Cytopenia and Hematopoietic Recovery after Low Intensity Conditioning Transplants

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Aim. To compare hematopoietic reconstitution after low intensity conditioning transplants and standard allogeneic hematopoietic stem cell transplantation (HSCT).

Methods. We retrospectively analyzed the kinetics of cytopenia of 50 consecutive patients treated with HSCT during a 60 day posttransplant period. Twenty four patients were treated with a low intensity regimen (Fludarabine, 2 Gy total body irradiation) and 26 patients with the standard conditioning regimen. Patients who received the low intensity HSCT were analyzed in two groups, patients with engraftment of donor hematopoiesis and those who rejected the graft.

Results. Patients treated with low intensity conditioning, regardless of its outcome, experienced significantly less severe cytopenia than the patients from the control group. Except for reticulocytes, the development of cytopenia was significantly slower in these patients, and the duration of severe cytopenia was significantly shorter. However, full neutrophil recovery (absolute neutrophil count >1.0×10⁹/L) took longer in patients with low intensity HSCT.

Conclusions. The kinetics of cytopenia and hematopoietic recovery after low intensity conditioning HSCT significantly differ from standard HSCT. There is no difference in the initial hematopoietic recovery between patients with or without engraftment after low intensity conditioning. This indicates that the onset, severity, and duration of the cytopenia are influenced primarily by the intensity of the conditioning and by the immunosuppressive regimen after transplantation. Effects are more pronounced for neutrophils than for platelets and reticulocytes.

Key words: hematologic neoplasms; hematopoietic stem cell transplantation; transplantation conditioning

Low intensity conditioning transplants represent a novel concept of allogeneic hematopoietic stem cell transplantation (HSCT). Specifically designed to be less toxic, they exploit the graft versus malignancy (GvM) effect as a primary form of therapy. The curative potential of this effect has been well documented by many investigators; molecular remissions following donor lymphocyte infusion being the most direct evidence (1,2). The main focus in low intensity allografting is on short-term intensive immunosuppression to ensure engraftment and the development of a GvM effect. This approach differs from the traditional transplant strategy, which relies on maximal tumor cytoreduction, employing highly intensive chemoradiotherapy for cancer cure (3,4).

In the last few years, the number of patients treated with low intensity conditioning has increased rapidly and the preliminary data are encouraging (5-7). Sustained engraftment and an impressively high tumor response with complete remissions observed in many patients with hematological malignancies and in some with solid tumors have proven the feasibility of this approach. The transplants are generally well tolerated. Substantial decrease in early transplant related toxicity and mortality has been documented, despite the fact that most series included elderly persons and patients with advanced disease.

At present there are still unresolved issues. The overall long term efficacy of this approach remains to be determined. More extensive observation periods are needed. Graft versus host disease (GvHD) remains a major concern. In addition, few data exist concerning the hematopoietic reconstitution. Low intensity conditioning regimens may allow for a “mixed chimerism” and recovery of both the recipient and donor hematopoiesis may occur. In contrast to conventional allogeneic HSCT which invariably causes aplasia, low intensity conditioning produces a temporary and milder cytopenia. The correlation between treatment intensity and degree of cytopenia appears logical and is easily understood. Quantitative aspects and effects on kinetics of cytopenia have not yet been examined. To investigate both of them was the aim of this study.
Patients and Methods

Study Design
This study was designed to retrospectively compare the kinetics of hematopoietic reconstitution in two homogeneous parallel cohorts of consecutive patients receiving low intensity conditioning transplant or conventional allogeneic HSCT at a single institution. The data were collected from the patient charts. The evaluation period included the first 60 days after transplantation for hematopoietic recovery and up to 56 months for the analysis of patient survival.

Patients and Study Groups
Twenty four consecutive adult patients with hematological malignancies treated with low intensity conditioning allogeneic HSCT between October 1999 and October 2001 were included in the study. The indications for low intensity conditioning transplantation at our institution were age above 50 years for patients with leukemia and age above 40 years for patients with lymphomas and myeloproliferative disorders. Patients younger than 40 years were included when severe other organ dysfunction was present. Table 1 summarizes the patient characteristics. Briefly, all but one patient with leukemia were older than 50 years. Twenty one out of 24 patients had advanced disease. Most patients received a HLA-identical graft from a family donor and all patients received peripheral blood stem cells.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics*</th>
<th>Conditioning</th>
<th>low intensity</th>
<th>standard</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years (median/range)</td>
<td>53 (33-63)</td>
<td>33 (19-55)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>13/11</td>
<td>17/9</td>
<td>0.565</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute leukemia (AML/ALL)</td>
<td>3 (30)</td>
<td>12 (7/5)</td>
<td>0.054</td>
<td></td>
</tr>
<tr>
<td>chronic leukemia (CML/CLL)</td>
<td>8 (3/5)</td>
<td>9 (9/0)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>lymphomas/MM</td>
<td>6 (2/4)</td>
<td>3 (1/2)</td>
<td>0.282</td>
<td></td>
</tr>
<tr>
<td>MDS/MPS</td>
<td>7 (7/0)</td>
<td>2 (1/1)</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>advanced disease stage†</td>
<td>21</td>
<td>16</td>
<td>0.054</td>
<td></td>
</tr>
<tr>
<td>Donor type</td>
<td>related/unrelated</td>
<td>20/4</td>
<td>23/3</td>
<td>0.697</td>
</tr>
<tr>
<td>HLA identical/one antigen mismatch</td>
<td>23/1</td>
<td>25/1</td>
<td>1.000</td>
<td></td>
</tr>
</tbody>
</table>

Graft product:
stem cell source: BM/PB 0/24 0/26 1.000
stem cell dose CD34+×10^6/kg 7.09 8.52 0.908
(median, range) (1.19-25.53)/(2.25-15.29)
median follow up, months (range) (15-62)/(24-13-56) <0.001
survival (No. of patients alive) 15 23 0.047

Causes of death (No. of patients):
disease progression 7 1 0.021
GvHD 2 2 1.000

*Abbreviations: AML – acute myeloblastic leukemia; ALL – acute lymphoblastic leukemia; CML – chronic myelogenous leukemia; CLL – chronic lymphocytic leukemia; MM – multiple myeloma; MDS/MPS – myelodysplastic/myeloproliferative syndromes; BM – bone marrow; PB – peripheral blood sample; GvHD – graft versus host disease.
†Advanced disease stage: AML or ALL more advanced than first remission, CML advanced disease stage† more advanced than first chronic phase or other diagnosis.

Results

Patient Survival and Causes of Death
At the median follow up of 15 months (range 6-28 months), 17 of 24 patients treated with low intensity conditioning were alive. Seven patients died of progressive disease and 2 patients of GvHD. In the control group, with a median follow up of 24 months (range 13-56 months), 23 patients were alive. One patient died of disease progression and 2 patients of GvHD.

Extent and Kinetics of Cytopenia
Neutrophils. Only 2 patients with donor engraftment had a decline in neutrophils to <0.1×10^9/L. Two patients had no neutropenia (<1.0×10^9/L). In 25 patients the lowest neutrophil count was between 0.1×10^9/L and 0.5×10^9/L. The neutrophil nadir (median 0.33×10^9/L, range 0.05-1.8×10^9/L) was significantly higher than in the control group (p<0.001) and occurred later after transplantation (median 12.5 days, range 6-31 days, p<0.001). The kinetics of recovery differed between standard and low intensity HSCT. It took longer to accomplish full neutrophil recovery (ANC>1.0×10^9/L) in patients treated with low intensity HSCT compared with the controls. The median time with a neutrophil count of <1.0×10^9/L was 17.5 days (range 3-32 days) (Table 2, Fig. 1). The neutrophil count reached >1.0×10^9/L by +36 post-transplant day, which was significantly different from (30 mg/kg) on day -8, cyclophosphamide (60 mg/kg/day) on days -6, and -5, and TBI (6×2 Gy) on days -3, -2, and -1. Methotrexate (MTX) and CSA on days +1, +3, +6 and +9 to +80, respectively, were given for GvHD prophylaxis. Patients were hospitalized in single rooms with high-efficiency particulate air filtration at the stem cell transplant unit. Antiviral, antifungal, and Pneumocystis carinii pneumonia prophylaxis were given. Transfusion support consisted of leucodepleted and irradiated blood components at threshold values of <80 g/L hemoglobin and <20×10^9/L thrombocytes. Supportive care included nutritional and metabolic support, mouth care, pain relief and prevention, and treatment of chemotherapy induced nausea and vomiting.

Control Group
The control group included 26 adult patients (Table 1) who underwent a conventional allogeneic HSCT during the same time period at the same institution. Excluded from the analysis were patients who died before day 60 (n=2) and patients submitted to a double transplant program (n=7) (8). As summarized in Table 1, they were significantly younger (p<0.001) than the study group patients, with only 3 patients above the age of 50 years. They were comparable to the study group with regard to disease distribution, donor type, stem cell source, and stem cell dose infused.

Transplant Procedure and Patient Assessment
The low intensity conditioning regimen consisted of Fludarabine (30 mg/m^2) on days -8, -5, and -2 and total body irradiation (TBI) (2 Gy/sq m) on day 0. Cyclosporine (CSA) and mycophenolate mofetil (MMF) on days -1 to +35 and 0 to +28, respectively, were given to prevent graft rejection and as GvHD prophylaxis. The conventional conditioning regimen was based on etoposide (30 mg/kg) on day -8, cyclophosphamide (60 mg/kg/day) on days -6, and -5, and TBI (6×2 Gy) on days -3, -2, and -1. Methotrexate (MTX) and CSA on days +1, +3, +6 and +3 and -3 to +80, respectively, were given for GvHD prophylaxis. Patients were hospitalized in single rooms with high-efficiency particulate air filtration at the stem cell transplant unit. Antiviral, antifungal, and Pneumocystis carinii pneumonia prophylaxis were given. Transfusion support consisted of leucodepleted and irradiated blood components at threshold values of <80 g/L hemoglobin and <20×10^9/L thrombocytes. Supportive care included nutritional and metabolic support, mouth care, pain relief and prevention, and treatment of chemotherapy induced nausea and vomiting.

After hospital discharge, the scheduled follow up included 2-3 clinic visits per week for the first month and then once or twice per week or as clinically required.

Chimerism was assessed in an unfractioned peripheral blood sample in monthly intervals using polymerase chain reaction (PCR) – based analysis of short tandem repeats (STR) (9).
+22 posttransplant day seen in the control group (p=0.004). Recovery to >0.5×10^9/L occurred later after transplantation (day +28) than in the control group (day +19) as well, although the difference was not significant (p=0.076) (Fig 1).

Four patients with donor engraftment had a second decrease in the neutrophil count (median 0.38×10^9/L, range 0.09-0.8×10^9/L) between day 40 and 60 (median 47). The relationship to GvHD, cytomegalovirus infection, or decline in donor type chimerism was not found. Compared to the initial neutropenia (median 0.14×10^9/L, range 0.11-0.39×10^9/L) the second neutropenia was similar in its severity and duration.

Six of 8 patients with autologous reconstitution of hematopoiesis had a decline in the neutrophil count (median 0.38×10^9/L, range 0.09-0.8×10^9/L) between day 40 and 60 (median 47). The relationship to GvHD, cytomegalovirus infection, or decline in donor type chimerism was not found. Compared to the initial neutropenia (median 0.14×10^9/L, range 0.11-0.39×10^9/L) the second neutropenia was similar in its severity and duration.

Platelets. Five patients with donor engraftment had a platelet count of <50×10^9/L and in 2 patients the platelets fell to <20×10^9/L. Platelet nadir was significantly higher than in the control group (median 62.5×10^9/L, range 4-359×10^9/L, p<0.001) and occurred later after transplantation (median 10 days, range 0-25 days, p=0.028). Thrombocytopenia was also of shorter duration than in the control group (Table 3). The number of days with thrombocytopenia of <20×10^9/L and of <50×10^9/L ranged from 0 to 35 days (median 0 days) and from 0 to 13 days (median 0 day) (p<0.001), respectively.

In patients with autologous reconstitution of hematopoiesis the platelet nadir (median 39×10^9/L, range 39-112×10^9/L) and the time it occurred (median 12 days, range 10-60 days) were similar as in patients with donor engraftment. The nadir of platelets was reached on day 12 (median, range 10-60) and >50×10^9/L within 6 days (median, range 6-23) days. One patient did not accomplish a platelet count of >20×10^9/L by 60 posttransplant day because of disease progression.

All patients in the control group had a decline of the platelet count to <20×10^9/L (Table 3). The median time with a platelet count of <20×10^9/L was 6 days (range 2-53 days). Platelet nadir was 12×10^9/L (range 12-39×10^9/L) and was reached on +6 post-transplant day. Platelet counts increased to >50×10^9/L within 6 days (median, range 0-60).

**Figure 1.** Neutrophil kinetics. Rhombs – patients with donor engraftment; open squares – patients with autologous reconstitution of hematopoiesis; triangles – control.

<p>| Table 2. Frequency, intensity, and duration of neutropenia after low intensity and standard conditioning hematopoietic stem cell transplantation (HSCT) |</p>
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Nadir×10^9/L</th>
<th>Day of nadir post HSCT</th>
<th>Days in neutropenia*</th>
<th>No. of patients with neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low intensity HSCT: patients with donor engraftment (n=16)</td>
<td>0.33 (0.05-1.8)</td>
<td>12.5 (6-31)</td>
<td>0 (0-3)</td>
<td>4.5 (0-28)</td>
</tr>
<tr>
<td>patients with autologous reconstruction of hematopoiesis (n=8)</td>
<td>0.21 (0-0.6)</td>
<td>16.5 (7-36)</td>
<td>0 (0-18)</td>
<td>5 (0-60)</td>
</tr>
<tr>
<td>Standard HSCT (control) (n=26)</td>
<td>0.05 (0-0.09)</td>
<td>2 (1-7)</td>
<td>10 (5-14)</td>
<td>12 (6-18)</td>
</tr>
<tr>
<td>*Median (range)</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

<p>| Table 3. Frequency, intensity, and duration of thrombocytopenia after low intensity and standard conditioning hematopoietic stem cell transplantation (HSCT) |</p>
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Nadir×10^9/L</th>
<th>Day of nadir post HSCT</th>
<th>Days in thrombocytopenia</th>
<th>No. of patients with thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low intensity HSCT: patients with donor engraftment (n=16)</td>
<td>66.5 (4-359)</td>
<td>10 (0-25)</td>
<td>0 (0-35)</td>
<td>0 (0-13)</td>
</tr>
<tr>
<td>patients with autologous reconstruction of hematopoiesis (n=8)</td>
<td>39 (4-119)</td>
<td>12 (10-60)</td>
<td>0 (0-60)</td>
<td>6 (0-60)</td>
</tr>
<tr>
<td>Standard HSCT (control) (n=26)</td>
<td>12 (6-19)</td>
<td>6 (1-11)</td>
<td>6 (2-53)</td>
<td>9 (4-53)</td>
</tr>
<tr>
<td>*Median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 4. Frequency, intensity, and duration of reticulocytopenia after low intensity and standard conditioning hematopoietic stem cell transplantation (HSCT).

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Nadir ×10⁹/L</th>
<th>Day of nadir after HSCT</th>
<th>Days in reticulocytopenia</th>
<th>No. of patients with reticulocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low intensity HSCT:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patients with donor engraftment (n=16)</td>
<td>13.4 (6.2-36.6)*</td>
<td>5 (0-14)</td>
<td>1.5 (0-12)</td>
<td>10</td>
</tr>
<tr>
<td>patients with autologous reconstitution</td>
<td>24.95 (6-82)</td>
<td>7.5 (5-35)</td>
<td>0 (0-60)</td>
<td>3</td>
</tr>
<tr>
<td>of hematopoiesis (n=8)</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Standard HSCT (control) (n=26)</td>
<td>2.45 (0.6-11.7)</td>
<td>6 (-1-13)</td>
<td>17 (14-30)</td>
<td>25</td>
</tr>
</tbody>
</table>

*Median (range).

Reticulocytes. Reticulocytopenia in patients with donor engraftment was significantly less severe than in the control group (median nadir 12 ×10⁹/L, range 2-37 ×10⁹/L, p<0.001). However, all patients had a decline of the reticulocyte count to <40 ×10⁹/L and in 10 patients the reticulocytes fell to <20 ×10⁹/L. The speed of the decline of the reticulocytes was similar in all 3 groups. The nadir was achieved on +5 posttransplant day (p=0.663). The time patients were reticulocytopenic with <20 ×10⁹/L reticulocytes and <40 ×10⁹/L reticulocytes was significantly shorter than in the control group (p<0.001).

Five patients with autologous reconstitution of hematopoiesis had the reticulocytes decreased to <40 ×10⁹/L and 3 of them to <20 ×10⁹/L. Reticulocytopenia was of similar extent as in patients with donor engraftment (median nadir 24.95 ×10⁹/L, range 6-82 ×10⁹/L, p=0.055), but significantly less severe than in the control group (p<0.001). The speed of the reticulocyte decline was similar in all 3 groups. Reticulocyte recovery to >20 ×10⁹/L and >40 ×10⁹/L took 0 days (range 0-60 days) and 6.5 days (range 0-60 days) respectively and was similar to the patients with donor engraftment but significantly shorter than in the control group (p<0.001). The reticulocyte count of one patient did not recover to >20 ×10⁹/L by day 60.

All patients in the control group had severe reticulocytopenia and reticulocyte nadir was 2.5 ×10⁹/L (range 0.6-11.7 ×10⁹/L) on +6 posttransplant day (range day -1 to 13) (Table 4). All patients had a decrease of their reticulocyte count to <20 ×10⁹/L. Recovery to >20 ×10⁹/L and >40 ×10⁹/L took a median of 17 days and 18 days, respectively.

Discussion

The data presented confirm and extend initial observations on cytopenia after low intensity conditioning HSCT. In the majority of patients the cytopenia was less severe and of shorter duration. Some patients, however, experienced severe cytopenia even after low intensity HSCT. This was more pronounced in the erythroid lineage and the platelets and less obvious in the myeloid lineage. Second, the speed of the decline in peripheral blood cell counts was slower and the nadir occurred later posttransplant. Again, there was a difference in the speed of the decline among the three hematopoietic lineages. Furthermore, the recovery from severe neutropenia was more rapid after low intensity conditioning than after standard HSCT, but full recovery of granulocytes to normal values occurred later.

Cytopenia after HSCT is a complex phenomenon. The kinetic of its occurrence is different for the three hematopoietic lineages, the onset, speed of decline of blood counts, severity, duration, and speed of recovery are influenced by many factors like the conditioning regimen used, the stem cell dose, the stem cell source, and the donor type, and it is complicated by graft rejection, graft versus host disease, infections, and drug treatment (10).

So far, few data exist on cytopenia and hematopoietic recovery after low intensity HSCT. Usually only mild hematological toxicity is reported (11-16). Such statements need to be balanced. Data reported depend on the regimen employed. All patients treated with fludarabine and cyclophosphamide experienced severe neutropenia (11) and suffered from substantial organ toxicity (12). Similarly, 13 of 15 patients had neutrophil counts of <0.5 ×10⁹/L after treatment with a conditioning regimen containing fludarabine, cytarabine, and idarubicin (13) and all patients had severe neutropenia after cyclophosphamide and antithymocyte globulin (16). Details of neutropenia kinetics in patients treated with 200 cGy TBI with or without fludarabine have not been reported (15).

The myelosuppression induced by the treatment with 200 cGy TBI in humans, with or without stem cell support, is unknown. Dogs irradiated with the same TBI dose and without stem cell support, had the nadir for granulocytes 20 days after the treatment and the platelet count was lowest between day 16 and day 24 (17).

Conventional high dose chemotherapy induces severe cytopenia and a rapid disappearance of host peripheral blood cells as shown in our control group (10). TBI based regimens induce a faster decline of the blood counts than non TBI based regimens (18). These observations support the concept that the intensity of the conditioning regimen parallels the severity of the cytopenia induced. The duration of the cytopenia is determined by the speed of the disappearance of the host cells and the rate of the appearance of cells generated by the infused stem cell graft. Several factors have been shown to influence hematopoietic recovery after HSCT. The stem cell dose infused is of great importance. This has been confirmed repeatedly and was put into focus again in the context of umbilical cord blood cell transplants: a high stem cell dose speeds up hematopoietic recovery (19-22). Recovery is faster with peripheral blood as the stem cell source compared with the bone marrow as well. Recipients of HLA-identical sibling grafts show a faster engraftment than recipients of unrelated donor
grants (23,24). The observation that engraftment is faster in patients with severe aplastic anemia compared to patients with chronic myeloid leukemia (25) indicates that the space for the incoming donor cells (patients with aplastic anemia would have abundance of space, patients with chronic myelogenous leukemia a minimum only) may be more important than the conditioning itself, and that the effects of the conditioning are indirect and related to its impact on “marrow cleaning”.

The patients included in both groups of the present study had similar cell doses, all patients received peripheral blood stem cell grafts, and the proportion of related and unrelated transplants was similar. Patients with aplastic anemia were not included in the study population. The major differences between our study groups and the control group were the toxicity of the conditioning and the posttransplant immunosuppressive regimen.

Residual host cells may compete with reconstitution of donor hematopoiesis. The amount and activity of the remaining host cells are influenced by the intensity of the conditioning as well as by the immunosuppressive regimen used. Our data shows clear differences between the kinetic of recovery from severe cytopenia and the kinetic of recovery to full reconstitution.

Four of 16 patients with engraftment showed secondary neutropenia. The phenomenon of secondary neutropenia has been described in few studies and been linked to cell dose. Patients with a stem cell dose of $<3 \times 10^8$ CD34$^+$ cells/kg or $<3.5 \times 10^8$ nucleated cells/kg were found to be at greater risk for developing secondary neutropenia (26,27). It has been suggested, that initial engraftment of neutrophils may depend more on committed precursors than on stem cells and the role of T cells has been discussed (28). Three of the patients who experienced a second neutropenia had chronic lymphocytic leukemia, one had a myelodysplastic syndrome. The occurrence of secondary neutropenia was not related to GvHD or infection, without decline in donor chimerism and all patients had received a cell dose $>3.5 \times 10^8$ CD34$^+$ cells/kg and their cell dose was not different from those without secondary neutropenia. This may indicate that the necessary cell dose to achieve full engraftment without secondary neutropenia might be higher in low intensity conditioning than in standard HSCT (29).

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