Bone loss following hematopoietic stem cell transplantation: a long-term follow-up

Claudia M. S. Schulte and Dietrich W. Beelen

Transplantation-associated bone loss is a well-known phenomenon, however, effects of hematopoietic stem cell transplantation are insufficiently characterized. We conducted a prospective, unicentric, long-term follow-up in 280 patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Bone mineral density (BMD) was measured before transplantation and then yearly for at least 4 years. Patients received vitamin D plus calcium until steroid withdrawal. Mean baseline BMD was normal. We demonstrated significant bone loss with nadir BMD at month 6 for the spine and at month 24 for total body and femoral neck. Average annual bone loss was 0.6% for spine, 0.4% for total body, 2.3% for femoral neck, and 3.5% for Ward triangle. While spine and total body BMD returned to baseline, bone loss at femoral neck sites was attenuated, but BMD did not return to baseline until month 48 ($P < .0001$ for femoral neck and Ward triangle). Univariate factor analysis of 15 potential risk factors for rapid bone loss revealed a positive correlation of bone loss with steroid and cyclosporine A use, baseline BMD, and loss of muscle mass (overwhelming power of steroid use in multifactor analysis). Such rapid BMD changes probably increase fracture risk consequent to irreversible microarchitectural changes even if osteodensitometry shows long-term recovery.

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Introduction

Organ transplant recipients benefit from greatly improved survival, however, long-term complications such as osteoporosis and osteoporotic fractures adversely affect life quality and therefore have to be addressed. Transplantation of solid organs such as heart, kidney, liver, and lung is associated with rapid bone loss and increased susceptibility to osteoporotic fragility fractures. Transplantation-associated bone loss has been demonstrated to occur preferentially during the first year after transplantation, with at least partial recovery during further follow-up. Data on the temporal sequence of bone loss in long-term survivors following hematopoietic stem cell transplantation (HSCT) are sparse. However, these patients are exposed to numerous bone toxic factors: induction and consolidation therapy of the underlying hematological disease; malignancy-related changes in bone structure, especially in acute leukemia; dose-dependent toxicity of high-dose chemotherapy to bone marrow osteoprogenitors; conditioning regimen for transplantation, including total body irradiation (TBI); graft-versus-host disease (GVHD) and its treatment with steroids and cyclosporine A; immobilization; and hypogonadism following TBI. Cross-sectional studies of bone loss after HSCT revealed conflicting data: 5 of 25 patients, examined at least one year after HSCT (mean, 3; range, 1-10 years) showed osteoporotic bone mineral density (BMD) 29; 29 long-term survivors with a median survival of 5 years (minimum, 3 years) showed BMD within normal limits (Z-score > -1.5) except 2 male patients with hypogonadism. Prospective studies of bone loss are sparse; the study with longest observation time presents follow-up of 11 patients observed for 3 years. Data demonstrate rapid bone loss during the first 6 months after transplantation (5.7% at the lumbar spine and 6.9% to 8.7% at the femoral neck sites) with no further decline between months 6 and 12 and even recovery of bone mass during further follow-up. Ebeling first evaluated likely mechanisms for bone loss in 39 patients with a longer prospective follow-up (at least 3 consecutive BMD measurements within median follow-up of 30 months [range, 5-64 months]). Post- allo-bone marrow transplantation bone loss correlated best with the cumulative prednisolone dose and was negatively related to duration of cyclosporine therapy and baseline desoxypyridinoline concentrations. In contrast to a cross-sectional and a recent prospective study, the 10 auto-HSCT patients acting as controls in this study showed an increase or insignificant decrease of bone mass following auto-SCT.

The aim of this prospective study was to analyze long-term changes of BMD and determinants of bone loss in patients undergoing allogeneic HSCT. Data from a cohort of 280 patients followed for at least 4 years after allogeneic HSCT are presented.

Patients, materials, and methods

Study population and design

Enrolled in the study were 280 adult men and women, age 16 to 59 years, who underwent allogeneic HSCT during the period from September 1, 1995, to May 31, 1999, in our institution. Exclusion criteria were disorders known to affect bone and mineral metabolism (primary hyperparathyroidism, thyrotoxicosis, and serum creatinine above 2.5 mg/dL before...
transplantation). The University Hospital of Essen, Germany, ethics committee approved the study protocol, and the patients gave informed consent for the procedures.

BMD measurements were performed at the lumbar spine, right hip, and total body before transplantation, at discharge, 6 and 12 months after HSCT, and then yearly. A questionnaire regarding physical activity, diseases predisposing to osteoporosis, family and social history, dietary habits, and nicotine/alcohol abuse was filled in at baseline. After transplantation, patients received 1000 mg calcium plus 1000 IU vitamin D daily until withdrawal of steroid medication. All women received hormone replacement therapy (HRT) with estrogens and cyclical or continuous progesterone. The choice of HRT depended on the prescribing physician but always included at least 0.625 mg estradiol equivalent.

**Patient follow-up**

Details of patient follow-up are summarized in Table 1. Patients were followed for at least 4 years; the longest observation period was 7.5 years. Lost to follow-up were 150 patients because of patient death, most within the first year after transplantation. Due to start-up of bone-active medication, 26 patients had to be excluded. Start of bone-active medication depended on the prescribing physician. Reasons for prescription of corticosteroids were occurrence of either osteoporotic fracture or osteonecrosis of the femoral head. All 26 patients received 1000 mg calcium plus 1000 IU vitamin D daily until withdrawal of steroid medication. Of the 124 patients who were followed for at least 6 months after transplantation, 28 patients had to be excluded because of death, most within the first 6 months of transplantation.

Obviously, not every patient attended every scheduled appointment, however, long-term follow-up was high for such a long-term study, with corresponding attendance rates from 75% to 96% per visit (Table 1). Many patients skipped more than 2 of the 6 scheduled appointments after HSCT. Long-term bone loss (Table 2) was defined as the average bone loss per year, calculated either at the 4- or 5-year interval in 81 patients (67 patients with the 4-year follow-up plus 14 patients, who missed the 4-year follow-up but completed the 5-year follow-up). Risk factor analysis for long-term bone loss (Tables 2-3) was performed in these 81 patients.

**Cytostatic chemotherapy, preparative regimens, and GVHD prophylaxis**

Before transplantation, patients received different cytoreductive regimens for underlying hematological disease. For chronic phase chronic myeloid leukemia (CML), standard therapy included hydroxyurea or busulfan and human interferon-alpha; for acute myeloid leukemia (AML), standard therapy included hydroxyurea until transplantation, partially in combination with interferon-alpha and sevelamer carbonate (MMF). The cumulative steroid dose (expressed in prednisolone equivalents) and the number of days under medication with cyclosporine A and/or mycophenolate mofetil (MMF). The cumulative steroid dose (expressed in prednisolone equivalents) and the number of days under medication with cyclosporine A and MMF were recorded in detail. The total steroid dose applied was expressed in total gram and milligram prednisolone equivalent per day since transplantation (calculated by dividing the total cumulative steroid dose by the number of days since transplantation).

Grading of acute (grades 0 to IV) and chronic GVHD (yes/no) was performed according to the established classifications.

**Bone mineral density assessment**

Bone mineral density was measured by Dual Energy X-Ray Absorptiometry (DEXA) at lumbar spine (average BMD of the second, third, and fourth vertebrae) and proximal left femur (femoral neck, trochanter, Ward triangle). A single DEXA machine was used for all measurements.

<table>
<thead>
<tr>
<th>Time after transplant, mo (SD)</th>
<th>No. of patients eligible for follow-up</th>
<th>Cause of patient censorship</th>
<th>Loss to follow-up, no.</th>
<th>No. of patients tested (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (59 ± 24)</td>
<td>240</td>
<td>Death, no. 1</td>
<td>3</td>
<td>180 (75)</td>
</tr>
<tr>
<td>6 (199 ± 31)</td>
<td>174</td>
<td>Medication, no. 5</td>
<td>0</td>
<td>132 (76)</td>
</tr>
<tr>
<td>12 (392 ± 53)</td>
<td>138</td>
<td>Medication, no. 5</td>
<td>0</td>
<td>133 (90)</td>
</tr>
<tr>
<td>24 (762 ± 76)</td>
<td>115</td>
<td>Medication, no. 5</td>
<td>1</td>
<td>104 (80)</td>
</tr>
<tr>
<td>36 (1136 ± 101)</td>
<td>93</td>
<td>Medication, no. 7</td>
<td>0</td>
<td>81 (87)</td>
</tr>
<tr>
<td>48 (1479 ± 106)</td>
<td>85</td>
<td>Medication, no. 7</td>
<td>0</td>
<td>67 (79)</td>
</tr>
</tbody>
</table>

Total number of patients in the study population = 280.

**Table 2. Amount of long-term bone loss after allogeneic stem cell transplantation and its correlating factors**

<table>
<thead>
<tr>
<th>Bone loss (percent/year ± SD)</th>
<th>Spine</th>
<th>Total body</th>
<th>Femoral neck</th>
<th>Ward triangle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone dose †† ††</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative steroid total</td>
<td>0.43</td>
<td>0.48</td>
<td>0.39‡</td>
<td>0.28‡</td>
</tr>
<tr>
<td>Cum steroid per day</td>
<td>0.43</td>
<td>0.48</td>
<td>0.41‡</td>
<td>0.3‡</td>
</tr>
<tr>
<td>Exposure to CyA (52% ± 34% of days*)</td>
<td>0.2 NS</td>
<td>0.23‡</td>
<td>0.01 NS</td>
<td>0.09 NS</td>
</tr>
<tr>
<td>Loss of body weight (1.2% ± 2.7%/year*)</td>
<td>0.26‡</td>
<td>0.47</td>
<td>0.13 NS</td>
<td>0.07 NS</td>
</tr>
<tr>
<td>Loss of muscle mass (2.1% ± 2%/year*)</td>
<td>0.39‡</td>
<td>0.54</td>
<td>0.2 NS</td>
<td>0.12 NS</td>
</tr>
<tr>
<td>Z-score baseline</td>
<td>0.22‡</td>
<td>0.23‡</td>
<td>0.36‡</td>
<td>0.24‡</td>
</tr>
</tbody>
</table>

*The mean ± 1 standard deviation of the corresponding parameter. †The correlation coefficients and the P values. P* values classified as ns = not significant, †P < .05, ‡P < .001, ‡P < .0001.

CyA indicates cyclosporin A; NS, not significant; Z-score correlation given for the corresponding site of measurement.

Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), Hodgkin disease, and multiple myeloma had different combination chemotherapies with higher doses of cytoreductive medication. These patients are later referred to as “high-toxicity chemotherapy group.”

The different standard preparative regimens for conditioning therapy and for GVHD prophylaxis have been previously described in detail. Most, fractionated total-body irradiation plus cyclophosphamide or busulfan plus cyclophosphamide were part of the conditioning therapy. Parenteral nutrition with glucose, amino acids, and lipids (calorie intake 35 kcal/kg BW/d) was supplemented by water- and fat-soluble vitamins including 200 IU of ergocalciferol (vitamin D3). GVHD prophylaxis with cyclosporine A and metotrexate was started at day -1. Acute GVHD was treated with cyclosporine A plus corticosteroids, starting with 2 mg/kg body weight and dose escalation or reduction depending on the response of GVHD symptoms. Chronic GVHD was treated with prednisolone (1-2 mg/kg/d) in combination with cyclosporine A and/or mycophenolate mofetil (MMF). The total steroid dose (expressed in prednisolone equivalents) and the number of days under medication with cyclosporine A and MMF were recorded in detail. The total steroid dose applied was expressed in total gram and milligram prednisolone equivalent per day since transplantation (calculated by dividing the total cumulative steroid dose by the number of days since transplantation).
A quality assurance test was performed daily with a standard block of tissue-equivalent material with 3 bone-simulating chambers of known bone mineral content and monthly with an anthropomorphic spine phantom.

Total body composition was measured by Dual Energy X-Ray Absorptiometry (DEXA; Lunar DPX-L) as a total body scan, with the body compartments of fat mass, lean mass (muscle, fluid, connective tissue, etc), and bone mineral. Data were expressed in kilogram fat mass, kilogram lean (= muscle) mass, and total kilogram body weight (fat mass + lean mass + bone mineral content).

### Bone loss analysis

Analysis of bone loss was performed for all data available at each point of time. Data are given in absolute values and in percent change from baseline. Percentage of change was calculated by subtracting the value at a given time point from the baseline value and dividing by the baseline value. To equalize time intervals, values were divided by the number of days since baseline and multiplied by the time the analysis was scheduled (day 60 for the discharge value, day 180 for the 6-month value, day 365 for the one-year value, and so on).

### Fractures

Fractures were determined by chart review. Radiographs of the affected areas as indicated by clinical symptoms (for example, bone pain) diagnosed new fractures. Radiographic screening for asymptomatic vertebral fractures was not performed in this study population due to the low prevalence of pre-existing osteoporosis.

### Risk factors for osteoporosis

We performed a univariate analysis of various potential risk factors for osteoporosis and rapid bone loss to obtain information on the etiology of HSCT-associated osteoporosis. Evaluated were 15 potential risk factors for rapid bone loss (Table 4), divided into risk factors present and known before transplantation, those associated with transplantation and known at baseline, and those developing and changing with time after transplantation.

### Statistical methods

All data are presented ± 1 SD. Replicate BMD and Z-scores were analyzed using repeated measure analysis of variance (ANOVA). Data collected from patients until dropout from study (due to death, loss to follow-up, or medication) were included in the statistical analysis. Plots of all individual bone density trajectories were generated and inspected. Fisher exact test and between-subject ANOVA were used to test the possible variations between nominal variables (Table 4). The correlation between change in BMD and change in continuous variables was tested by correlation analysis (Spearman coefficient). All statistical analyses were performed using JMP (SAS institute) for Macintosh software.

### Results

#### Characteristics of the patient population and follow-up

The shortest observation time was 4 years; the longest current follow-up to month 12, data were not stratified for menopausal status.

As summarized in Table 5, hematological diagnosis included CML (n = 154), AML (n = 67), ALL (n = 22), myelodysplastic syndromes (n = 20), non-Hodgkin lymphoma (n = 6), and 11 patients with other diseases (severe aplastic anemia [n = 5], multiple myeloma [n = 3], Hodgkin disease [n = 2], and one case of myelosarcoma).

Time between diagnosis of hematological disease and transplantation was longer in CML (27 ± 33 months) than in MDS (26 ± 67 months) than in NHL (24 ± 7.4 months) and acute leukemia (17 ± 18 months).

Conditioning therapy before transplantation included radiation in most of the 230 cases and was performed as radio-chemotherapy including cyclophosphamide in 228 cases.

Of the 183 patients receiving their allogeneic transplant from related donors, 142 cases were HLA identical and 41 were HLA mismatches. Of the 97 patients receiving their transplant from unrelated donors, 84 cases were HLA identical and 13 were HLA.
mismatches. Transplantation was performed with bone marrow in 161 cases and with peripheral blood stem cells in 119 cases. Of these patients, 27% developed no acute GVHD; 28%, grade I; 24%, grade II; 10%, grade III; and 10%, grade IV. Forty-five percent of patients developed chronic GVHD.

Details of immunosuppressive therapy regimen are summarized in Figure 1. The number of patients without immunosuppressive therapy increased with time from transplantation to 42% of patients without immunosuppressive medication 4 years after transplantation.

BMD before bone marrow transplantation
Mean pretransplantation BMD was within normal limits (Table 6). Few patients suffered from pre-existing osteoporosis.

Analysis of risk factors for pre-existing osteoporosis demonstrated no major influence for the factors 1-6, those present at transplantation:

1. Underlying hematological disease. Patients with ALL tended to have lower baseline Z-scores compared to patients with AML and especially with CML and MDS. However, statistical significance was reached only for comparison of ALL and CML patients at the femoral neck sites (Z-score femoral neck: ALL/AML 0.55/1.29 versus CML/AML 0.31/1.1, \( P = .006 \); Z-score Ward triangle: ALL/AML 0.41/1.33 versus CML/AML 0.49/1.2, \( P = .008 \)), but not for any other type of diagnosis or site of measurement.

2. Time between diagnosis and transplantation. No significance for any BMD site.
3. Treatment before transplantation. Patients who had received “high-dose chemotherapy” before transplantation showed slightly lower Z-scores than patients who had received “low-dose chemotherapy,” differences reaching significance for all sites of measurement: spine (−0.44 ± 1.3 versus −0.13 ± 1.23, P = .04), femoral neck (−0.2 ± 1.17 versus 0.36 ± 1.09, P = .0003), Ward triangle (−0.11 ± 1.2 versus 0.49 ± 1.2, P = .0003), total body BMD (0.3 ± 0.97 versus 0.55 ± 0.96, P = .04).

4. Patient age. No significance for any BMD site.

5. Gender. No significance for any BMD site.


**Bone loss after bone marrow transplantation**

Replicate BMD values and Z-scores at the lumbar spine, total body, and femoral neck sites before transplantation, at discharge, and at 6, 12, 24, 36, and 48 months are shown in Table 6 (analyzed using repeated measure ANOVA).

There was a significant reduction of spine BMD during the first year after transplantation, with a trend to recover during further follow-up. At month 48, spine BMD had returned to the baseline level (P = .1).

The reduction of BMD at the total body compartment was less marked compared to the spine and occurred later with nadir BMD 2 years after transplantation. At month 48, total body BMD also had returned to baseline level (P = .07).

The reduction of BMD at femoral neck sites was more dramatic, with lowest BMD 24 months after transplantation. There was still significant bone loss during year 3 and 4 after transplantation. At month 48, BMD had not returned to baseline level for the femoral neck (P < .0001) and Ward triangle (P < .0001).

Cumulative BMD changes for different sites are summarized in Figure 2. Average bone loss per year was significantly higher at the femoral neck sites than at the spine and total body compartment (Figure 2; Table 2). Expressed in absolute bone loss in g/cm², bone loss at month 48 averaged 0.038 ± 0.11 g/cm² at the spine, 0.12 ± 0.12 g/cm² at the femoral neck, 0.16 ± 0.14 g/cm² at Ward triangle, and 0.02 ± 0.06 g/cm² at the total body compartment.

**Correlates of bone loss during further follow-up**

We performed a univariate analysis of all 15 above-named risk factors for long-term bone loss after transplantation, factors known at transplantation as well as factors developing with time after transplantation. As stated in “Patients, materials, and methods,” this risk factor analysis was performed in 81 patients (67 patients who performed the 4-year follow-up, plus 14 patients who missed the 4-year follow-up but performed the 5-year follow-up).

Univariate risk factor analysis revealed steroid and cyclosporine A medication, loss of body weight (especially of muscle), and the baseline BMD as parameters with significant correlation with the observed bone loss (Table 2). None of the other factors such as age at transplantation, sex, or type of diagnosis were of any significance for future bone loss. While steroid medication was strongly correlated with changes of bone mass at all BMD sites, cyclosporine A medication showed weak correlation for spine and total body but not for the femoral neck sites. Bone loss at the spine and total body was strongly correlated with loss of muscle mass and with loss of body weight. This correlation was not confirmed for femoral neck sites. Baseline Z-scores were positively correlated with bone loss at the corresponding sites.

Multivariate analysis revealed steroid medication to be a much stronger predictor for high bone loss compared to all other

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**Table 6. Z-scores after allogeneic stem cell transplantation at different BMD sites**

<table>
<thead>
<tr>
<th></th>
<th>Lumbar spine</th>
<th>Total body</th>
<th>Femoral neck</th>
<th>Ward triangle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Z-score (SD)</strong></td>
<td>% patients*</td>
<td>P value†</td>
<td>% patients*</td>
<td>P value†</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.21 (1.27)</td>
<td>0.44 (0.97)</td>
<td>0.11 (1.16)</td>
<td>0.23 (1.25)</td>
</tr>
<tr>
<td></td>
<td>27/4.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>0.51 (1.22)</td>
<td>0.45 (1.0)</td>
<td>NS</td>
<td>-0.27 (1.33)</td>
</tr>
<tr>
<td></td>
<td>32/5.5</td>
<td></td>
<td></td>
<td>-0.11 (1.32)</td>
</tr>
<tr>
<td>Month 6</td>
<td>0.82 (1.16)</td>
<td>0.28 (0.96)</td>
<td>†</td>
<td>0.7 (1.17)</td>
</tr>
<tr>
<td></td>
<td>38/6.7</td>
<td></td>
<td></td>
<td>38/10</td>
</tr>
<tr>
<td>Month 12</td>
<td>0.77 (1.18)</td>
<td>0.15 (0.95)</td>
<td>†</td>
<td>0.69 (1.14)</td>
</tr>
<tr>
<td></td>
<td>38/5.7</td>
<td></td>
<td></td>
<td>38/10</td>
</tr>
<tr>
<td>Month 24</td>
<td>0.68 (1.13)</td>
<td>0.1 (0.94)</td>
<td>†</td>
<td>0.76 (1.17)</td>
</tr>
<tr>
<td></td>
<td>31/6.8</td>
<td></td>
<td></td>
<td>42/10</td>
</tr>
<tr>
<td>Month 36</td>
<td>0.36 (1.4)</td>
<td>0.35 (1.18)</td>
<td>†</td>
<td>0.62 (1.31)</td>
</tr>
<tr>
<td></td>
<td>27/9.3</td>
<td></td>
<td></td>
<td>31/5.13</td>
</tr>
<tr>
<td>Month 48</td>
<td>0.42 (1.28)</td>
<td>NS</td>
<td>0.27 (1)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>35/4.6</td>
<td></td>
<td></td>
<td>40/5.95</td>
</tr>
</tbody>
</table>

*The percentage of patients with osteopenia (T-score ≤ 1 and > −2.5) and the percentage of patients with osteoporosis (T-score ≤ −2.5).
†P value comparing the corresponding Z-score with the baseline Z-score.
‡P < .05, †P < .001, §P < .0001.
NS indicates not significant.
Bone loss was highest during the first year after transplantation. This bone loss was pronounced at the femoral neck sites compared to the spine.10,35 Bone loss was 1.1% per year in young patients compared to 3% per year in older patients (P = .01). These age-dependent differences were not explained by differences in steroid intake. However, only very young patients seem to be protected from bone loss. The described age-dependent difference could not be confirmed comparing patients younger or older than 40 to patients younger or older than 50 (median age of the population, 38 years).

Outcome of patients with pre-existing osteoporosis

Spinal osteoporosis (T-score ≤ −2.5) was present before transplantation in 12 patients. Of these 12 patients, 8 died within the first year after transplantation (days 32, 34, 61, 65, 96, 191, 204, and 330 after transplantation) and did not develop bone complications such as overt fracture until death. Four patients with pre-existing osteoporosis (current follow-up 46, 56, 72, and 73 months after transplantation) did not develop overt bone complications until follow-up, 3 patients receiving antiresorptive therapy, one patient receiving vitamin D and calcium.

Femoral neck osteoporosis (T-score ≤ −2.5) was present before transplantation in 2 patients. None of these patients developed overt fracture until last follow-up (current follow-up 56 and 74 months after transplantation). One patient started with antiresorptive therapy 9 months after transplantation.

Osteoporotic fractures and antiresorptive therapy after transplantation

As mentioned in “Patients, materials, and methods,” radiographic screening for vertebral fractures was not performed. This probably results in underestimation of fracture incidence in the cohort. To give a sense of the clinical outcome regarding osteoporotic fractures and antiresorptive therapy, we summarized clinical data of all patients who suffered from an osteoporotic fracture and/or received antiresorptive therapy (Table 7). We observed clinically overt osteoporotic fracture of vertebrae or femoral neck in 10 patients. In 5 of these 10 patients antiresorptive therapy was started at occurrence of fracture (patients no. 1, 19, 28, 32, and 34). None of these patients developed a second fracture during further follow-up. None of 4 patients who were not treated with antiresorptive medication after fracture occurrence developed another fracture within further follow-up. One patient developed a femoral neck fracture under current antiresorptive therapy (patient 4).

Antiresorptive therapy was started in 31 patients. In 22 patients antiresorptive therapy was started in preventive intention, in most cases in response to an osteoporotic BMD result. In the remaining 9 patients antiresorptive therapy was started in response to fracture (n = 5), for osteoporotic pain syndrome without radiologic evidence of fracture (n = 1, patient no. 12), for pre-existing osteoporosis (n = 1, patient no. 22), or in response to an avascular bone necrosis (n = 2, patient nos. 15 and 18).

Discussion

Transplantation of hematopoietic stem cells (either from a peripheral or bone marrow source) is an accepted treatment modality performed in steadily increasing numbers. Despite constantly increasing survival rates, transplantation of blood stem cells is still associated with significant morbidity and mortality. The often-young patients who survive long-term after HSCT are confronted with new life-long problems if they develop chronic osteoporosis–associated pain syndromes and osteoporotic fractures.

Strongest risk factors for osteoporosis are female sex and old age (so-called postmenopausal and senile osteoporosis). Within the numerous other risk factors for osteoporosis, corticosteroid use is most important. Transplantation-associated bone disease is classified as a specific type of steroid-induced osteoporosis. However, the dose-effect curve for steroid use in the development of transplantation-associated osteoporosis still is not as clear as expected and desirable. Data also are sparse for the temporal sequence of bone loss after transplantation and fractures rates. All this hinders the establishment of general recommendations for prophylaxis and treatment of transplantation-associated osteoporosis.

In order to obtain data on the temporal sequence of bone loss at different sites (spine, total body, and femoral neck) after HSCT, we measured BMD before HSCT and at 6 fixed time points after transplantation in 280 consecutive allogeneic HSCT recipients. We demonstrated rapid early decline of BMD during the first year after transplantation. This bone loss was pronounced at the femoral neck compared to spine and total body compartment. While spinal and total body BMD showed recovery during further follow-up, BMD continuously declined at the femoral neck sites. Average annual long-term bone loss accounted for 0.62%/year at the spine and 0.4%/year at the total body compartment, an amount comparable with the bone loss seen in a population with such age distribution. With 2.3%/year for the femoral neck and 3.5%/year at the Ward triangle, long-term bone loss at the femoral neck exceeded bone loss seen in the general population of young people.

In agreement with previous findings, the incidence of pre-existing osteoporosis was low in our cohort (4.3% spinal osteoporosis, 0.9% femoral neck osteoporosis). However, the high-risk patients (those who receive a significant amount of steroids before transplantation, such as ALL and NHL patients) were underrepresented in the cohort. Our data showing that ALL patients exhibit significantly lower femoral neck BMD than CML patients points to the importance of pretreatment for baseline BMD. In agreement with findings after solid organ transplantation16 and 2 prospective studies after HSCT,10.22 we demonstrated significant early decline of bone mass. We could validate the previously described phenomenon of bone loss being pronounced at femoral neck sites compared to the spine.10,35 Bone loss was highest during the first year for all
Follow-up for 3 more years revealed site-specific differences. At the lumbar spine and total body no further bone loss occurred but even recovery of bone mass was demonstrated, and the 4-year BMD had returned to baseline values. The amount of femoral neck bone loss attenuated after the first year after transplantation but continued for the total observation period of 4 years.

Expectedly, there was significant loss to follow-up particularly during the first year after transplantation. Of the 150 cases of loss to follow-up because of patient death, 112 occurred within the first year after transplantation. Loss to follow-up for other reasons was very small, and 26 patients were excluded from bone loss analysis because antiresorative therapy was started.

The demonstration of significant, persistent bone loss at the femoral neck, but not at the spine, is consistent with findings of Schimmer and Gandhi. However, while the tendency for preferential femoral BMD loss is comparable, the amount and temporal sequence of bone loss differ significantly between our cohort of allo-HSCT patients and the cohorts of auto-HSCT patients of Schimmer and Gandhi. We assume that allogeneic and autologous transplantation are not comparable with respect to changes to bone mass. This issue has to be addressed in future studies.

The pathogenesis of bone loss in hematopoietic stem cell transplantation has been subject to many speculations. Risk factors under discussion are numerous, and their individual ability to predict bone loss is difficult to evaluate. General risk factors for osteoporosis, such as the patient’s age, sex, body indices, and the malignancy itself, have been discussed as pre-existing individual risk factors. Physical inactivity during the stay on the transplantation unit, nutritional deficits with consecutive changes in body indices, hypogonadism following the conditioning therapy, direct toxicity of high-dose chemotherapy to the bone, and the administration of steroids and cyclosporine A for prevention and treatment of GVHD and GVHD itself are named as further transplantation-associated risk factors.

Because the relevance and value of single factors for bone loss are unclear, we performed a detailed risk factor analysis for most of the above-named risk factors (Table 4). This approach has not been performed until now. We could demonstrate that only few factors were significantly associated with risk for rapid bone loss, namely,
cumulative steroid dose and average steroid dose per day, average duration of exposure to cyclosporine A, and negative changes in body mass, especially muscle mass and high baseline BMD.

In the multivariate analysis, the effects of changes in body mass were highly exceeded by the steroid effect. The good correlation between loss of muscle mass and amount of steroid intake per day confirms the muscle-catabolic effects of steroids (Table 3). Compared to the effects of steroid therapy, cyclosporine A use was of minor importance. Long-term cyclosporine A therapy for chronic GVHD has far less burden for the bone than the devastating effects of long-term steroid therapy. The temporal evolution with constantly increasing correlation coefficients nicely illustrates that numerous factors besides steroids must influence bone loss early after transplantation.

By the end of the first year after transplantation, bone mass either starts to recover (spine and total body) or bone loss is attenuated (femoral sites). This improvement is probably due to multiple factors, including reduction in cyclosporine A dosage, resolution of pretransplantation conditions that were deleterious to skeletal health (such as immobilization or malnutrition), and convalescence from the profound damage associated with the conditioning therapy and transplantation procedure itself. In contrast to the short-term follow-up, long-term bone loss is clearly and mainly determined by intensity of steroid application.

The significance of the observed changes in BMD after HSCT with respect to fracture risk has not been established. Large epidemiological studies have demonstrated the potential of BMD to predict future fracture risk. Until now, first short-term data do not indicate a significantly increased risk after autologous transplantation.\(^{10}\) The situation after allogeneic transplantation is unclear. Long-term follow-up is absolutely necessary to assess long-term fracture risk in these young patients. Long-term fracture risk is determined not only by BMD; after correction for BMD, vertebral fracture itself is a potent risk factor for future fracture.\(^{40}\) Furthermore, fracture risk is associated with history of falls, attributes of bone geometry, and, increasingly studied by 3-dimensional bone CT, with microarchitecture.\(^{41,42}\) In this context, the observation of dramatic decrease in BMD with later recovery of bone mass in transplant patients is of special interest. We do not know whether the microarchitectural changes of bone structure occurring in the context of transplantation are irreversible, while osteodensitometric BMD values return to normal and suggest convalescence. Before evidence-based recommendations for the prevention and treatment of SCT-associated osteoporosis can be given, the implications of our findings require further long-term study of large cohorts, including fracture rates.

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References


Erratum

In the article by Sayeh et al entitled “IgG antiplatelet immunity is dependent on an early innate natural killer cell–derived interferon-γ response that is regulated by CD8+ T cells,” which appeared in the April 1, 2004, issue of Blood (Volume 103:2705-2709), a negative symbol was omitted in several places. The last 2 subsections of “Results” should refer to “CD4+ lymphocytes,” as should “Discussion.” The Figure 5 title should refer to “CD4+ peripheral blood lymphocytes.”
Bone loss following hematopoietic stem cell transplantation: a long-term follow-up

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