Autografting

Obesity and autologous stem cell transplantation in acute myeloid leukemia

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Summary:

In the bone marrow transplant setting, several authors hypothesized that severely overweight patients are at increased risk of transplant-related toxicity, but different definitions of obesity, different body weight groupings and heterogeneous samples of patients were analyzed. To overcome these limitations, we retrospectively considered a homogeneous group of 54 patients (median age 36.5 years), with a diagnosis of de novo acute myeloid leukemia (AML), autografted in first complete remission (CR) with the Bu-Cy2 conditioning regimen, dosed on actual body weight. Patients were classified into three groups (obese, non-obese, underweight) using body mass index (BMI = kg/m²); for each group we analyzed transplant-related toxicity and mortality, overall survival and disease-free survival (OS/DFS). In spite of the relatively small number of patients, in our results high BMI appears a predictive factor for an increase of treatment-related toxicity and mortality. Moreover, 30 (55%) patients are currently alive in continuous CR, and after a median follow-up of 76.5 months (range 14–137) statistically significant differences in OS and DFS were detected between obese and non-obese groups (P = 0.012 and 0.021, respectively). Our study suggests that obesity may represent an independent risk factor for autograft in AML and further investigations are warranted. Bone Marrow Transplantation (2001) 28, 365–367

Keywords: autograft; AML; obesity

Immediate and long-term outcomes after marrow transplantation in hematologic malignancies are influenced by numerous risk factors such as advanced disease, older age, previous treatment and biological characteristics.1–6 Besides these factors which are generally accepted, others have remained controversial. Ample evidence suggests that obesity is a factor contributing to a greater risk of inferior health, disease, and premature death.7 Several authors have hypothesized that severely overweight patients are at increased risk of transplant-related toxicity and mortality, but weight has not been yet considered as a proven risk factor in the setting of the transplant procedure.8–10

Obese individuals have altered pharmacokinetics for many medications when compared with the non-obese. Many drugs are relatively lipid insoluble and, therefore, distribute poorly into adipose tissue; obese patients tend to have a greater proportion of fat to total body weight than do non-obese patients. In addition, obesity may be associated with alterations in hepatic and renal functions.11–14 Consequently, these differences raise the possibility that obese individuals may be ‘overtreated’ and thus suffer excessive toxicity.

For obese patients, chemotherapy dose modifications are recommended by some authors, but not by others.8,15–17 Dose adjustments towards ideal body weight are often made, but no uniform clinical dosing guidelines based on weight have been established. A recent study demonstrated marked variability among institutions performing bone marrow transplants according to the method of dose adjustment used.18 Several different definitions of obesity are used in the literature and other studies have been published using different body weight groupings and analyzing heterogeneous samples of patients. Recognizing these limitations, and to evaluate the impact of obesity on the outcome of stem cell autografting in acute myeloid leukemia (AML), we retrospectively analyzed a group of patients homogeneous for diagnosis, disease status and for type of chemotherapy regimen and method of chemotherapy dosing. In this study, the patients were grouped using body mass index (BMI)19 and for each group we analyzed the possible association between obesity and an increase of treatment-related toxicity, transplant-related mortality, overall survival (OS) and disease-free survival (DFS).

Patients and methods

We reviewed the records of more than 1000 consecutive patients with various hematologic malignancies, who underwent autologous stem cell transplantation at the Hematologic Unit of the University ‘La Sapienza’ of Rome between January 1981 and April 1999.

Only patients responding to the following criteria were considered eligible for this retrospective study: (1) age
more than 20 and less than 60 years; (2) a diagnosis of \textit{de novo} acute myeloid leukemia (AML) of all morphological subtypes as defined by French–American–British (FAB) classification, apart from acute promyelocytic leukemia (FAB-M3);\textsuperscript{20} (3) disease responding to first line therapy; (4) autologous peripheral blood and/or marrow stem cell transplantation performed in first complete remission (CR); (5) conditioning regimen consisting of busulphan (Bu) at 4 mg/kg p.o. in divided doses daily for 4 days and cyclophosphamide (Cy) at 60 mg/kg once daily i.v. for 2 days;\textsuperscript{21,22} (6) chemotherapy dosing based on actual body weight (ABW); and (7) follow-up for at least amount 1 year.

To examine outcome in relation to obesity, patients were grouped on the basis of their relative weight recorded before beginning the preparatory regimen. The measure of relative weight was the body mass index (BMI), which was calculated by dividing the weight (kg) by the square of the height (m\textsuperscript{2}). Definitions from the National Center for Health Statistics were utilized to classify obesity as a BMI of 27.8 kg/m\textsuperscript{2} or more in men and 27.3 kg/m\textsuperscript{2} or more in women. Excessive thinness was defined as a BMI less than or equal to 20.7 kg/m\textsuperscript{2} in men and 19.1 kg/m\textsuperscript{2} in women.\textsuperscript{16,19}

Patients were classified into three groups based on BMI: group I = obese, group II = non-obese, group III = underweight.

To assess transplant-related toxicity for each group of patients, we considered leukocyte and platelet recovery (number of days with granulocytes lower than 0.5 \times 10\textsuperscript{9}/l and the number of days with platelets lower than 20 \times 10\textsuperscript{9}/l), the incidence of mucositis grade III–IV WHO,\textsuperscript{23} hemorrhagic cystitis, documented infections and the occurrence of transplant-related deaths.

The Kaplan–Meier method was used to calculate probability of OS and DFS. OS was estimated using death as an event and time of last live contact as a censor and DFS using relapse or death as events, and time of last live contact as a censor.\textsuperscript{24} Comparisons between groups were performed using log-rank statistics.\textsuperscript{25}

### Results

#### Patient distribution by age and weight

On the basis of our eligibility criteria, the study sample included 54 patients with a median age of 36.5 years (range 20–60). Of these, 23 (42\%) were female, and 31 (58\%) male. Patients were classified into three groups based on BMI: group I, obese, \( n = 9 \) (17\%); group II, non-obese, \( n = 37 \) (62\%); group III, excessively thin, \( n = 8 \) (15\%).

#### Transplant-related toxicity

Our analysis showed a correlation between obesity and delay of granulocyte engraftment: the median time to recovery of a granulocyte count greater than 0.5 \times 10\textsuperscript{9}/l was 33 days (range 25–108) in group I, 24 days (range 13–69) for group II and 17.5 days (range 14–50) for group III.

We observed a significant difference in the incidence of documented infections in obese vs non-obese patients (78\% vs 44\%; \( P = 0.04 \)). No differences were recorded in platelet engraftment or in the incidence of mucositis and hemorrhagic cystitis between the three groups.

#### Transplant-related mortality

Twenty-four (45\%) patients died. Six transplant-related deaths were recorded, with obvious differences between the three groups: no transplant-related deaths were documented in underweight patients; three (33\%) toxic deaths were observed in obese individuals and three (8\%) in non-obese patients (\( P = 0.04 \)).

#### Survival by weight category

At the time of analysis, 30 (55\%) patients are alive and in continuous CR, with a median follow-up of 76.5 months (range 14–137).

The median duration of remission was 22.5 months (range 1–137). Of all 54 patients, 19 (35\%) experienced a hematologic relapse after a median of 8 months (range 2–24) from transplant.

The OS probability is 0.55 projected to 137 months from transplant for the entire group of patients, and 0.22 at 86 months, 0.63 at 137 months and 0.56 at 135 months for patients obese, non-obese and excessively thin, respectively.

The DFS is 0.53 projected to 137 months for all patients, and 0.22 at 86 months for obese individuals, 0.58 at 137 months for non-obese and 0.62 at 135 months for excessively thin patients.

Table 1 shows that both OS and DFS among the obese patients were significantly lower than in non-obese (\( P = 0.012 \) and \( P = 0.021 \), respectively). Because the survival of excessively thin patients did not differ significantly from that of the patients with normal weight, excessively thin patients were excluded from the analysis.

#### Discussion

It is well known that obesity is an independent risk factor for numerous medical problems, such as coronary heart disease and cancers of the colon, prostate, endometrium, cervix, ovary, and breast.\textsuperscript{7} Moreover, several authors\textsuperscript{17} have shown in retrospective studies that obese women with breast cancer have a decreased DFS and OS when compared to their non-obese counterparts.

Obese individuals have altered pharmacokinetics for many medications, including chemotherapeutic agents, so

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<tr>
<th>Total patients ((n = 54))</th>
<th>Underweight patients ((n = 8))</th>
<th>Normal-weight patients ((n = 37))</th>
<th>Obese patients ((n = 9))</th>
<th>( P )</th>
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<tr>
<td>OS Probability</td>
<td>0.55</td>
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<tr>
<td>DFS Probability</td>
<td>0.53</td>
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potentially longer drug exposure may cause increased therapy-related toxicity. As a consequence, oncologists frequently treat obese patients with reduced doses of drugs in an effort to decrease chemotherapy toxicity, but little clinical data exist to either support or refute this procedure. Some studies of cancer patients have shown no support for empiric chemotherapy dose reductions based on body weight,\textsuperscript{16,17} but rather, that adjustment in patients with a substantial disparity between actual and ideal weight can be safely undertaken without significant increase in relapse rate.\textsuperscript{8} This report from the Stanford University group retrospectively examined whether significant deviation from ideal BMI is associated with an increase in non-relapse mortality or relapse. BMI adjusted for age was retrospectively found to be an independent predictive factor for non-relapse mortality without significant increase of relapse; the authors concluded that patients with low and high indices compared with the mean for their age had a poorer outcome.

Our results, on a homogeneous cohort of AML autograft patients, confirm that less favorable outcomes tended to be related to patients classified as obese. Our results suggest that BMI appears to be a predictive factor for an increase in treatment-related toxicity and mortality, suggesting the possibility that obesity represents an independent risk factor for autografting in AML.

Moreover, in the current study, statistically significant differences in survival, OS and DFS, were detected between the obese and non-obese groups; the small number of patients does not allow evaluation of whether or not obese individuals have a higher risk of relapse. This topic requires further investigation in a large series of patients, including those treated with other conditioning regimens including total body irradiation.

In view of the clear association between obesity and treatment-related toxicity and mortality, as previously reported by Coghlin Dickson et al.,\textsuperscript{8} we agree that dose adjustment and possible weight normalization should be considered in overweight patients.

Since obesity may influence distribution and elimination of antineoplastic agents, and since obesity is an increasingly common problem, prospective clinical studies aimed at evaluating the pharmacokinetics of chemotherapeutic agents in obese individuals undergoing high-dose treatments are warranted, in an attempt to provide a standard method for individualizing drug therapy in these patients.

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References


