Allogeneic transplant outcomes are not affected by body mass index (BMI) in patients with haematological malignancies

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Abstract: Bone marrow transplantation is frequently used as a consolidation therapy in patients with haematological malignancies to improve outcome of these patients. Obese individuals have larger absolute lean body and fat masses than non-obese individuals of the same age, gender and height, which might lead to altered pharmacokinetics of chemotherapeutic agents. Data on the impact of body mass on transplant outcome is conflicting.
This study included 331 patients (M: 230; F: 101) with 336 allogeneic transplant episodes from two large teaching hospitals in the West Midlands region in United Kingdom. 105 patients had acute myeloid leukaemia, 83 non Hodgkin's lymphoma, 3 myeloma, 21 Hodgkin's lymphoma, 34 acute lymphoblastic leukaemia, 19 chronic myeloid leukaemia, 22 chronic lymphocytic leukaemia, 24 myelodysplasia, 7 T cell non Hodgkin's lymphoma 6 aplastic leukaemia and 7 myelofibrosis
At transplantation 40% (N=133) patients had normal and 60%(N=198) high BMI with 14% of patients being obese (BMI>30). After a median follow-up of 24 months (range:2-79), the mean overall survival(OS) in patients undergoing allograft with normal BMI was 31 months as compared to 39 with high BMI (p:0.06). The mean progression free survival(PFS) in patients undergoing allograft with normal BMI was 33 months as compared to 38 with high BMI (p:0.13).16% of the patients in the high and obese BMI group developed acute GvHD with 8% grade III-IV and 28% in the normal BMI group with 14% grade III-IV acute GvHD.(p.0.11).17% of the patients in the high BMI group developed chronic GvHD and 30% of the patients in the normal BMI group (p:0.09).However higher infection rates and more days of inpatient stay in the first year post transplant were observed in the high BMI and obese patients but there was no difference in ITU admissions.
This study shows that high BMI and obesity does not adversely impact on either OS or PFS in patients undergoing allogeneic transplantation for haematological malignancies but it does have a significant impact on infection rates and hospitalisation of high BMI and obese patients. We recommend patients with high BMI should not be excluded from allogeneic transplantation however good supportive care should be undertaken and careful patient selection on the basis of comorbidity index in order to avoid the risks from the increased rates of infection.

Response to Reviewers: I am really grateful for your comments
The changes suggested by the reviewer has been incorporated in the materials and methods and also in the table with the patient characteristics(disease status at transplant, disease type, related unrelated donor equally distributed between the two groups)
I have also added the D+100 mortality as well as the 1st year mortality for both groups
Disease split (myeloid vs lymphoid showed similar results in both groups)

***Conflict of interest**

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Running title

Allogeneic Transplantation outcomes in different BMI groups

Key words

Body mass index, allogeneic bone marrow transplants, overall survival,disease free survival, graft versus host disease

Conflicts of interest

No conflicts of interest to declare

Abstract

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This study included 331 patients (M: 230; F: 101) with 336 allogeneic transplant episodes from two large teaching hospitals in the West Midlands region in United Kingdom. 105 patients had acute myeloid leukaemia, 83 non Hodgkin's lymphoma, 3 myeloma, 21 Hodgkin's lymphoma, 34 acute lymphoblastic leukaemia, 19 chronic myeloid leukaemia, 22 chronic lymphocytic leukaemia, 24 myelodysplasia, 7 T cell non Hodgkin's lymphoma 6 aplastic leukaemia and 7 myelofibrosis

At transplantation 40% (N=133) patients had normal and 60%(N=198) high BMI with 14% of patients being obese (BMI>30). After a median follow-up of 24 months (range:2-79), the mean overall survival(OS) in patients undergoing allograft with normal BMI was 31 months as compared to 39 with high BMI (p:0.06). The mean progression free survival(PFS) in patients undergoing allograft with normal BMI was 33 months as compared to 38 with high BMI (p:0.13).16% of the patients in the high and obese BMI group developed acute GvHD with 8% grade III-IV and 28% in the normal BMI group with 14% grade III-IV acute GvHD.(p.0.11).17% of the patients in the high BMI group developed chronic GvHD and 30% of the patients in the normal BMI group (p:0.09).However higher infection rates and more days of inpatient stay in the first year post transplant were observed in the high BMI and obese patients but there was no difference in ITU admissions.

This study shows that high BMI and obesity does not adversely impact on either OS or PFS in patients undergoing allogeneic transplantation for haematological malignancies but it does have a significant impact on infection rates and hospitalisation of high BMI and obese patients. We recommend patients with high BMI should not be excluded from allogeneic transplantation however good supportive

care should be undertaken and careful patient selection on the basis of comorbidity index in order to avoid the risks from the increased rates of infection.

Introduction

Bone marrow transplantation is frequently used as a consolidation therapy in patients with haematological malignancies to improve outcome. Obese individuals have larger absolute lean body and fat masses than non-obese individuals of the same age, gender and height, which might lead to altered pharmacokinetics of chemotherapeutic agents [1]. Although obesity seems to provide a survival benefit in dialysis patients, obesity has traditionally been considered a contraindication for transplantation of both bone marrow transplant recipients as well as solid organ transplants [2]. It was widely adopted that obesity will contribute to worse transplant outcomes, including lower rates of engraftment and patient survival and higher rates of delayed graft function and infection [3].

Immediate and long-term outcomes after bone marrow transplantation in hematologic malignancies are influenced by numerous risk factors such as advanced disease, older age, previous treatment and biological characteristics. 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. 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.

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.[4,5,6] Consequently, these differences raise the possibility that obese individuals may be 'overtreated' and thus suffer excessive toxicity. Also prolonged immobility of the

obese patients undergoing a bone marrow transplant was also implicated in the adverse outcome of the bone marrow transplant procedure.

For obese patients, chemotherapy dose modifications are recommended by some authors, but not by others. Dose adjustments towards ideal body weight are often made, but no uniform clinical dosing guidelines based on weight have been established[7]. A recent study demonstrated marked variability among institutions performing bone marrow transplants according to the method of dose adjustment used. 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[8,9].

Materials and methods

In this study, the patients were grouped using body mass index (BMI) and for each group we analyzed the possible association between obesity and overall survival (OS) as well as progression-free survival (PFS) , GvHD and days of inpatient stay. BMI was calculated as the patients weight in Kg divided by the square of the patients height in square meters. This study included 331 allograft patients (M: 230; F: 101) from two teaching hospitals who underwent 336 allogeneic transplant episodes.(table 1 patient characteristics) 325 patients were transplanted with PBSC from a sibling or an unrelated donor and 11 from bone marrow stem cells.190 patients underwent an allogeneic transplant from a sibling donor and 146 from an unrelated donor. The median Cd34 dose was 5.5 $x10^6$. 209 patients were in complete remission and 127 patients were in partial remission or refractory disease. 105 patients had acute myeloid leukaemia, 83 non Hodgkin's lymphoma, 3 myeloma, 21 Hodgkin's lymphoma, 34 acute lymphoblastic leukaemia, 19 chronic myeloid leukaemia, 22 chronic lymphocytic leukaemia, 24 myelodysplasia, 7 each T cell non Hodgkin's lymphoma 6 aplastic leukaemia and 7 myelofibrosis. Median age of the patients was 44 yrs (18-61).The median follow up for the patients was 24 months (2-79 months) At transplantation 40%(n=133) patients had normal and 46%(n=152) high BMI.14% of patients(n=46) were grossly obese. Disease status, related or unrelated donor and type of disease were equally distributed between the group of patients. Patients with normal BMI were those with a BMI>18 and <25.Overweight patients were defined as

having a BMI of > 25 and <30 and obese patients were defined as those with a BMI > 30.

We have also performed a subgroup analysis for the patients who were grossly obese with a BMI more than 30.The aim of the study was to determine whether patients with high BMI had a worse overall survival as it was reported by previous studies and also whether there was an effect on the progression free survival, GvHD and infection rates. Statistical analysis was carried out using SPSS 13.0 for Windows. The overall survival was calculated from the date of transplant to the date of death or date of last follow up. Progression free survival is calculated from the date of transplant to the date of relapse. Both reduced intensity and full intensity transplants were considered and different conditioning regimen were used (Cy/TBI, By/Cy, Mel/TBI, TBI/Etoposisde, Flu/Mel/Campath, Flu/Cy/Alemtuzumab, BEAM/Campath). The maximum surface area used for the administration of chemotherapy was 2,2 even though surface area could be higher depending on the height and weight of the patient.

Table 1.Patient characteristics

Age	18-65 yrs (median 44 yrs)	
Follow up	2–79months (median 24m)	
Stem cell source	Bone marrow n=11	Low BMI :4 High BMI:7
	PBSC n=325	Low BMI:133 High BMI:192
Transplant type	Sibling n=190	Low BMI:73 High BMI:117
	Unrelated n=146	Low BMI:64 High BMI:82
CD 34 dose	2.2- 9.5 (median 5.5)	
Disease type	Myeloid n=161	Low BMI:64 High BMI:97
	Lymphoid n=170	Low BMI:69 High BMI:101

BMI	<25 n=133	
	>25 n=152	
	>30 n=46	
CR	Yes n=209	Low BMI:87 High BMI:122
	No n=127	Low BMI:50 High BMI: 77
Gender	Male n=230	
	Female n=101	

Results

All patients except from three (two on the lower BMI side and one on the high BMI side) engrafted with a median time to neutrophil engraftment of 14 days in the normal BMI group and 14.7 in the high BMI group. Platelet engraftment was evident 17 days post transplant in the normal BMI group and 18.9 in the high BMI group. The days of inpatient stay in the first year post transplant was higher in the high BMI and obese group , 54 days and 61 days respectively, compared to the normal BMI group where the average length of inpatient stay was 46 days(odds ratio=1.8;95% confidence interval = 1.1 to 2.9;p =0.03) . Also the infection risk was increased on the high and obese BMI group than the normal BMI group (odds ratio=1.8;95% confidence interval = 1.1 to 2.6;p =0.05) but the ITU admission rates were similar to all groups. The first 100 days post transplant mortality was 15% in the high BMI group and 11% in the normal BMI group. However in the first year post transplant 63% of the patients in the high BMI group were alive compared to 56% in the normal BMI group of patients

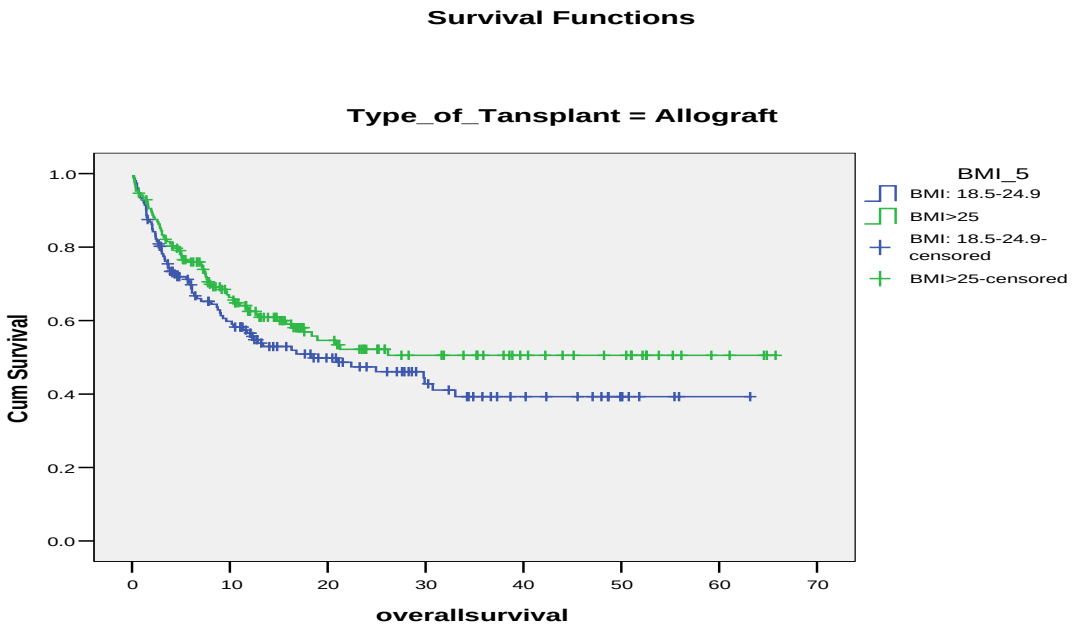

Figure 1.Overall survival in the 2 groups

After a median follow-up of 24 months (range:2-79) the mean overall survival in patients undergoing allograft with normal BMI was 31 months as compared to 39 with high BMI and 38 months for the obese group(p : 0.06) The mean progression free survival in patients undergoing allograft with normal BMI was 33 months as compared to 38 with high BMI and 34 months in the obese group (p:0.13)(Figure 1 overall survival).Patients with a high BMI and in the obese group had a significantly lower incidence of graft versus host disease compared to the normal BMI patient group. 16% of the patients in the high BMI and obese group developed acute GvHD with 8% grade III-IV and 28% in the normal BMI group with 14% grade III-IV acute GvHD(p:0.11). 17% of the patients in the high BMI group developed chronic GvHD and 30% of the patients in the normal BMI group (p:0.09). When we split the analysis depending on disease type (lymphoid vs myeloid) no change in the transplant outcomes has been observed between the two groups of patients

Discussion

Despite detailed evaluation of disease-associated prognostic factors, little is known about the impact of high BMI in autograft and even less for allograft patients for haematological malignancies. Most of the studies in the international literature have shown that obesity adversely affects the overall survival of the patients undergoing allogeneic bone marrow transplant.[10,11] 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.

In our study we have showed that there was a trend for improved overall survival in patients with high BMI compared to patients with normal or low BMI in the allograft patients which is in agreement with the study by Deeg et al [12,13]. Moreover there was no statistical significance between normal or high BMI transplant patients and progression free survival. Despite the increased overall survival in the high BMI group there was an increased rate of infection risk in this group of patients as well as the obese group and this seemed to affect the days of inpatient stay for these group of patients. Interestingly ITU admission rates were similar in all BMI groups. Also the slightly increased morbidity in the first 100 days post transplant in the high BMI group is attributed to the increased rate of infection and furthermore the decreased mortality in the first year in the high BMI group is probably related to the lower risk of severe GvHD

Previous single-institution studies have demonstrated a significant disadvantage for overweight and obese patients both in patients undergoing an autologous and an allogeneic bone marrow transplants[14,15]. Tarella et al. reported outcomes for 121 patients receiving autografts for NHL, 28 of whom had a BMI >28 kg/m^2. In that study, 5 of 28 overweight/obese patients never received an autograft; 6 of the remaining 23 patients had unspecified dose reductions that may have affected lymphoma-free and overall survival. As in this study, there was no difference in the TRM. In a retrospective study by Meloni et al. that examined outcomes in 54 patients receiving autografts for acute myeloid leukemia, 9 of whom were obese, there was a significant difference in TRM. In that study, patients did not receive dose adjustments on the basis of overweight. Conversely, a study from the Fred Hutchinson Cancer Research Center retrospectively reviewed outcomes in their large series of allografts and autografts and found no significant survival disadvantage of normal BMI compared to overweight patients .When Fred Hutchinson Cancer Research Center results only for allografts for chronic myeloid leukemia were reviewed by Hansen et al there was a slight survival disadvantage for the overweight and obese patients; this suggests that when disease factors such as relapse are less problematic, then mildly adverse effects of overweight can be discerned [16].

The rate of both acute and chronic GvHD has been lower in the high BMI group of our patients which probably accounts for the increased overall survival in these patients despite the higher incidence of infection. Recent studies showed that adipose tissue derived mesenchymal cells could prevent GvHD in allogeneic bone marrow transplant recipients. These studies showed that human adipocyte derived mesenchymal stem cells inhibited the proliferation and cytokine secretion of human primary T cells in response to mitogens and allogeneic T cells[17,18,19].

In conclusion our study showed that overweight and obese patients receiving allogeneic bone marrow transplant for haematological malignancies do not experience inferior outcomes compared with normal-weight patients. Consideration of these patients for allogeneic bone marrow transplant should not be adversely influenced by obesity alone. The higher infection rates seen in the high and obese BMI group though emphasises the need for better supportive care along with the optimum selection of patients in these groups based on their comorbidity index score.Future studies focusing on the incidence of late effects post transplant according to different BMI risk groups should be conducted in order to obtain a full understanding of the effects of body mass index on allograft patients.

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