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Breaking another dogma: Successful hematopoietic stem cell transplantation in patients over 60 years of age: A single institution's, 20-year experience

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RESUMEN

Dado que el trasplante de células hematopoyéticas es un procedimiento que tiene un riesgo alto de morbilidad y mortalidad en sujetos añosos, muchas instituciones se niegan a trasplantar pacientes mayores de 50 o 55 años. Con el advenimiento de mejores medidas de apoyo para efectuar trasplantes hematopoyéticos en sujetos añosos, se ha observado una tendencia a trasplantar a pacientes mayores; sin embargo, la edad sigue siendo una barrera para el éxito del trasplante hematopoyético. En una sola institución y en un periodo de 20 años se efectuaron 284 trasplantes de células hematopoyéticas (130 trasplantes autólogos y 154 trasplantes alogénicos), empleando los métodos de acondicionamiento "mexicanos". En los pacientes autotrasplantados mayores (n = 30) o menores (n = 100) de 60 años de edad, la supervivencia global fue de 67% a 180 meses y de 58% a 229 meses, respectivamente (p NS), en tanto que la mediana de supervivencia global no ha sido alcanzada en ninguno de los grupos, fueron mayores de 180 y 229 meses, respectivamente (p NS). En los pacientes a quienes se realizaron alotrasplantes mayores (n = 8) o menores (n=146), las supervivencias globales fueron de 50% a 138 meses y 38% a 155 meses, respectivamente (p NS), en tanto que las medianas de supervivencia global fueron de 60 y 20 meses, respectivamente (p NS). Luego de transplantar a 38 sujetos añosos mayores de 60 años con nuestros métodos simplificados para llevar a cabo estos procedimientos, concluimos que los resultados a largo plazo no son distintos de los obtenidos con los mismos métodos en sujetos menores de 60 años de edad.

Palabras clave: trasplante de células hematopoyéticas, pacientes añosos, edad.

ABSTRACT

Being hematopoietic stem cell transplantation a procedure with a higher risk of morbidity and mortality in older patients, many institutions place a limit of 50 to 55 years for HSCT. With better supportive care the ability to perform transplants successfully in older patients has steadily improved; however, age continues to have a significant impact. In a single institution along a 20-year period, 284 patients were grafted (130 autografts and 154 allografts. In autografted patients above (n = 30) or below (n = 100) 60 years of age, the overall survival (OS) was 67% at 180 months and 58% at 229 months respectively, whereas the median OS has not been reached in any groups, being above 180 and 229 months respectively (p NS), whereas in allografts, in patients above (n = 8) or below (n = 146) 60 years of age, the OS was 50% at 138 months and 38% at 155 months respectively, whereas the median OS was 60 and 20 months respectively (p NS). We conclude that grafting 38 individuals aged 60 years or more (30 autografts and 8 allografts), we have found that the long term-results are similar to those obtained in individuals younger than 60 years.

Key words: BMT, allograft, autograft, age.

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A number of factors have been identified that consistently impact results obtained following treatment with hematopoietic stem cell transplantation (HSCT). These factors include disease status at transplantation, type of donor, recipients´ age and comorbid medical conditions. Since HSCT has been considered as a procedure with a higher risk of morbidity and mortality in older patients, many institutions place a limit of 50 to 55 years for HSCT. Consequently, older patients may not be offered potentially curative treatment for a variety of diseases.[1] With better supportive care the ability to perform transplants successfully in older patients has steadily improved; however, age continues to have a significant impact. A worsening in outcome has been observed with advancing age, which is most apparent for patients older than 60 years of age. The reasons for this effect are complex and include overall condition, comorbid medical issues, potential differences in disease characteristics, and ability to tolerate the rigors of allogeneic transplantation.[2] In allogeneic HSCT, the introduction of reduced-intensity conditioning (RIC) has allowed the transplantation of older individuals, whereas following autologous HSCT there is less impact of age and successful transplantations can be performed for patients even older than 60 years of age.[2]

The widespread practice of HSCT faces several problems in the world, derived mainly from the high costs of the procedure when conducted using traditional methods. In order to cope with this problem, we have implemented in México procedures to make HSCT, both autologous and allogeneic, more affordable to patients living in our country and in other developing countries.[3] The simplification of these procedures has resulted in an increased number of patients both autografted and allografted in México. In the case of autografts, the changes have relied on the use of non-frozen autologous peripheral blood stem cells and short conditioning schedules delivered as outpatients, whereas in the case of allografts, changes have relied mainly in conducting the allografts fully on an outpatient basis and employing RIC conditioning preparative schedules.[3]

MATERIAL AND METHODS

a) Patients:

Data were analysed from all patients who underwent HSCT in the Centro de Hematología y Medicina Interna de Puebla of the Clínica Ruiz between May 1993 and October 2012. Patients were stratified according to age at the time of transplantation: Above or below 60 years. Comorbidity was analyzed according to Charlson et al.[4]

b) Auto HSCT:

The peripheral blood stem cell (PBSC) mobilization schedule was begun at least 30 days after the last dose of chemotherapy. Subcutaneous G-CSF (10 μg/kg/day/5 days) was given for mobilization of stem cells. Using either a peripheral vein or a Majurkar-type subclavian catheter, the apheresis procedures were performed on days – 3, – 2 and – 1, using a Haemonetics V-50 PLUS machine (Haemonetics Corporation, Braintree MA) or a Baxter C-3000 PLUS machine (Baxter Healthcare, Deerfield IL), and the Spin-Nebraska protocol.[5] The apheresis objective was to reach at least 1 x106 viable CD34+ cells/kg. Intravenous melphalan, 200 mg/m^2 in a single I.V. dose was used on day –1 in all patients. Ondansetron (8 mg i.v. every 12 h after chemotherapy), ciprofloxacin (250 mg bid) and fluconazole (200 mg bid) were used in all patients. Antibiotics and antimycotics were used until granulocytes were greater than 0.5 x 109/L. All patients had daily laboratory workup and clinical studies. The products of the apheresis and 1 ml aliquots were kept in ACD-A (Baxter Healthcare, Deerfield IL) at 4oC, in 300 mL transfer packs (Baxter Healthcare, Deerfield IL) composed of gas impermeable, polyvinyl chloride plastic film for up to 72 hours. Enumeration of the total white mononuclear cells (MNC) and CD34 positive cells was done by flow-cytometry[6] in an EPICS Elite ESP apparatus (Coulter Electronics, Hialeah, FL), using for the latter subpopulation the anti-CD34 monoclonal antibody HPCA-2 (Becton Dickinson, San José CA), gating in propidium iodide-excluding CD45 (+) MNC population according to forward and 90° angle light scattering. Additional viability studies of the MNC used propidium iodide exclusion and anti-cell antibodies on a flow cytometer. No purging procedures were performed. The apheresis products obtained on days – 3, – 2 and – 1 were reinfused to the patients on days 0, +1 and +2 respectively after keeping them in the conventional blood bank refrigerator.

c) Allo-HSCT:

The "Mexican method" of RIC was used in all patients.[7] A Karnofsky score of 100% was required to conduct the allograft. In all instances, the donor was a sibling with

compatible (5/6) or identical (6/6) HLA. The study protocol was approved by the Institutional Review Board and the Ethics Committee of the institution. Written consent was obtained from all patients. Subcutaneous G-CSF (10 µg/kg/day) was given to the sibling donors on days -5 to +2, and one to three aphaeresis procedures were planned for days 0, +1 and +2 by means of a Haemonetics V-50 PLUS machine (Haemonetics Corporation, Braintree, MA), a Baxter C-3000 PLUS machine (Baxter Healthcare, Deerfield, IL), an AMICUS (Baxter Healthcare, Deerfield, IL) or a COBE-Spectra (Gambro, Lakewood, CO) using the Spin-Nebraska protocol.[4] The endpoint of collection was the processing of 5000-7000 mL of blood/m^2 in each aphaeresis procedure, providing a total amount of at least 2 x 106 viable CD34+ cells/kg of the weight of the recipient. The Mexican method of non-ablative conditioning used in this study consisted of the following: oral busulphan, 4 mg/kg, given on days -6 and -5; IV cyclophosphamide, 350 mg/m^2, on days -4, -3 and -2; and IV fludarabine, 30 mg/m^2, on days -4, -3 and -2. In 5 patients with very severe aplastic anaemia, busulphan was not used, and the cyclophosphamide dose was doubled on days -4 through -1; oral cyclosporin A (CyA) was administered at 5 mg/kg starting on day –1. In all the patients IV methotrexate (5 mg/m^2) was given on days +1, +3, +5 and +11., CyA was continued through day 180, with adjustments made to obtain serum CyA levels of 150–275 ng/mL, and then tapered over 30-60 days. If GVHD was present, CyA was tapered over a longer period. Ondansetron (1 mg IV every hour for 4 h after IV chemotherapy), an oral quinolone, and an azole were used in all patients until granulocyte counts were greater than 500 x 106/L for 3 consecutive days. The PBSC aphaeresis products were infused on days 0 to +1. The total counts of white blood cells, mononuclear cells (MNCs) and CD34+ cells were enumerated by flow cytometry[8] with an EPICS Elite ESP machine (Coulter Electronics, Hialeah, FL), using the anti-CD34 monoclonal antibody HPCA-2 (Becton Dickinson, San José, CA). No purging procedures were performed. Engraftment was defined as an absolute neutrophil count of >0.5 x 109/L for at least 3 consecutive days, and platelet engraftment was defined as occurring on the first of 7 consecutive days with a platelet count of >20 x 109/L, without a platelet transfusion. Graft failure was defined as the failure to reach an absolute granulocyte count of >0.5 x 109/L on day +30. Chimerism was assessed in cases involving a sex mismatch with a fluorescent in situ hybridisation technique to mark the X and Y chromosomes.[9] In cases with an ABO mismatch, a flow cytometry-based approach was used, whereas polymorphic markers (STRs)[10] were analysed in the absence of any mismatch.

d) Statistics:

The primary objective of the analysis was to assess the survival after the HSCT. Overall survival (OS) was calculated from the day of HSCT until the day of death or the last follow-up and was estimated according to the Kaplan-Meier method[10] using the log-rank chi-square test.

RESULTS

a) Patients:

284 patients were included in the study, 130 were autografted and 154 were allografted. The Tables 1 and 2 depict some of the salient features of the patients.

b) Autografts:

130 individuals were autografted. There were 41 patients with multiple myeloma, 36 with acute leukemia, 4 with breast carcinoma, 4 with chromic myelogenous leukemia, 3 with Hodgkin´s lymphoma, 6 with non-Hodgkin´s lymphoma. The median age was 48 years (range 6-72); there were 69 males and 61 females. Patients were stratified according to age: 30 (23%) had 60 or more years when autografted, whereas 100 had less than 60 years. A median of three apheresis sessions were needed to collect a minimum of 1 x 106 CD34 viable cells/kg of the recipient; the range was 2 to 4 sessions to obtain enough CD34+ cells. All patients were conditioned with intravenous melphalan. In cases in which more than three apheresis sessions were needed to obtain a minimum of 1 x 106 CD34 viable cells/kg of the recipient, the dose of melphalan was adjusted to 180 mg/m^2 (90% of the planned dose). The median number of transplanted CD34 viable cells was 1.4 x 106 CD34 viable cells/kg of the recipient; the range was 0.6 to 64. In all cases the viability of the CD34 cells was above 85% prior to being reinfused to the patients.

c) Allografts:

154 individuals were allografted. There were 38 patients with acute leukemia, 24 with chronic myelogenous leukemia, 6 with multiple myeloma, 8 with NHL, 3 with

Table 1. Salient features of the 130 patients which were autografted, according to the age group.

	≥ 60 years	*< 60 years*	*p*
Number	30	100	
Median age, years	66	56	
Age range, years	60 - 72	6 - 59	
Comorbidity index, median (range)	4.9 (3-7 – 10.8)	2.5 (0 – 9.9)	0.01
Median overall survival	> 180 months	> 229 months	NS
180-months overall survival	67%	62%	NS
229-months overall survival	-	58%	NS
100-day mortality	17%	27%	NS
Multiple myeloma	17	24	
Hodgkin´s lymphoma	0	3	
Acute lymphoblastic leukemia	0	20	
Acute myelogenous leukemia	1	15	
Breast carcinoma	2	2	
Non-Hodgkin´s lymphoma	2	4	
Chronic myelogenous leukemia	1	3	
Primary myelofibrosis	0	1	
Others	7	28	

Table 2. Salient features of the 154 patients which were allografted, according to the age group.

	≥ 60 years	*< 60 years*	*p*
Number	8	146	
Median age, years	62	30	
Age range, years	60 – 70	2 – 59 years	
Comorbidity index, median (range)	4.5 (4 – 6)	1.2 (0 – 8.5)	0.01
Median overall survival	60 months	20 months	NS
138-months overall survival	50 %	64 %	NS
155-months overall survival	-	38 %	NS
100-day mortality	25%	26 %	NS
Chronic myelogenous leukemia	0	24	
Acute lymphoblastic leukemia	0	28	
Non-Hodgkin´s lymphoma	0	8	
Acute myelogenous leukemia	4	6	
Multiple myeloma	2	4	
Primary myelofibrosis	1	2	
Myelodysplasia	1	1	
Aplastic anemia	0	3	
Others	0	70	

aplastic anemia, 3 with melofibrosis, 2 with myelodysplasia. The median age was 32 years (range 2–70); there were 92 males and 62 females. Patients were stratified according to age: 8 had 60 or more years when autografted, whereas 146 had less than 60 years. A median of two apheresis sessions in the donor were needed to collect a minimum of 1 x 106 CD34 viable cells/Kg of the recipient; the range was 2 to 4 sessions to obtain enough CD34+ cells. All patients were conditioned with the "Mexican" conditioning regimen.[2,7] The median number of transplanted CD34 viable cells was 2.2 x 106 CD34 viable cells/kg of the recipient; the range was .2 to 17.7. In all cases the viability of the CD34 cells was above 85% prior to being infused to the patients.

d) Overall survival (OS):

In the whole group of 284 patients, the OS of the patients was 47% at 229 months, with a median OS of 51 months.

In autologous HSCT, the OS of the 130 patients was 60% at 229 months, with a median OS which has not been reached, being above 229 months. According to age, the OS was not different in individuals above or below 60 years of age. In patients above or below 60 years of age, the OS was 67% at 180 months and 58% at 229 months respectively, whereas the median OS has not been reached in any group, being above 180 and 229 months respectively (p NS). See Figure 1.

In allogeneic HSCT, the OS of the 154 patients was 42% at 155 months, with a median OS of 14 months. According to age, the OS was not different in individuals above or below 60 years of age. In patients above or below 60 years of age, the OS was 50% at 138 months and 38% at 155 months respectively, whereas the median OS was 60 and 20 months respectively (p NS).

DISCUSSION

The simplification of the HSCT procedures has resulted in an increased number of patients both autografted and allografted in México.[3] In autografts, the use of non-frozen autologous peripheral blood stem cells and short conditioning schedules delivered as outpatients, whereas in allografts, conducting them fully on an outpatient basis and employing RIC conditioning preparative schedules have made possible grafting patients who in the past would not have been considered for this therapeutic approach.[3] The changes done in México in the preparative regimens for grafting have also allowed transplanting safely aged individuals.[3,12] Other authors have also shown that allografts can be safely conducted in aged individuals if reduced-intensity conditioning schedules are employed.[13-18] Using the "Mexican method" to allograft individuals, Solano-Genesta et al report having grafted 13 patients aged 60 or more years,[12] with results similar to those obtained in younger individuals. We are now informing the results of grafting 38 individuals aged 60 years or more (30 autografted and 8 allografted), in whom we have found that the long term-results are similar to those obtained in individuals younger than 60 years, despite the fact that the comorbidity index was significantly higher in patients aged above 60 years.

We conclude that, employing the simplified Mexican methods to both autograft and allograft individuals, aged individuals, above 60 years of age, can be safely and successfully grafted.

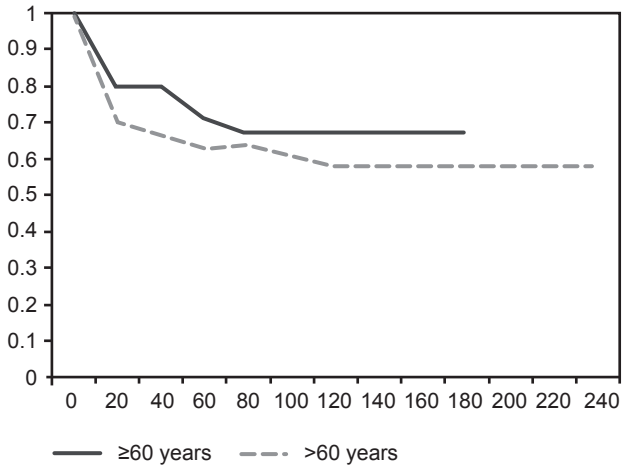

Figure 1. Overall survival of the 130 patients who were autografted, according to the age group. Survival is expressed in months. Differences are not statistically significant.

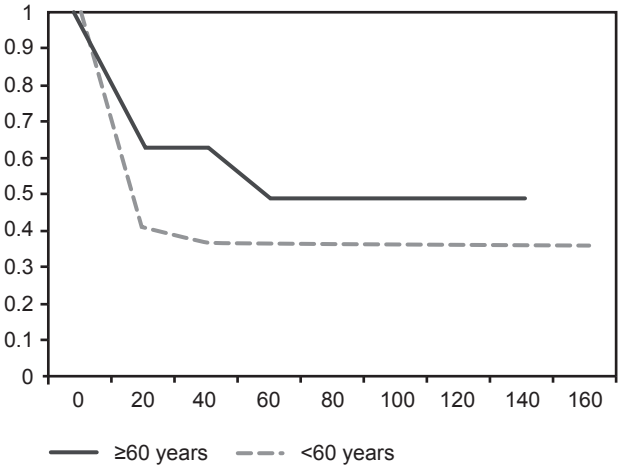

Figure 2. Overall survival of the 154 patients who were allografted, according to the age group. Survival is expressed in months. Differences are not statistically significant.

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