J.J.W.M. Janssen, P.C. Huijgens*

Department of Haematology, VU University Medical Centre, Amsterdam, the Netherlands, tel.: +31 (0)20-444 26 04, fax: +31 (0)20-444 26 01, *corresponding author

ABSTRACT

Allogeneic stem cell transplantation is a potentially curative procedure for patients with haematological malignancies. Conventional, myeloablative conditioning is, however, poorly tolerated by patients of advanced age, those receiving second transplants and those with concomitant diseases. Based on recognition of the importance of a graft-versus-disease (GVD) effect in curing malignant haematological disease, reduced intensity conditioning (RIC) as preparation for allogeneic stem cell transplantation has been developed for these patients. Although large prospective randomised clinical trials with significant follow-up are lacking, transplant-related morbidity and mortality of RIC transplants seem to compare favourably with conventional conditioning in this group of patients.

INTRODUCTION

High-dose myeloablative chemotherapy followed by allogeneic haematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for several haematological malignancies. Prior to the infusion of donor stem cells, high-dose chemotherapy and/or radiotherapy, collectively called 'conditioning', is used to eliminate the disease. In addition, immunosuppressive drugs are administrated to prevent graft rejection and extensive graft-versus-host disease (GVHD), which, in its acute form, is featured by potentially life-threatening allogeneic T-cell responses primarily affecting the immune system, skin, intestinal tract and liver. Patients undergoing HSCT therefore experience a prolonged period of profound immunodeficiency, which renders them highly susceptible to opportunistic, potentially life-threatening, infections. The risk of regimen-related toxicity and graft-versus-host disease rises with increasing age and poor performance status of the patient. Although allogeneic transplantation after myeloablative conditioning has been successfully performed in patients over the age of 60, this procedure is generally limited to younger patients (<55 to 60 years) in good health status.[1-7] Since the median age for many haematological malignancies to occur is over 50 years, only a minority of patients can benefit from myeloablative allogeneic HSCT.[2]

In the past years, it has become increasingly evident that the curative potential of HSCT is not primarily due to the myeloablative conditioning regimen. The graft-versus-disease (GVD) effect, i.e. allo-reactivity of donor immune cells against the host's tumour, plays a major role in controlling or even eradicating the patient's malignancy.[2,8] This phenomenon was first described in chronic myeloid leukaemia (CML), in which relapses were successfully treated with donor lymphocyte infusions (DLI). Responses to DLI and a GVD effect were not only seen in patients with CML, but also in patients with other haematological malignancies who relapsed after allogeneic transplantation.[9,10] This implicates that the intensity of the conditioning regimen may not be as important as previously believed and less aggressive preparative treatments may be suitable if the immunosuppressive effect of the regimen is sufficient to establish donor engraftment.[3] Recognition of the importance of this GVD effect for success in allogeneic HSCT for haematological malignancies has led to a new therapeutic strategy, reduced intensity conditioning (RIC) transplantation (synonyms: reduced

intensity stem cell transplantation (RIST), reduced intensity transplant (RIT), 'mini'-transplant).[4,5,11,12] The purpose of RIC is to enhance tolerance of the host to the graft while permitting the establishment of donor haematopoiesis and using antidisease properties of donor lymphocytes for disease eradication, at the same time avoiding the extensive early toxicity of standard myeloablative HSCT.[4,11] By exploiting the GVD effect and reducing the toxicity of the transplantation,[3,13] elderly patients, recipients of second transplants and patients with severe concomitant other organ disease, who are at high risk of transplant-related mortality (TRM), may be successfully treated by this new RIC approach.[8,14]

REDUCED INTENSITY CONDITIONING

The use of donor lymphocyte infusions (DLI) and recognition of a GVD effect have been central to the philosophy of RIC stem cell transplantation. Differences in susceptibility to GVD effects are seen among different malignancies, as shown in *table 1*.[15] Patients with chronic myeloid leukaemia are most likely to respond, but responses have also been seen in patients with acute myeloid leukaemia, chronic lymphocytic leukaemia, myeloma and lymphoma. Patients with acute lymphoblastic leukaemia (ALL) seem least likely to respond.[16-18] Recognition of this potency of DLI has driven the development of RIC regimens, which are increasingly being used for allogeneic HSCT.

Several regimens have been investigated in an attempt to reduce procedure-related toxicity in elderly or heavily pretreated patients, or in patients with medical comorbidities precluding the use of myeloablative preparative regimens.[19] Most protocols for RIC regimens use fludarabine combined with low-dose total body irradiation (TBI),[20] low-dose cyclophosphamide[15,21,22] or high-dose alkylating agents such as melphalan.[8,12,23,24] Examples of different RIC regimens are shown in *table 2*. Reported TRM of these regimens varies between 15 and 20%,[19,25,26] which is low compared with conventional conditioning considering

Table 1

Complete response rates after donor lymphocyte infusion (DLI) in different haematological diseases

DIAGNOSIS		INCIDENCES OF COMPLETE RESPONSES AFTER DLI
Chronic myeloid leukaemia:	Overall	60%[9]
	Chronic phase	76%
	Accelerated phase	33%
	Blastic phase	17%
Acute myeloid leukaemia/myelodysplastic syndrome		15-26%[9,18]
Acute lymphoblastic leukaemia		3-15%[9,18]
Chronic lymphocytic leukaemia		29%[60]
Multiple myeloma		5-29%[18,67]

Table 2

Reduced intensity conditioning regimen

HOUSTON[23]	LONDON[36]
Fludarabine (25 mg/m²) x 5	Fludarabine (25 mg/m²) x 5
Melphalan (90 mg/m²) x 2; or (140 mg/m²) x 1	Cyclophosphamide (1 g/m²) x 2
PBSCT	PBSCT/BMT
GVHD prophylaxis: tacrolimus/methotrexate	GVHD prophylaxis: cyclosporine/methotrexate
HOUSTON[74]	**BARCELONA[78]**
Fludarabine (25 mg/m²) x 5	Fludarabine (30 mg/m²) x 5
Cyclophosphamide (1g/m²) x 3	Melphalan (70 mg/m²) x 2 or (80 mg/m²) x 1 or busulphan
ATG (20 mg/kg) x 3	(1 mg/kg x 10 doses) x 3
PBSCT/BMT	PBSCT
GVHD prophylaxis: tacrolimus or cyclosporine/methotrexate	GVHD prophylaxis: cyclosporine A/methotrexate
JERUSALEM[52]	**SEATTLE[20]**
Fludarabine (30 mg/m² daily, 5 days)	Fludarabine (30 mg/m²) x 3
Busulphan (4 mg/kg daily, 2 days)	TBI 200 cGy TBI (dual cobalt source or linear accelerator, 7 cGy/min)
ATG (10 mg/kg) x 4	
PBSCT	PBSCT
GVHD prophylaxis: cyclosporine/methotrexate	GVHD prophylaxis: cyclosporine/MMF

PBSCT = peripheral blood stem cell transplantation; GVHD = graft-versus-host disease; BMT = bone marrow transplantation; ATG = antihuman T-lymphocytes globulin; TBI = total-body irradiation; MMF = mycophenolate mofetil.

the advanced age and concomitant disease or previous treatments of the patients receiving these transplants. Fludarabine is an effective immunosuppressive, rather than myeloablative, agent. It eliminates T-cells and is used to augment pretransplantation immunosuppression in order to improve the engraftment of donor cells for a better exploitation of the GVD effect.[2,15] In addition, to reduce the frequency of acute GVHD, T-cell depletion (TCD) by anti-lymphocyte serums such as antithymocyte globulin (ATG) and CAMPATH-1H is used in some protocols.[14,19,24,27,28] A dose-dependent effect of ATG on acute GVHD was shown by Mothy *et al.* with a tendency toward better progression-free survival (PFS) for patients receiving a low ATG dose as compared with patients receiving a high ATG dose (25 and 22% respectively).[19] A disadvantage of TCD is the increased rejection rate seen in TCD RICs. However, a formal comparison between T-cell undepleted and depleted RIC as concerns, for example, overall survival has not yet been made.

The occurrence of moderate to severe GVHD increases the risk of life-threatening infections.[19,26,29,30] On the other hand, GVHD also has a beneficial role since it is associated with decreased risk of disease progression in several studies.[12,19,25,31,32] As GVHD is poorly tolerated by elderly or debilitated patients, this can explain higher rates of TRM after RIC in patients ≥60 years (TRM 18% <60 years *vs* 35% ≥60 years) as shown by Gómez-Núñez *et al.*[25] However, TRM appears to be unacceptably high (>50%), only in the presence of additional adverse factors, such as poor performance score and a previous autologous HSCT. Therefore, age itself should not preclude RIC transplants. A conditioning regimen based on a combination of the antitumour and immunosuppressive activity of melphalan and the immunosuppressive activities of both melphalan and fludarabine was developed by the MD Anderson group. They reported consistent engraftment and durable remissions in some patients with advanced haematological malignancies,[33] which was subsequently confirmed by other groups. In combination with ATG, it also leads to engraftment in recipients of matched unrelated donor grafts.[23]

DLI can be used in addition to RIC regimens to enhance the GVD effect.[11] Indications for DLI after RIC allografts are mixed donor and recipient chimerism, disease progression, failure of the transplantation to achieve a complete remission, and as pre-emptive treatment against disease relapse or on the assumption that they may eliminate undetectable minimal residual disease.[5,19,34-36] Complications of DLI are acute and chronic GVHD and especially pancytopenia,[9] probably due to depletion of host-derived normal haematopoiesis from the marrow. Timing and dosage of DLI should therefore be adapted accurately to chimerism and tumour response.[5]

TOXICITY OF REDUCED INTENSITY CONDITIONING REGIMENS

Toxicity of treatment can be divided into regimen-related toxicity and toxicity associated with GVHD. In general, short-term regimen-related toxicities are mild after RIC treatment,[25] but they may still be significant, depending on the conditioning regimen that is used. As the dose of melphalan in the fludarabine-melphalan regimen is 140 to 180 mg/m^2, significant mucosal, pulmonary, renal, hepatic and cardiac toxicity is to be expected[33,37] and was, in fact, not different from that observed in parallel studies by Besien *et al.* in patients treated with conventional regimens including TBI.[33]

Martino *et al.* showed no significant differences in the probability of infection-related mortality between a standard conditioning regimen and a RIC regimen consisting of fludarabine in combination with busulphan or melphalan, 19 and 17% respectively, although less *Streptococcus viridans* septicaemias and CMV infections were seen in the RIC group.[26] Similar rates of infection between RIC and HSCT are contradictory to the assumption that a nonmyeloablative regimen in RIC should lead to fewer infections. A possible explanation could be the profound immunodeficiency due to immunosuppressive treatment against GVHD. Moreover, median age of patients receiving conventional HSCT was lower compared with patients receiving RIC, 38 and 54 years respectively.

Toxicity of the gastrointestinal (GI) tract is currently one of the most important dose-limiting factors for high-dose treatment with autologous or allogeneic, haemopoietic stem cell support.[38] Clinical GI toxicity of RIC transplants has been reported as being very moderate, depending on the regimen used.[28,38] Also, preclinical studies offer good reasons for the assumption that allogeneic transplantation with RIC causes less damage to the gut mucosa barrier than myeloablative conditioning.[22] Therefore, Johansson *et al.* investigated the intestinal barrier function in patients undergoing HSCT with RIC.[38] A significant increase in intestinal permeability during transplantation was measured in patients who received conventional, myeloablative conditioning, while patients receiving RIC did not develop any significant increase in intestinal permeability. All patients receiving myeloablative therapy were in need of therapy against GI toxicity (nausea/vomiting, oral pains, and/or diarrhoea) during transplantation, while only two out of nine RIC transplant patients needed this therapy. Most patients receiving RIC were able to continue enteral feeding during the transplant course.[38]

A frequent and often lethal complication of bone marrow transplantation is veno-occlusive disease (VOD). VOD is a

clinical syndrome resulting from hepatic toxicity, appearing shortly after bone marrow transplantation and is characterised by hyperbilirubinaemia, fluid retention, and painful hepatomegaly.[39,40] Results of previous studies have shown incidences of VOD ranging from 0 to 70% and mortality of VOD ranging from 20 to 50%, depending on the diagnostic criteria used in each study.[41] After RIC, the incidence of VOD is clearly reduced. In a study of 21 patients by Mothy *et al*. VOD was observed in one out of 21 patients (5%) with haematological malignancies receiving RIC and Picardi *et al*. observed no VOD of the liver in their study of 22 patients receiving RIC.[42,43] These data are especially impressive since patients who were given RIC allo-transplants had often already been extensively pretreated.

A common complication of conventional HSCT with myeloablative conditioning regimens is haemorrhagic cystitis (HC), which may result from cyclophosphamide in the conditioning regimen or from viral infection. Yamamoto *et al*. investigated HC following RIC.[44] HC was defined as two or more episodes of macroscopic haematuria in sterile urine with normal coagulation status, without any history or evidence of renal stones or genitourinary malignancy. HC was associated with immunosuppression, which can be brought about by GVHD prophylaxis. Also, busulphan use in the preparative regimen increased the risk of HC. The incidence of HC after RIC was not significantly different from that following conventional HCST (11.7% following RIC and 9.7% following conventional HSCT). However, HC after RIC tended to be milder, with lower blood transfusion requirements and the duration was shorter compared with conventional HCST.[44]

Although there is a beneficial GVD effect associated with GVHD, toxicity of acute and chronic GVHD remains a major problem, also after RIC. Incidences of acute and chronic GVHD are comparable between RIC and conventional HSCT;[20,23] however, a delayed onset of acute GVHD is frequently seen after RIC.[45,46] Moreover, patients receiving RIC often show clinical features of acute and chronic GVHD simultaneously,[47] questioning the usefulness of the standard definitions of acute and chronic GVHD, where chronic GVHD was categorised as all GVHD occurring after more than 100 days. GVHD severity partly depends on GI toxicity, since translocation of bacteria and/or endotoxin to the systemic circulation is a potent stimulator of release of inflammatory cytokines, which are important mediators of GVHD. Reduced dose intensity of conditioning caused less intestinal toxicity and a subsequent reduction of acute GVHD.[48] To improve safety and outcome of transplantation, prevention and treatment of GVHD should be further explored without abrogating the GVD effect, possibly by modulation of immunosuppressive schedules or manipulation of T-cell subsets in the stem cell graft.

CLINICAL RESULTS

Chronic myeloid leukaemia

Since very recently, imatinib, a tyrosine-kinase inhibitor, is considered the first-line treatment for chronic phase chronic myeloid leukaemia (CML). However, a small number of patients prove to be resistant to the drug or present in advanced stages of the disease, where its activity is clearly reduced. For these patients allogeneic HSCT is still a therapeutic option.

The existence of a graft-versus-disease (GVD) effect was first clinically identified[49] and later confirmed by the results of donor leucocyte infusions (DLI) in patients with CML. More than 70% of patients with CML can be curatively treated with allogeneic HSCT if they are less than 55 to 60 years of age and in the first chronic phase of the disease. Unfortunately, in older patients, and in patients with advanced disease, results remain poor.[50] Based on the recognition of the GVD effect, RIC regimens have been developed and given to patients who are not eligible for conventional allogeneic HSCT. Patients with CML seemed good candidates to evaluate RIC protocols because CML is a rather indolent disease, at least in the chronic phase.[51]

Or *et al*. reported a study of 24 patients in the first chronic phase of CML who underwent nonmyeloablative HSCT with a RIC regimen consisting of fludarabine and busulphan.[52] Recipients of matched unrelated donors also received ATG. This protocol was well tolerated, and all patients were alive at day 100 after transplantation. After a follow-up period of up to 70 months (median 42 months), three patients died as a consequence of GVHD, at day 116, 499 and 726. Both overall survival and disease-free survival were 85%, within an observation period of 7 to 63 months (median 37 months), with no patients relapsing during this period.[52]

Giralt *et al*. showed that 19 out of 27 patients with CML who were too old for conventional HSCT achieved complete remission, defined by standard morphological criteria and/or conventional cytogenetic analysis, after treatment with fludarabine and melphalan, with a probability of disease-free survival after one year of 34% for all patients.[23] Bornhäuser *et al*. described 44 patients with CML after allografting using RIC with fludarabine and busulphan.[51] They demonstrated that this treatment provided durable engraftment and low relapse rates. Although conventional conditioning remains the standard in advanced or imatinib-resistant disease, on the basis of these limited studies it can be concluded that reduced intensity conditioning should be considered in elderly patients with CML or in patients with poor performance status.

Acute myeloid leukaemia and myelodysplastic syndrome

One important option for curative treatment for myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) is allogeneic haematopoietic stem cell transplantation, in which the efficacy of allografting is partly due to the GVD effect.[49] Sibling donor transplantation for patients with AML or MDS who are older than 60 years, which is the median age for AML, has been shown to induce complete remission after RIC regimens in small series.[20,23] For this reason, several RIC regimens have been investigated in patients with MDS or AML who were considered poor candidates for conventional HSCT. In a study by Taussig *et al.* the use of a RIC regimen consisting of fludarabine and cyclophosphamide allowed allografting in patients (median age 54 years) with MDS or AML, who were not eligible for conventional allogeneic HSCT.[36] After a median follow-up of 26 months, 11 out of 16 patients were still alive, and low incidences of acute GVHD and TRM were seen after HSCT following the RIC regimen, which compares favourably with survival data of standard AML treatment in this age group.

A combination of melphalan and fludarabine was tested in 34 patients with high-risk AML and nine patients with MDS, receiving a matched unrelated donor (MUD) or a fully matched or one-antigen-mismatched related donor, by Giralt *et al.*[23] Of these, 26 achieved complete remission, with a probability of disease-free survival after one year of 26% for all patients. This study demonstrates that this RIC treatment allowed engraftment of unrelated and mismatched donors with acceptable levels of toxicity in older patients with associated comorbidities. The risk for grade III to IV GVHD was 19% for transplants from related donors and 39% for transplants from unrelated donors in this patient group, whose median age was more than 50 years. However, in most studies, disease recurrence and GVHD continue to be important causes of treatment failure.

Acute lymphoblastic leukaemia

Five-year survival of adults with acute lymphoblastic leukaemia (ALL) is less than 40%.[53] To improve survival rates of these patients, high-dose therapy followed by autologous or allogeneic HSCT has been investigated. Of all leukaemias treated with allo-HSCT, ALL was shown to be one of the least susceptible for GVD[10,15,54] probably due to the rapid kinetics of disease relapse.[55] Also, ALL was found to be unresponsive to adoptive immunotherapy with DLI.[10,55] However, Passweg *et al.* postulated a GVD effect in ALL patients, based on the finding that lower relapse risks were seen in patients with clinically manifest acute and/or chronic GVHD.[56] Also, Arnold *et al.* showed a GVD effect in their study of 22 high-risk (relapsed or Philadelphia-chromosome positive) ALL patients treated with nonmyeloablative HSCT.[57] The RIC regimen used in this study consisted of fludarabine combined with busulphan and ATG, which was more intensive compared with other protocols with reduced intensity. Four of 22 patients were alive in complete remission 5, 14, 19 and 30 months after transplant. They conclude from their study that nonmyeloablative HSCT is feasible in adult ALL patients, however only in a subgroup of patients. Promising results have been shown by Martino *et al.* in a study of 27 adult high-risk ALL patients who were ineligible for conventional allogeneic HSCT.[58] After a median follow-up of 809 days, nine patients were still alive, of whom eight were alive without disease and one with a relapse ALL on day 321. Although ALL patients may not be optimal candidates for RIC regimens and larger studies are lacking, for elderly patients or patients with severe comorbidity, RIC may be considered a therapeutic option. However, especially in ALL patients with uncontrolled disease, the chance for cure by using RIC treatment probably remains very low.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is the most frequent leukaemia in Western countries. It is characterised by clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes and spleen. The median age of patients at diagnosis is 65 years. Only 10 to 15% of the patients are less than 50 years at time of diagnosis. With a median survival of about ten years, CLL is often indolent.[59] The prognosis of patients with progressive CLL is however unfavourable, with a median survival of 24 to 72 months.[60] Reports of remission after DLI or after withdrawal of immunosuppressive drugs after allogeneic HSCT were evidence of existence of a GVD effect in CLL.[60] However, TRM after conventional myeloablative allogeneic HSCT in patients with CLL turned out to be almost 50%.[61] By introducing RIC regimens, transplant-related mortality may be substantially lowered in these patients. Slow kinetics of tumour cell growth in CLL allows enough time for the graft to exert an antileukaemic effect. A regimen consisting of fludarabine, busulphan and ATG was studied in 30 CLL patients by Schetelig *et al.*[62] Twelve patients achieved complete remission and 16 patients achieved a partial remission. After a median period of 24 months, 23 patients were alive. Death occurred because of disease progression or TRM. However, TRM after RIC followed by HCST was low. Dreger *et al.* reported results of 77 CLL patients receiving RIC.[3] After a median follow-up of 18 (1 to 44) months, event-free survival and overall survival were 56 and 72% respectively. Hence, although few studies have been performed in patients with CLL, and randomised controlled trials are lacking, RIC may be beneficial in CLL patients with poor prognostic characteristics.[62]

Multiple myeloma

Multiple myeloma is a B-cell malignant disorder characterised by the expansion of plasma cells producing a

monoclonal immunoglobulin.[2,63] Although response rates, disease-free and overall survival improved after high-dose chemotherapy followed by autologous transplantation of haematopoietic cells compared with standard chemotherapy in patients with multiple myeloma, the chance for cure remains low.[63,64] Because of high TRM associated with conventional allograft procedures, no improvement in overall survival compared with those achieved by autologous HSCT was seen.[16,65] Therefore, allogeneic HSCT has not been considered a routine treatment for most patients. This high treatment-related mortality is related to the median age at diagnosis of multiple myeloma, which is greater than 55 years. For the 15 to 20% of the patients who are below 50 years, allogeneic HSCT may be a better treatment, particularly because of the existence of a graft-versus-myeloma effect.[63] Low intensity conditioning regimens have been developed to avoid the high procedure-related mortality of conventional allogeneic transplants. A study by Einsele *et al.* showed that long-term disease control can be attained in patients with multiple myeloma by allogeneic HSCT following a RIC regimen consisting of fludarabine, cyclophosphamide, antithymocyte globulin and low-dose total body irradiation.[66] Moreover, in this study, the occurrence of chronic GVHD seemed to improve tumour control post-transplant, further supporting a graft-versus-myeloma effect. Lokhorst *et al.* included in their study 54 patients with relapsed myeloma who initially received T-cell depleted transplants after conventional myeloablative conditioning.[67] A response on DLI was observed in 28 patients, of whom 19 were partial and nine were a complete response. This study confirms the potential of DLI to induce responses by means of a GVD effect, which can therefore be an effective treatment for patients with relapsed myeloma. Shaw *et al.* showed that RIC protocols using CAMPATH were associated with faster engraftment, less severe acute GVHD and lower nonrelapse mortality at day 100 compared with myeloablative regimens.[68] A significantly higher overall survival after the RIC regimen compared with the myeloablative regimen was observed (54 and 18% respectively), showing the importance of further optimising the RIC regimen for myeloma patients. The Dutch HOVON cooperative study group is currently exploring a strategy in which multiple myeloma patients are sequentially treated with autologous HSCT followed by RIC allogeneic HSCT. Conditioning consists only of low dose TBI (2Gy). Results are expected within several years.

Lymphoma

Depending on the stage of the disease, up to 80% of patients with relapsed Hodgkin's disease (HD) can be cured with chemotherapy and/or radiotherapy. Patients who fail to enter complete remission after the initial treatment are increasingly being treated with high-dose chemotherapy or a combination of chemotherapy and radiotherapy to achieve long-term disease control.[69] Findings that relapse rates after allo-HSCT seemed lower than after auto-HSCT,[70] and that patients developing acute GVHD showed lower relapse rates,[71] may implicate the possibility of a GVD effect. Also, in low-grade non-Hodgkin's lymphomas (NHL), curative potential of allo-HSCT, due to GVD effect, was seen.[72,73] Based on the existence of this GVD effect, patients with Hodgkin's disease and non-Hodgkin's lymphoma were treated with myeloablative allogeneic transplants. Because of high TRM and adverse effects of GVHD, results have however been disappointing, possibly related to extensive pretreatment of patients eligible for allo-HSCT.[71,73] For this reason, the feasibility of RIC regimens was explored. Small studies have been performed on allo-HSCT after RIC in patients with HD,[27,61,74-76] and low-grade NHL.[77] RIC allo-HSCT clearly shows reduced TRM (20 to 25%) in extensively pretreated patients compared with conventional HSCT (50 to 85%).[78] In addition, chances of relapse seem to compare positively with autologous transplants.[73] Although results seem promising, the number of patients included in most studies is still small.

The role of allogeneic transplants in intermediate and high-grade lymphoma has not yet been established in large clinical trials. A small number of these patients have been treated with RIC, but progression was seen shortly after transplant.[14] No studies with larger patient groups have been performed, but according to the kinetics of the tumour growth, it seems likely that RIC regimens may not allow a curative GVD effect in patients with active disease.

CONCLUSIONS

As no prospective randomised trials have been performed comparing conventional *vs* RIC HSCT no definitive answers can be given to questions as to which conditioning regimen is optimal for patients with haematological malignancies. Up to now, most of the patients who received allogeneic transplants after RIC were those who were ineligible for conventional conditioning, making formal comparisons concerning overall survival and transplant-related mortality extremely difficult to interpret. GVHD is an ongoing problem that may initially be less severe after RIC, but eventually no advantage is attained compared with conventional conditioning in this respect. Relapses continue to be a great problem and may be more frequent after RIC. Many different regimens for RIC are being explored and at present it is unclear which of them is most appropriate for the disease the transplant is being performed for. However, it is evident that allogeneic transplants can now be performed with acceptable toxicity in patients who would have been ineligible for this potentially curative treatment only a few years ago, before RIC regimens were introduced. Therefore, in principle, in all patients with haematological

malignancies who are not candidates for conventional transplants, RIC HSCT should be considered, although for older patients after previous autologous transplants and with poor performance status even this still leads to unacceptable toxicity. Whether RIC has the potential to replace conventional conditioning in younger patients and in those without concomitant diseases is still unknown, but should be a topic of future studies. Adequate trials and longer follow-up are needed to optimise protocols, to determine the optimal timing of the procedure in the course of the disease and to evaluate the long-term outcome and toxicity of this treatment.

REFERENCES

1. Bertz H, Potthoff K, Finke J. Allogeneic stem-cell transplantation from related and unrelated donors in older patients with myeloid leukemia. J Clin Oncol 2003;21:1480-4.
2. Corradini P, Tarella C, Olivieri A, et al. Reduced-intensity conditioning followed by allografting of hematopoietic cells can produce clinical and molecular remissions in patients with poor-risk hematologic malignancies. Blood 2002;99:75-82.
3. Dreger P, Brand R, Hansz J, et al. Treatment-related mortality and graft-versus-leukemia activity after allogeneic stem cell transplantation for chronic lymphocytic leukemia using intensity-reduced conditioning. Leukemia 2003;17:841-8.
4. Gratwohl A, Baldomero H, Passweg J, Urbano-Ispizua A. Increasing use of reduced intensity conditioning transplants: report of the 2001 EBMT activity survey. Bone Marrow Transplant 2002;30:813-31.
5. Perez-Simon JA, Caballero D, Diez-Campelo M, et al. Chimerism and minimal residual disease monitoring after reduced intensity conditioning (RIC) allogeneic transplantation. Leukemia 2002;16:1423-31.
6. Platzbecker U, Ehninger G, Schmitz N, Bornhauser M. Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation in myeloid diseases. Ann Hematol 2003;82:463-8.
7. Armitage JO. Bone marrow transplantation. N Engl J Med 1994;330:827-38.
8. Martino R, Caballero MD, Canals C, et al. Allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning: results of a prospective multicentre study. Br J Haematol 2001;115:653-9.
9. Collins RH Jr, Shpilberg O, Drobyski WR, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. J Clin Oncol 1997;15:433-44.
10. Kolb HJ, Schattenberg A, Goldman JM, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. European Group for Blood and Marrow Transplantation Working Party Chronic Leukemia. Blood 1995;86:2041-50.
11. Gilleece MH, Dazzi F. Donor lymphocyte infusions for patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukaemia. Leuk Lymphoma 2003;44:23-8.
12. Valcarcel D, Martino R, Caballero D, et al. Chimerism analysis following allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning. Bone Marrow Transplant 2003;31:387-92.
13. Robinson SP, Goldstone AH, Mackinnon S, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Blood 2002;100:4310-6.
14. Seropian S, Bahceci E, Cooper DL. Allogeneic peripheral blood stem cell transplantation for high-risk non-Hodgkin's lymphoma. Bone Marrow Transplant 2003;32:763-9.
15. Carella AM, Champlin R, Slavin S, McSweeney P, Storb R. Mini-allografts: ongoing trials in humans. Bone Marrow Transplant 2000;25:345-50.
16. Bertz H, Burger JA, Kunzmann R, Mertelsmann R, Finke J. Adoptive immunotherapy for relapsed multiple myeloma after allogeneic bone marrow transplantation (BMT): evidence for a graft-versus-myeloma effect. Leukemia 1997;11:281-3.
17. Mandigers CM, Meijerink JP, Raemaekers JM, Schattenberg AV, Mensink EJ. Graft-versus-lymphoma effect of donor leucocyte infusion shown by real-time quantitative PCR analysis of t(14;18). Lancet 1998;352:1522-3.
18. Kolb HJ, Schmid C, Barrett AJ, Schendel DJ. Graft-versus-leukemia reactions in allogeneic chimeras. Blood 2004;103:767-76.
19. Mohty M, Bay JO, Faucher C, et al. Graft-versus-host disease following allogeneic transplantation from HLA-identical sibling with antithymocyte globulin-based reduced-intensity preparative regimen. Blood 2003;102:470-6.
20. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. Blood 2001;97:3390-400.
21. Carella AM, Giralt S, Slavin S. Low intensity regimens with allogeneic hematopoietic stem cell transplantation as treatment of hematologic neoplasia. Haematologica 2000;85:304-13.
22. Khouri IF, Keating M, Korbling M, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. J Clin Oncol 1998;16:2817-24.
23. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. Blood 2001;97:631-7.
24. Mattsson J, Uzunel M, Brune M, et al. Mixed chimaerism is common at the time of acute graft-versus-host disease and disease response in patients receiving non-myeloablative conditioning and allogeneic stem cell transplantation. Br J Haematol 2001;115:935-44.
25. Gomez-Nunez M, Martino R, Caballero MD, et al. Elderly age and prior autologous transplantation have a deleterious effect on survival following allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning: results from the Spanish multicenter prospective trial. Bone Marrow Transplant 2004;33:477-82.
26. Martino R, Caballero MD, Canals C, et al. Reduced-intensity conditioning reduces the risk of severe infections after allogeneic peripheral blood stem cell transplantation. Bone Marrow Transplant 2001;28:341-7.
27. Kottaridis PD, Milligan DW, Chopra R, et al. In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. Blood 2000;96:2419-25.
28. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow

transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 1998;91:756-63.
29. Fukuda T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood 2003;102:827-33.
30. Junghanss C, Marr KA, Carter RA, et al. Incidence and outcome of bacterial and fungal infections following nonmyeloablative compared with myeloablative allogeneic hematopoietic stem cell transplantation: a matched control study. Biol Blood Marrow Transplant 2002;8:512-20.
31. Martino R, Caballero MD, Simon JA, et al. Evidence for a graft-versus-leukemia effect after allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning in acute myelogenous leukemia and myelodysplastic syndromes. Blood 2002;100:2243-5.
32. Perez-Simon JA, Diez-Campelo M, Martino R, et al. Impact of CD34+ cell dose on the outcome of patients undergoing reduced-intensity-conditioning allogeneic peripheral blood stem cell transplantation. Blood 2003;102:1108-13.
33. Van Besien K, Devine S, Wickrema A, et al. Regimen-related toxicity after fludarabine-melphalan conditioning: a prospective study of 31 patients with hematologic malignancies. Bone Marrow Transplant 2003;32:471-6.
34. Marks DI, Lush R, Cavenagh J, et al. The toxicity and efficacy of donor lymphocyte infusions given after reduced-intensity conditioning allogeneic stem cell transplantation. Blood 2002;100:3108-14.
35. Sureda A, Schmitz N. Role of allogeneic stem cell transplantation in relapsed or refractory Hodgkin's disease. Ann Oncol 2002;13(suppl 19):128-32.
36. Taussig DC, Davies AJ, Cavenagh JD, et al. Durable remissions of myelodysplastic syndrome and acute myeloid leukemia after reduced-intensity allografting. J Clin Oncol 2003;21:3060-5.
37. Samuels BL, Bitran JD. High-dose intravenous melphalan: a review. J Clin Oncol 1995;13:1786-99.
38. Johansson JE, Brune M, Ekman T. The gut mucosa barrier is preserved during allogeneic, haemopoietic stem cell transplantation with reduced intensity conditioning. Bone Marrow Transplant 2001;28:737-42.
39. Carreras E, Bertz H, Arcese W, et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. Blood 1998;92:3599-604.
40. McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med 1993;118:255-67.
41. Carreras E, Granena A, Rozman C. Hepatic veno-occlusive disease after bone marrow transplant. Blood Rev 1993;7:43-51.
42. Mohty M, Faucher C, Vey N, et al. High rate of secondary viral and bacterial infections in patients undergoing allogeneic bone marrow mini-transplantation. Bone Marrow Transplant 2000;26:251-5.
43. Picardi A, Fabritiis PP, Cudillo L, et al. Possibility of long-term remission in patients with advanced hematologic malignancies after reduced intensity conditioning regimen (RIC) and allogeneic stem cell transplantation. Hematol J 2004;5:24-31.
44. Yamamoto R, Kusumi E, Kami M, et al. Late hemorrhagic cystitis after reduced-intensity hematopoietic stem cell transplantation (RIST). Bone Marrow Transplant 2003;32:1089-95.
45. Levine JE, Uberti JP, Ayash L, et al. Lowered-intensity preparative regimen for allogeneic stem cell transplantation delays acute graft-versus-host disease but does not improve outcome for advanced hematologic malignancy. Biol Blood Marrow Transplant 2003;9:189-97.
46. Mineishi S, Kanda Y, Saito T, et al. Impact of graft-versus-host disease in reduced-intensity stem cell transplantation (RIST) for patients with haematological malignancies. Br J Haematol 2003;121:296-303.
47. Schetelig J, Kroger N, Held TK, et al. Allogeneic transplantation after reduced conditioning in high risk patients is complicated by a high incidence of acute and chronic graft-versus-host disease. Haematologica 2002;87:299-305.
48. Hill GR, Crawford JM, Cooke KR, et al. Total body irradiation and acute graft-versus-host disease: the role of gastrointestinal damage and inflammatory cytokines. Blood 1997;90:3204-13.
49. Horowitz MM, Gale RP, Sondel PM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. Blood 1990;75:555-62.
50. Sullivan KM, Anasetti C, Horowitz M, et al. Unrelated and HLA-nonidentical related donor marrow transplantation for thalassemia and leukemia. A combined report from the Seattle Marrow Transplant Team and the International Bone Marrow Transplant Registry. Ann NY Acad Sci 1998;850:312-24.
51. Bornhauser M, Kiehl M, Siegert W, et al. Dose-reduced conditioning for allografting in 44 patients with chronic myeloid leukaemia: a retrospective analysis. Br J Haematol 2001;115:119-24.
52. Or R, Shapira MY, Resnick I, et al. Nonmyeloablative allogeneic stem cell transplantation for the treatment of chronic myeloid leukemia in first chronic phase. Blood 2003;101:441-5.
53. Avivi I, Rowe JM, Goldstone AH. Stem cell transplantation in adult ALL patients. Best Pract Res Clin Haematol 2002;15:653-74.
54. Egerer G, Goldschmidt H, Zoz M, Ho AD. Autologous bone marrow transplantation in adult patients with acute lymphoblastic leukemia. Leuk Lymphoma 2003;44:9-14.
55. Massenkeil G, Nagy M, Lawang M, et al. Reduced intensity conditioning and prophylactic DLI can cure patients with high-risk acute leukaemias if complete donor chimerism can be achieved. Bone Marrow Transplant 2003;31:339-45.
56. Passweg JR, Tiberghien P, Cahn JY, et al. Graft-versus-leukemia effects in T lineage and B lineage acute lymphoblastic leukemia. Bone Marrow Transplant 1998;21:153-8.
57. Arnold R, Massenkeil G, Bornhauser M, et al. Nonmyeloablative stem cell transplantation in adults with high-risk ALL may be effective in early but not in advanced disease. Leukemia 2002;16:2423-8.
58. Martino R, Giralt S, Caballero MD, et al. Allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning in acute lymphoblastic leukemia: a feasibility study. Haematologica 2003;88:555-60.
59. Rozman C, Montserrat E. Chronic lymphocytic leukemia. N Engl J Med 1995;333:1052-7.
60. Keating MJ, O'Brien S, Lerner S, et al. Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. Blood 1998;92:1165-71.
61. Michallet M, Archimbaud E, Bandini G, et al. HLA-identical sibling bone marrow transplantation in younger patients with chronic lymphocytic leukemia. European Group for Blood and Marrow Transplantation and the International Bone Marrow Transplant Registry. Ann Intern Med

1996;124:311-5.
62. Schetelig J, Thiede C, Bornhauser M, et al. Evidence of a graft-versus-leukemia effect in chronic lymphocytic leukemia after reduced-intensity conditioning and allogeneic stem-cell transplantation: the Cooperative German Transplant Study Group. J Clin Oncol 2003;21:2747-53.
63. Kulkarni S, Powles RL, Treleaven JG, et al. Impact of previous high-dose therapy on outcome after allografting for multiple myeloma. Bone Marrow Transplant 1999;23:675-80.
64. Desikan R, Barlogie B, Sawyer J, et al. Results of high-dose therapy for 1000 patients with multiple myeloma: durable complete remissions and superior survival in the absence of chromosome 13 abnormalities. Blood 2000;95:4008-10.
65. Vesole DH, Tricot G, Jagannath S, et al. Autotransplants in multiple myeloma: what have we learned? Blood 1996;88:838-47.
66. Einsele H, Schafer HJ, Hebart H, et al. Follow-up of patients with progressive multiple myeloma undergoing allografts after reduced-intensity conditioning. Br J Haematol 2003;121:411-8.
67. Lokhorst HM, Wu K, Verdonck LF, et al. The occurrence of graft-versus-host disease is the major predictive factor for response to donor lymphocyte infusions in multiple myeloma. Blood 2004;103:4362-4.
68. Shaw BE, Peggs K, Bird JM, et al. The outcome of unrelated donor stem cell transplantation for patients with multiple myeloma. Br J Haematol 2003;123:886-95.
69. Urba WJ, Longo DL. Hodgkin's disease. N Engl J Med 1992;326:678-87.
70. Appelbaum FR, Sullivan KM, Thomas ED, et al. Allogeneic marrow transplantation in the treatment of MOPP-resistant Hodgkin's disease. J Clin Oncol 1985;3:1490-4.
71. Gajewski JL, Phillips GL, Sobocinski KA, et al. Bone marrow transplants from HLA-identical siblings in advanced Hodgkin's disease. J Clin Oncol 1996;14:572-8.
72. Dreger P, Glass B, Seyfarth B, et al. Reduced-intensity allogeneic stem cell transplantation as salvage treatment for patients with indolent lymphoma or CLL after failure of autologous SCT. Bone Marrow Transplant 2000;26:1361-2.
73. Verdonck LF. Allogeneic versus autologous bone marrow transplantation for refractory and recurrent low-grade non-Hodgkin's lymphoma: updated results of the Utrecht experience. Leuk. Lymphoma 1999;34:129-36.
74. Anderlini P, Giralt S, Andersson B, et al. Allogeneic stem cell transplantation with fludarabine-based, less intensive conditioning regimens as adoptive immunotherapy in advanced Hodgkin's disease. Bone Marrow Transplant 2000;26:615-20.
75. Bertz H, Illerhaus G, Veelken H, Finke J. Allogeneic hematopoetic stem-cell transplantation for patients with relapsed or refractory lymphomas: comparison of high-dose conventional conditioning versus fludarabine-based reduced-intensity regimens. Ann Oncol 2002;13:135-9.
76. Carella AM, Cavaliere M, Lerma E, et al. Autografting followed by non-myeloablative immunosuppressive chemotherapy and allogeneic peripheral-blood hematopoietic stem-cell transplantation as treatment of resistant Hodgkin's disease and non-Hodgkin's lymphoma. J Clin Oncol 2000;18:3918-24.
77. Nagler A, Slavin S, Varadi G, et al. Allogeneic peripheral blood stem cell transplantation using a fludarabine-based low intensity conditioning regimen for malignant lymphoma. Bone Marrow Transplant 2000;25:1021-8.
78. Martino R, Caballero MD, de la Serna J, et al. Low transplant-related mortality after second allogeneic peripheral blood stem cell transplant with reduced-intensity conditioning in adult patients who have failed a prior autologous transplant Bone Marrow Transplant 2002;30:63-8.