Allogeneic haematopoietic stem cell transplantation with reduced intensity conditioning regimens ("minitransplants")

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During the recent years it became evident that allogeneic haematopoietic stem cell transplantation with reduced intensity conditioning is feasible. Though less toxic than conventional stem cell grafting severe adverse effects have been reported and are not uncommon. Due to the still short observation periods realistic outcome estimations cannot be made yet. Nevertheless allografting with reduced intensity conditioning is a promising new therapeutic option and hopefully its true position in the treatment of haematologic and oncologic diseases will become more clear in the next future.

Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) is an accepted therapeutic option for various haematological malignancies, severe aplastic anaemia, haemoglobinopathies and immunodeficiency disorders. Recently it has been shown that allogeneic HSCT may also be an effective treatment for selected solid organ tumours, especially in renal cell carcinoma [1].

For many years allogeneic HSCT was based on the concept that the administration of a maximum tolerable myeloablative dose of chemo- and radiotherapy (conditioning regimen), inducing long-term or often irreversible bone marrow aplasia and requiring rescue with a haematopoietic graft, is essential, first, to eliminate or at least drastically reduce tumour cell burden, second to clear the marrow of host haematopoietic cells, and third to be sufficiently immunosuppressive to allow successful donor stem cell engraftment resulting in complete haematopoietic chimerism [2, 3]. These high-dose regimens result in considerable toxicity and hence in substantial morbidity and mortality in graft recipients. Until recently dose reduction of conditioning regimens was not considered because it was expected to result in engraftment failure and high relapse rates. For this reason even higher intensity preparative regimens were explored with the aim of reducing posttransplant disease relapses [4].

It was early recognised that immunocompetent graft cells react against the host normal tissues (skin, liver, gut), leading to so-called "graft-versus-host" disease (GvHD), a cause of substantial additional morbidity and mortality [5]. It was because of these risks that haematopoietic stem cell transplantation was for many years restricted to young and otherwise healthy patients.

It has recently become evident that GvHD partly results from cytokine production induced by the toxicity of preparative regimens [6]. It was therefore postulated that reduced-intensity conditioning could result in a lower incidence and severity of GvHD.

As early as 1957 it was suggested, on the basis of a murine leukaemia model, that the graft itself exerted some antileukaemic properties [7], the so-called "graft-versus-leukaemia effect" (GvL) or "graft-versus-tumour effect" (GvT). The existence of the GvL or GvT effect in humans, linked to the existence of GvH disease, was first documented by Weiden et al. in 1981 [8]. In the 1980s, when T-cell depletion for GvH disease prevention became popular, a significant increase in leukaemia relapse [9], especially in chronic myeloid leukaemia patients, provided indirect evidence for the importance of the GvL effect. A link to the T-cell content of the graft was suggested. In 1981 Slavin et al. showed that after minimal conditioning with total lymphoid irradiation histoincompatible marrow grafts resulted in eradication of leukaemia in mice [10].

Finally, in 1990 Kolb et al. [11] used donor lymphocyte infusions (DLI) for successful treatment of relapsed chronic myeloid leukaemia months or years after bone marrow transplantation, thus providing the first direct evidence of a GvL effect of DLI in humans.

In recent years the pioneering work of Shimon Slavin [10, 12, 14], Rainer Storb [13–15], Sergio Giralt [21, 22], Richard Champlin [14, 21, 22] and Andrea Carella [14, 20, 23] has shown that engraftment of allogeneic haematopoietic stem cells after non-myeloablative conditioning regimens is feasible.

The new concept

The increasing evidence that alloreactivity of donor immune cells is essential for the control or eradication of the host tumour cells has in the last few years led to the development of a totally new concept of allogeneic haematopoietic stem cell transplantation: the reduction of the intensity of preparing regimens while maintaining a level of immunosuppression high enough for the engraftment of donor stem cells. Engraftment can take place either by the achievement of complete haematopoietic chimerism or by mixed chimerism with supposed host-versus-graft and graft-versus-host tolerance, subsequently resulting in complete chimerism, either with or without the addition of DLI [15].

Thus, in malignant diseases the main effect of this procedure is based on posttransplant exertion of the GvL or GvT effect. If the first course was unsuccessful additional transfusions of immunocompetent DLI could be administered to eradicate residual malignant host cells. In non-malignant diseases even partial replacement of the diseased bone marrow by normal haematopoietic stem cells (mixed chimerism) would result in cure [15]. It was postulated that reducing the intensity of the conditioning regimen may be associated with less toxicity and GvHD. Hence a lower transplant-related mortality and better overall survival could be expected. This would allow transplantation in elderly patients and in those with comorbidities not qualifying for standard dose conditioning stem cell transplantation.

General remarks on reduced-intensity regimens

Myelotoxic agents

Nearly all of the reduced-intensity conditioning regimens are based on purine analogues (mostly fludarabine) (Table 1), known to be potent T-cell immunosuppressive agents with low myelotoxicity. Purine analogues are combined with a variety of other cytotoxic agents such as melphalan, cyclophosphamide, Ara-C, idarubicin, busulfan etc.

The goal of this combination chemotherapy is, first, to induce enough immunosuppression to allow successful engraftment and, second, to exert some pretransplant cytotoxic antitumour activity.

Pretransplant immunosuppressive agents

Some investigators add antithymocyte globulin (ATG) to conditioning regimens [12] with the aim of better engraftment and less GvHD due to in vivo T-cell depletion.

Storb et al. [14, 15] even based their preparative regimen on low single-dose total body irradiation (TBI, 2 Gy) only. Previously they were able to show in a dog model [13] that single-dose TBI exerts enough immunosuppression, in combination with intensified posttransplant immunosuppression with cyclosporine A and mycophenolate mofetil, to allow donor stem cell engraftment with only minimal or absent myelotoxicity. Because they observed a high degree of mixed haematopoietic chimerism and graft rejection, especially in pretransplant immunocompetent patients or in other than HLA-identical sibling grafts, fludarabine was recently added prior to TBI [16].

Table 1

Reduced intensity conditioning regimens.

Regimen	reference
Fludarabine 30 mg/m² × 4, cytosine arabinoside 2 g/m² × 4, idarubicine 12 mg/m² × 3	[22, 23]
2-chlorodeoxyadenosine 12 mg/m² × 5, cytosine arabinoside 1 g/m² × 5	[22, 23]
Fludarabine 30 mg/m² × 4, melphalan 140–180 mg/m² ×1	[22, 23]
2-chlorodeoxyadenosine 12 mg/m² × 5, melphalan 180 mg/m² ×1	[23]
Fludarabine 30 mg/m² × 3–5, cyclophosphamide 300–1000 mg/m² × 2–3	[21, 23]
Fludarabine 30 mg/m² × 2, cytosine arabinoside 500 mg/m² × 2, cisplatin 25 mg/m² × 4	[21]
Fludarabine 30 mg/m² × 6, busulfan 4 mg/kg × 2, antithymocyte globulin 10 mg/kg × 4	[12, 23]
Cyclophosphamide 50 mg/kg × 4, antithymocyte globulin15–30 mg/kg × 3–4 pre-/posttransplant, thymic irradiation 7 Gy × 1	[24]
Fludarabine 25 mg/m² × 5, cyclophosphamide 60 mg/m² × 2	[1]
Single-dose TBI (200 cGy) ± fludarabine (30 mg/m² × 3)	[15, 16]

Selected specific reduced-intensity regimens and clinical results

Reduced-intensity conditioning HSCT is a fast growing field in which numerous clinical groups are now active. Most have designed their own preparative regimens. However, many are very similar to each other and it is beyond the scope of this review to discuss all of them. Therefore, only regimens were selected which included a considerable number of patients and follow-up data. Note that many of the data presented are only published in abstract form or as reviews. The specific regimens are shown in Table 1 and the corresponding clinical results in Table 2.

Table 2

Clinical data.

Regimen see Table 1	disease (n)	median (range) years	TRM	GvH	engraftment (chimerism)	outcome	reference
1 + 2	AML (22) MDS (3)	61	1/25	5 × grade II-IV	10/15	overall survival 28% at 1 year	[23]
1	CML (9)	55	1/9	1 grade IV	7/9	?	[23]
3 + 4	AML (34) MDS (9) CML (27) ALL/NHL (16)	52	36/86	?	52/86?	overall survival 29% at 2 years	[23]
5 + 6	CLL (6) Richter sy. (2) NHL (7)	55 (45–71)	1/15	3 × grade II 1 × grade IV	11/15	overall survival 50% at 1 year, median follow-up 180 days	[21]
5	HD (10) NHL (5) Breast cancer (4) CML (2) MDS (2)	36 (19–60)	1/23	10/23 grade I-III 3/23 grade III	14/23 (complete) 7/23 (mixed) 2/23 rejected	16/23 alive median follow-up 330 days	[23]
7	AML (8) ALL (2) CML (8) NHL (2) MDS (1) MM (1) Genetic dis. (4)	31 (1–61)	4/26	8 × grade I-II 4 × grade III-IV 9/25 cGvH	17/25 (complete) 9/25 (partial) (complete after ciclosporin withdrawal)	overall survival 85% at 8 months	[12, 23]
8	NHL (5)	30 (20–51)	2/5	5 × grade II-III	4/5 (mixed)	1/5 CR at d 460 1/5 PR at d 103	[24]
9	Renal cell carcinoma (19)	58 (37–65)	2/19	7 × grade II 1 × grade III 2 × grade IV 4 × cGvH	19/19 (mixed)	3/19 CR (alive at d 474–831) 4/19 PR (alive at d 287–582) 3/19 PR (died at d 155-203)	[1]
10	AML (11) CML (8) CLL (8) MM (8) HD (4) NHL (3) ALL (1) MDS (1) breast cancer (1) amyloidosis (1)	56 (31–72)	3/46	36% grade II-IV	9/46 rejection	?	[14]

Stem cell source and indications for reduced-intensity haematopoietic stem cell transplantation

Most of the transplants have been performed with cytokine-mobilised peripheral blood stem cells and a minority with bone marrow. Presently no data exist on whether the different stem cell sources are comparable in terms of engraftment and outcome.

The indications are the same as for conventional allografting but may include older or comorbid patients. The results seen in small studies of patients allografted for solid organ tumours are promising [1] but clearly more evidence is needed before this indication can be generally recommended.

Engraftment

Engraftment with complete donor-type chimerism in reduced-intensity conditioned allografts can either take place relatively early in the posttransplant course or be delayed by transition through a state of mixed chimerism that converts, either spontaneously or with the addition of DLI or by withdrawal of immunosuppression, into complete chimerism [12, 15]. Some recipients may remain long-term mixed chimeras, whereas others will even reject their grafts [17]. Therefore, frequent determination of the chimerism patterns by PCR or cytogenetics is warranted for early detection of graft failure.

Engraftment is believed to be dependent on the following factors:
- the host: pretreated patients show better engraftment than previously untreated patients (e.g. CML or MDS) [17].

- intensity of the conditioning regimen: higher intensity regimens are more effective in terms of engraftment but are more toxic.
- the graft: HLA-identical sibling transplants have better engraftment than HLA-mismatched sibling or unrelated matched grafts [17].
- peri- and posttransplant immunosuppression: more intense immunosuppression (ATG, mycophenolate mofetil) may enhance engraftment, while early discontinuation may convert mixed into complete chimerism.

It is believed that antitumour activity of the graft is optimal when engraftment is complete. Therefore, delayed complete chimerism – especially in fast-growing malignancies – may be detrimental, whereas this does not seem to be essential in non-malignant diseases where even partial engraftment allows correction of the underlying disorder [14, 15].

Posttransplant complications

The aim of low-intensity conditioning haematopoietic stem cell transplantation is reduction of posttransplant complications and consequent lowering of transplant-related mortality. Up to now this goal seems to have been achieved (Table 2). Nevertheless, all of the posttransplant complications occurring in conventional allografts have in fact been observed in reduced-intensity haematopoietic stem cell transplantation:

Graft-versus-host disease

Initially it was supposed that the incidence and severity of acute GvHD would be lowered in reduced-intensity conditioning allotransplants due to less cytokine activation and a transient state of mixed chimerism [18, 19] with host-versus-graft and graft-versus-host tolerance. Unfortunately there is growing evidence that the incidence of acute GvHD, although probably delayed by about 20–30 days [1], is not very different from that in conventional transplants (Table 2). Acute GvHD often seems to occur after sudden withdrawal of immunosuppressive therapy or after donor lymphocyte infusion [12] converting mixed to complete haematopoietic chimerism. This has led some authors to intensify posttransplant immunosuppression by the addition of short-course, low-dose methotrexate and/or by prolonged administration of cyclosporine A (Shimon Slavin, 3rd International Symposium on Allogeneic Peripheral Blood Progenitor Cell Transplantation; Montreux November 2000) and to withhold DLI in patients with active acute GvHD. Observation periods are still too short to estimate the true incidence of chronic GvHD, but many cases have already been described.

Furthermore, in allotransplants for solid tumours [1] and malignant lymphoma [20] at any rate, there seems to be a correlation between the occurrence of clinically significant acute GvHD and a tumour response.

Nevertheless, in view of the delayed occurrence of GvH disease, it is suggested that when the patient's condition is more stable the treatment of GvH disease could be more easily achieved with fewer adverse effects.

Infectious complications

Infectious complications remain a problem after reduced conditioning allografting. Life-threatening bacterial and fungal diseases may occur. CMV reactivation and disease have also been observed, but with a lower incidence and severity than in conventional transplants [21].

Other complications

Some cases with veno-occlusive disease of the liver have been described. They primarily occur with the more intensive reduced conditionings and most were reported to be mild [12].

So far no pulmonary haemorrhages, idiopathic interstitial pulmonary syndromes or other rare complications have been observed.

Outcome

Due to the diversity of reduced-intensity conditioning regimens covering various haematological malignancies with different disease states, non-malignant haematological diseases and even solid tumours, and also in view of the short observation periods, realistic estimations of overall survival, disease-free survival and relapse rate are not possible at present (Table 2). Larger studies with comparable or better identical preparative regimens in single diseases are needed.

Discussion

Conventional haematopoietic stem cell transplantation is an established procedure that results in long-term disease free survival in many patients with high-risk haematological malignancies, severe aplastic anaemia, haemoglobinopathies and severe immunodeficiency syndromes. Due to intensive (myeloablative) preparative regimens, which have been shown to reduce relapse incidence in surviving patients [4], transplant-related mortality, especially in older patients and those with a reduced performance status, is high and remains a major problem. The observation that haematopoietic engraftment can be achieved through different, mostly non-myeloablative conditioning regimes (Table 1) with variable intensity has led to the innovative concept of reduced-intensity allografting. The goal of this therapeutic approach is to reduce regimen-related toxicity and peritransplant mortality while retaining or even intensifying the graft-versus-tumour effect (DLI, early withdrawal of posttransplant immunosuppression).

There is now increasing evidence that transplant related mortality (at least in the first 30 to 100 days) can be reduced (Table 2) to about half of that expected from conventional transplants. But acute GvHD, though delayed, remains a considerable problem (Table 2), leading to significant morbidity and mortality during the first 100 days or even later. Whether there are significant differences between the various reduced-intensity conditioning regimens in the occurrence of transplant related mortality and acute GvHD is a question to be evaluated in future trials. In addition, bacterial, fungal or opportunistic infections either during neutropenia or as sequelae of GvHD and its treatment remain a severe problem [21].

A higher incidence of graft rejection compared to conventional transplants has been described, depending on the intensity of the conditioning used: very low intensive preparation regimens result in rapid autologous haematopoietic reconstitution without significant bone marrow aplasia occurring, while more intense regimens may lead to long-term bone marrow aplasia. The rate of mixed or complete haematopoietic chimerism is expected to depend on the intensity of the conditioning regimen. Less intensive preparative regimens will result more frequently in mixed chimerism and vice versa. It should be emphasised that in many studies engraftment is merely defined as a spontaneous rise in granulocytes and platelets above a defined threshold and not linked to the existence of complete haematopoietic chimerism.

There is, however, no doubt that at least some patients will remain long-term mixed haematopoietic chimeras, a state that is believed to be curative for most non-malignant haematological disorders but probably only for a minority of malignant diseases. Evidence that even mixed chimerism can result in complete remission of malignant lymphoma, at any rate in HLA mismatched reduced conditioning transplants, has recently been provided by Sykes et al. [24]. In these cases very long follow-up periods are warranted in order to determine late toxicity and efficacy of the reduced conditioning regimens. Secondary myelodysplastic syndromes and acute myeloid leukaemias due to residual host haematopoietic cells previously damaged by the preparative (TBI containing?) regimen must be considered in particular.

Because highly variable reduced-intensity preparative regimens in patients with different predominantly haematological diseases (Table 2) have been used and the observation periods are still short, no firm conclusions on the long-term outcome (overall survival, disease-free survival and relapse incidence) can be drawn. Hopefully, reduced transplant-related mortality will not be outweighed by higher relapse rates. Future large trials should compare the efficacy of the different reduced-intensity regimens in the various disease categories, in order to define the optimal cytoreductive and immunosuppressive regimens ensuring the best overall survival.

In conclusion, reduced-intensity conditioned allografting may be a promising new therapeutic approach. But until more data from prospective clinical trials or large registries are available to resolve the remaining questions, this therapy should in my opinion be reserved for patients with well defined, established indications for a haematopoietic stem cell graft who do not qualify for conventional transplantation (elderly patients, severe comorbidities). New indications (e.g. solid tumours) should be tested only in appropriate clinical trials. In view of the severe complications seen in reduced-intensity conditioned allografts, the term "miniallotransplants" is misleading and should be avoided [25].

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