Comparison of renal injury in myeloablative autologous, myeloablative allogeneic and non-myeloablative allogeneic haematopoietic cell transplantation

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Introduction

The term bone marrow transplantation has been replaced by the term haematopoietic cell transplantation (HCT). This is because the haematopoietic cells for transplantation now have several sources including bone marrow, cytopheresis of peripheral blood, and cord blood. HCT is now used to treat several haematological diseases (e.g., aplastic anaemia, β-thalassemia) and malignancies which otherwise are incurable. There are at present three major HCT procedures—these are myeloablative autologous, myeloablative and non-myeloablative allogeneic HCT. A non-myeloablative procedure for autologous HCT has been described. Renal injury and acute renal failure (ARF) are common complications of each of these procedures which affect both the morbidity and mortality of the recipient patient. The incidence and severity of the renal injury, however, are quite different in the three varieties of HCT. The purpose of this review, therefore, is to discuss the unique features of renal injury in autologous, myeloablative and non-myeloablative allogeneic HCT.

Autologous haematopoietic cell transplantation

With myeloablative autologous HCT, outpatient induction therapy is undertaken with high dose chemotherapy in an effort to eradicate the malignant cells [1]. This cytoreductive therapy is undertaken after haematopoietic cell harvest and storage of bone marrow or peripheral progenitor cells. Haematopoietic stem cells are collected from the bone marrow after repeated aspiration from the posterior iliac crest, or progenitor cells from peripheral blood by cytopheresis. The stem cells are then frozen at −196°C in 50 ml volume with 10% dimethyl sulfoxide. After cytoreduction and the HCT transplant of the patient’s own cells, reconstitution of the patient’s bone marrow occurs after about 3 weeks. During that period of time the complications of HCT occur including infections, bleeding, and organ toxicities. The major difference between myeloablative autologous and myeloablative allogeneic HCT is that immunosuppressive treatment is not necessary with autologous HCT as graft rejection and graft vs host disease do not occur.

The first study to examine specifically renal injury in autologous HCT was in 232 breast cancer patients with positive nodes (Stage II/III, N = 72) or metastases (Stage IV, N = 160) [2]. The source of the transplanted cells was 35 from the bone marrow and 197 progenitor cells from peripheral blood. The outpatient induction therapy included adriamycin, fluorouracil, and methotrexate. The high dose chemotherapy included cyclophosphamide (CPA), cisplatin, and carmustine (BCNU) or taxol with Mesna used at higher doses of CPA and BCNU. All patients received empirical intravenous antibiotics when the patient’s absolute granulocyte count was <500/µ and fever greater than 38.3°C. This antibiotic coverage included gentamicin 2.5 mg/kg then 1.5 mg/kg IV q. 8 h; piperacillin 3 gm q. 4 h and vancomycin 1 gm q. 12 h. If the fever persisted for longer than 48 h, antifungal therapy with amphotericin or fluconazole was added.

Renal dysfunction was assessed as follows: before chemotherapy (day −7), before haematopoietic cell support (day −1), and post-haematopoietic support (days 7, 14, 21 and 3 months). The maximal serum
Grade 1, N=81
Grade 2/3, N=49

the occurrence of at least two of the following criteria
The study had hepatic VOD. Hepatic VOD is defined as
less than 2-fold increase in hepatic enzymes), hepatic
venous occlusive disease (VOD), and lung toxicity on
univariate analysis. On multivariate analysis only lung
toxicity (P < 0.015), liver toxicity (P < 0.001) and sepsis
(P < 0.015) were significantly associated with Grade 2/3
dysfunction. The mortality 60 days post-procedure was
also significantly higher in the Grade 2/3 patients.

In Figure 1 are shown the results in renal function
from day −7 to day 21. Grades 2/3 are considered
severe renal dysfunction and are shown together. At
day −1 the decrement in estimated GFR was compar-
able in Grade 2/3 and Grade 1. Thereafter, the
decrement in GFR stabilized in the Grade 1 (n = 81)
but continued to decline in the Grade 2 and 3 patients
(n = 49). Dialysis was required in seven (3%) patients
(Grade 3 dysfunction). In Table 1 are shown the non-
renal variables in the same patients by the grades
of renal function. The patients with Grade 2/3 renal
dysfunction had more sepsis, liver toxicity (i.e. more
than 2-fold increase in hepatic enzymes), hepatic
venous occlusive disease (VOD), and lung toxicity on
univariate analysis. On multivariate analysis only lung
toxicity (P < 0.015), liver toxicity (P < 0.001) and sepsis
(P < 0.015) were significantly associated with Grade 2/3
dysfunction. The mortality 60 days post-procedure was
also significantly higher in the Grade 2/3 patients.

The overall severe renal dysfunction (Grade 2/3) in
this autologous HCT study of 232 patients was 21%, as
compared to previously reported 53% in myeloablative
allogeneic HCT [3]. Hepatic VOD has been reported in
allogeneic HCT to range from 22 to 54% [4,5] while
only 4.7% of patients in the present autologous HCT
study had hepatic VOD. Hepatic VOD is defined as
the occurrence of at least two of the following criteria
within 20 days of transplantation: (1) total serum
bilirubin >2 mg/dL, (2) hepatomegaly or right upper
quadrant pain, and (3) sudden unexplained weight gain
(>2% of baseline weight). Only two of 49 Grade 2/3
patients in the present study fulfilled the criterion of
hepatorenal syndrome. Two-thirds of the autologous HCT
Grade 2/3 patients were fluid overloaded during
the period of chemotherapy. Finally, in the present
autologous HCT study the mortality at 60 days post-
procedure was only 7%, a figure significantly below
the reported mortality in studies in which both
patients receiving allogeneic and autologous HCT
were included [3–5]. Autologous HCT, however,
cannot be used in patients who have bone marrow
involvement with the malignancy. Another potential
drawback of myeloablative autologous HCT is the lack
of graft vs tumour effect which may lead to an increased
risk of relapse. With the failure to demonstrate an
advantage of autologous HCT for patients with breast
cancer and positive nodes or metastatic disease as
compared to high-dose chemotherapy alone, the use
of autologous HCT has been decreasing while allogeneic
HCT is increasing (www.ibmtr.org/summaryslides).

Allogeneic myeloablative stem cell transplantation

A study was undertaken at the University of Colorado
to evaluate the occurrence and severity of renal injury
in 88 patients receiving myeloablative allogeneic HCT
[6]. The same grades of renal function loss (Grade 0–3)
were used as followed in the above autologous
HCT study. The estimated GFR was calculated in the
allogeneic study using the MDRD equation. The
haematopoietic cell support included bone marrow
or peripheral stem cells from related donors in 50%
of patients and from unrelated donors in 17% of
donors. Cryopreserved umbilical cord blood was used

Table 1. Non-renal variables in autologous haematopoietic cell transplantation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal renal function</th>
<th>Grade 1</th>
<th>Grade 2/3</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>102 (44)</td>
<td>81 (35)</td>
<td>49 (21)</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>Hypotension</td>
<td>18 (17)</td>
<td>10 (12)</td>
<td>13 (26)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (2)</td>
<td>1 (1.2)</td>
<td>5 (10)</td>
<td>&lt;0.015</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>14 (14)</td>
<td>16 (20)</td>
<td>7 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>5 (5)</td>
<td>6 (6)</td>
<td>16 (32.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hepatic VOD</td>
<td>2 (2)</td>
<td>2 (2.5)</td>
<td>7 (14)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lung toxicity</td>
<td>11 (11)</td>
<td>6 (7.4)</td>
<td>12 (24.5)</td>
<td>&lt;0.015</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (3.9)</td>
<td>3 (3.7)</td>
<td>9 (18.4)</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Fig. 1. A significant decline in GFR in both Grade 1 and 2/3 patients is present at the time of haematopoietic cell support on
day −1 (P < 0.001). After day −1, GFR is lower in patients with
Grade 2/3 vs Grade 0/1 (P < 0.001) from day 7 to day 21. Published
with permission from Merouani et al. [2].
as a source of haematopoietic progenitor cells in the remaining 33% of patients. The same antibacterial prophylaxis for neutropenia and empiric treatment of fever, as in the above autologous study, was also used in the allogeneic HCT patients. After 48 h of fever, antifungal therapy with amphotericin (0.6 mg/kg/day) was instituted. In contrast to autologous HCT, immunosuppressive therapy was necessary in the myeloablative allogeneic HCT patients due to T-cell response against minor histocompatibility antigens. In this regard, beginning one day before the HCT, prophylaxis for graft vs host disease (GVHD) was initiated with cyclosporine (CsA) and methotrexate or CsA and prednisone. This immunosuppressive therapy also prevented rejection of the donor haematopoietic cells. The goal for CsA whole blood levels was 350–400 mg/ml. The malignancies that were treated and the high dose conditioning regimens used to ablate the malignant and bone marrow cells are shown in Table 2.

There was no significant difference in the characteristics of the patients receiving the different conditioning regimens, i.e. with or without total body irradiation (TBI); with or without cyclophosphamide. The mean baseline GFR of the patients on day −7 was 110 ± 25 ml/min/m². Of the 88 patients, 81 (92%) had a decrease in estimated GFR (i.e. Grade 1–3). When considering only severe renal dysfunction (Grade 2 and 3) 69% of patients had a significant decline in renal function. This compares with 21% with severe renal dysfunction in the autologous HCT study [2]. In Figure 2 is shown the decline in creatinine clearance after the myeloablative allogeneic HCT. There was no statistically significant difference between the conditioning regimen or the type of malignancy treated and the occurrence of severe renal dysfunction or mortality. The overall rate of mortality at 2 months was 35% (31 of 88 patients) and 58% (51 of 88 patients) at 6 months for the myeloablative allogeneic HCT. The Grade 3 patients who were dialyzed had a very high mortality (24/29, 82.7%) as has been previously reported [3,4]. There was also an 87.5% mortality among the patients receiving ventilator support. The patients with severe renal dysfunction had significantly higher frequencies of sepsis, hepatic toxicity (>2× increase in AST and ALT), hepatic VOD and lung toxicity. Overall, 93% of the patients had some degree of hepatotoxicity. There was no significant difference between Grade 0–1 vs Grade 2 and 3 with respect to aminoglycoside and amphotericin therapy. There was also no difference between CsA blood levels and the grade of renal dysfunction or mortality.

In Table 3 are shown the differences in the rates of renal dysfunction and mortality in myeloablative autologous and allogeneic HCT from patients at the University of Colorado. There was significantly more severe renal dysfunction, hepatic VOD and lung toxicity with allogeneic HCT. The mortality rates were also much higher with the allogeneic transplantations. It should be noted that the autologous HCT and allogeneic HCT have been compared mainly for conceptual purposes. The two studies have been performed over different time periods and also the influences of

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Table 2. Baseline characteristics of patients who received a allogeneic haematopoietic cell transplantation (HCT)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Chronic myelogenous leukemia (CML)</td>
<td>22</td>
</tr>
<tr>
<td>Acute myelogenous leukemia (AML)</td>
<td>24</td>
</tr>
<tr>
<td>Non Hodgkin’s lymphoma (NHL)</td>
<td>15</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia (ALL)</td>
<td>10</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>7</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>4</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td>3</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia (CMML)</td>
<td>1</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1</td>
</tr>
</tbody>
</table>

| Conditioning regimens           |                    |
| Cyclophosphamide + busulfan    | 28                 |
| Busulfan + melphalan            | 24                 |
| Cyclophosphamide + TBI          | 3                  |
| Melphalan + TBI                 | 33                 |

TBI = Total body irradiation.

Modified from ref. [6] with permission.

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Table 3. Differences in the rates of renal dysfunction and mortality in autologous versus allogeneic HCT*

<table>
<thead>
<tr>
<th></th>
<th>Autologous</th>
<th>Allogeneic</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>232</td>
<td>88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 0 renal dysfunction</td>
<td>44%</td>
<td>8%</td>
<td>0.058</td>
</tr>
<tr>
<td>Grade 1 renal dysfunction</td>
<td>35%</td>
<td>23%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 2 renal dysfunction</td>
<td>14%</td>
<td>36%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 3 renal dysfunction</td>
<td>7%</td>
<td>33%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Venous occlusive disease</td>
<td>4%</td>
<td>16%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung toxicity</td>
<td>13%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>7%</td>
<td>58%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Results from ref. [2] and [6].
**The groups have been compared by Chi-square or Fisher Exact test where appropriate.
Comparison of renal injury
differing underlying malignancies and conditioning regimens cannot be excluded.

Non-myeloablative allogeneic haematopoietic stem cell transplantation

Because of the organ toxicity and high mortality of myeloablative HCT, the procedure is generally only available to younger patients without co-morbid disease. Since the occurrence of malignancies increases with age, there was a need to develop a less toxic HCT for older patients with malignancies who were not qualified for myeloablative allogeneic HCT. Thus, the non-myeloablative HCT approach has been initiated [7,8]. This procedure entails the use of a low-dose conditioning regimen designed not to eradicate the malignant cells but rather to provide sufficient immunosuppression to allow the engraftment of the HCT. The hypothesis is that the engrafted haematopoietic stem cells will cause an immunological graft vs malignancy response which would destroy the tumour cells. There were several observations which support this immunological approach against malignancies [9]. Specifically, an increased risk of relapse has been observed with myeloablative allogeneic HCT in twins and after T-cell depleted transplants [10,11]. An induction of remissions has also been observed by a donor lymphocyte infusion in patients who had relapsed after allogeneic HCT [12]. Lastly, donor-derived T-cell clones against malignant cells have been demonstrated [13].

The most characterized conditioning regime for non-myeloablative (mini-allo) HCT employs low dose total body radiation (TBI) (2 Gy) + IV fludarabine (30 mg/m2/day). This regime is less toxic than myeloablative allogeneic HCT and thus can be used in older, less healthy patients with lymphatic or haematological malignancies [7,8].

Mixed chimerism is an essential first step in the goal of the non-myeloablative HCT to cure malignancies. Mixed haematopoietic chimerism is when two haematopoietic systems co-exist in the same individual as occurs in the recipient of an allogeneic HCT. In non-malignant disorders mixed chimerism may be beneficial for diseases such as beta thalassemia, sickle cell disease, aplastic anemia, autoimmune diseases as well as organ graft survival. Development of full donor chimerism, however, is essential for cure of haematological malignancies in the recipient [9]. Mixed chimerism in the recipient is defined as the detection of donor T cells (CD3+) of 95% or less of the total T-cell population. Table 4 outlines the treatment plan of the Fred Hutchinson Research Institute for the non-myeloablative HCT for malignancies. Cyclosporine was given orally for post-transplant immunosuppression and the levels were targeted to the upper therapeutic range of 500 ng/ml until day 35. The treatment is initiated on an outpatient basis and to patients only admitted to control transplant complications. Cytoreduction with hydroxyurea may be necessary to suppress the white blood cell count to <10,000/μl prior to TBI.

While the non-myeloablative allogeneic HCT procedure has been shown to have fewer complications than the myeloablative allogeneic HCT, such as cytomegalovirus infection, only recently was the frequency and severity of renal dysfunction reported. In a study of 253 patients from four centres (Fred Hutchinson and University of Washington; City of Hope; Stanford University; and University of Colorado), severe renal failure (Grade 2 and 3) occurred in 40.4% of the patients over a 3 month period, a value significantly less than the 69% observed in the myeloablative allogeneic HCT [3,14]. Also, only 4.4% of patients needed dialysis, whereas in an earlier study of conventional (i.e. myeloablative) allogeneic HCT dialysis was required in 33% of patients [3,14]. These findings occurred even though the non-myeloablative patients were significantly older (53 vs 23 years) and had more co-morbidity. The overall mortality in this non-myeloablative HCT study was 34% at 1 year as compared to 58% in the study of myeloablative allogeneic HCT discussed earlier [6,14].

Most of the acute renal failure in the non-myeloablative study occurred within the first 3 months. Baseline characteristics and co-morbidities did not predict which patients would and would not develop renal dysfunction. The specific calcineurin inhibitor, cyclosporine (n = 238) or tacrolimus (n = 15), used for immunosuppression did not appear to make a difference in the frequency or severity of the renal failure. Interestingly, although a very small number of the 253 patients received haematopoietic cells from the bone marrow (4.3%) as compared to peripheral blood haematopoietic cells stimulated by granulocyte colony stimulating factor (95.7%), severe acute renal failure (Grades 2 and 3) occurred more frequently in the patients receiving the haematopoietic cells from the bone marrow as compared to peripheral blood (7.8 vs 2%, P < 0.02). After controlling for other variables, the requirement for ventilatory support was associated with a 10-fold increase in the incidence of ARF. This was the strongest correlation in the multivariate analysis for renal dysfunction. Pre-existing diabetes was also weakly associated with renal dysfunction. Figure 3 shows that as renal dysfunction becomes more

| Table 4. Outline of treatment plan and assessment of disease response and chimerism by disease and genetic marker analysis |
| Days -4 to -2: Fludarabine 30 mg/m2/day |
| Day 0: Low dose TBI (200 cGy) and PBSC transplant |
| Day -1 to +56: Immunosuppression with CSA/MMF |
| Day 28 and 56: Assess chimerism with VNTR or sex-markers |

If mixed chimerism (detectable donor CD3+ cells at <95% of CD3+ cells) on day 56 infuse donor lymphocytes on day 65

TBI = total body irradiation; PBSC = peripheral blood stem cells; VNTR = variable number of tandem repeats; CSA = cyclosporine; MMF = mycophenolate mofetil.

From ref. [9] with permission.
severe patient survival declines with the non-myeloa-
blative HCT. Patients who had acute renal failure had a
significantly higher mortality at 6 months (29.4 vs
16.5%, \( P < 0.05 \)) and at 1 year (42.1 vs 28.5%, \( P < 0.05 \))
as compared to those without kidney dysfunction. The
cause of the renal dysfunction in this non-myeloabla-
tive allogeneic HCT study appeared to be multifactorial,
including immnosuppression and sepsis, GVHD, drug
toxicity, and TBI. In contrast to myeloablative allo-
genetic HCT, hepatic VOD and hemolytic uremia
syndrome/thrombotic thrombocytopenic purpura
were virtually absent in this group of mini-allo treated
patients.

In summary, the consideration of renal injury
and dysfunction with HCT must involve the specific
procedure used. Severe ARF occurs with all three
varieties of HCT. However, in our studies the frequency
of ARF (Grade 2 and 3) increases significantly from
myeloablative autologous (21%) to non-myeloablative
allogeneic (40%) to myeloablative allogeneic (69%).
This increase in ARF correlates with a parallel increase
in mortality from 7 to 34% to 58% at 6–12 months
as well as progressive multiorgan involvement. With
all three HCT procedures, the combination of ARF
and dialysis, particularly with mechanical ventilation,
the mortality increases to greater than 80%.

Thus, efforts to decrease the frequency and severity
of ARF in both myeloablative and non-myeloablative
allogeneic HCT should be pursued in order to decrease
morbidity and mortality in these patients. Nephrologists
should be involved early in the care of the patient
receiving allogeneic HCT to identify small decrements
in renal function, assist in fluid balance and medication
dosing. Guidelines for timing, dose duration and
modality of dialysis for ARF in the setting of HCT
are clearly needed. Also, future studies need to identify
interventions and strategies that will focus on
decreasing ARF and subsequent mechanical ventila-
tion following HCT.

Conflict of interest statement. None declared.

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