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The Outcome of Autologous Stem Cell Transplantation: A Single Center Early Experience

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Running Title: Autologous SCT Outcome: A single Center Experience

Abstract: ***The aim of this article is to report the clinical outcome of adult autologous stem cell transplantation (AHSCT) in a single center in Saudi Arabia. All adult patients who underwent AHSCT and completed 36 months of follow up were included. The data were analyzed retrospectively, describing patients' demographic and disease characteristics, at diagnosis and, disease status before transplantation. We also describe their treatment outcomes including: response post-transplant, 3-year overall survival (OS) and 3-year disease free survival (DFS). Thirty-eight patients received auto-SCT between February 2010 and October 2013 and met the inclusion criteria, including 25malesand 13females.Hodgkin's Lymphoma (HL) is the commonest indication for ɑologous SCT in our study followed by Multiple myeloma (MM). The mean age at transplantation was 37 years. The 3-year OS was 79% and the DFS was 76%. Eight (21%) patients died after transplantation and 30 (79%) are still alive. The none-relapse mortality was 3% and 18% at one and three years, respectively. The median time for neutrophils and platelets engraftment was 12 days and 10 days respectively. The 3-year OS for the HL patients (n=23) was 87%, and the DFS was 87%. The 3-year OS for the MM patients (n=7) was 86% and the DFS was 57%. The results reported here indicate that the clinical outcomes are comparable to international results.***

Keywords: Autologous stem cell transplantation, Hodgkin's lymphoma, multiple myeloma, Saudi Arabia

1. Background

Hematopoietic stem cell transplantation (HSCT) was first attempted in medicine to treat aplastic anemia in 1939 and over time it has become a standard approach to treat and cure many malignant and non-malignanthematological diseases by autologous and allogeneic methods.[0]Autologous hematopoietic stem cell transplantation (AHSCT), performed either at the time of initial diagnosis or at relapse for different hematological malignancy,[Error! Reference source not found.[2]]is considered the standard of care for young patients (less than 70 years of age) with newly diagnosed multiple myeloma (MM) following induction therapy with chemotherapy.[3]AHSCT has proven to be more effective than chemotherapy alone in cases of relapsed or refractory Non Hodgkin Lymphoma (NHL) such as Diffuse Large B cell lymphoma and Hodgkin's lymphoma .[4],[5]It is also used less commonly in treatment of other malignancies at different phases including acute leukemias, other types of NHL, and certain autoimmune diseases.[2]

Our hospital is a tertiary care center and JCI accredited with a bed capacity of more than 900 beds. The Stem Cell Transplantation Program was newly established atour hospital in 2010.[6] The aim of this study is to demonstrate the 3-year outcome experience in adultAHSCT between 2010 until 2013 in terms of response rate, relapse, overall survival (OS), disease free survival (DFS) and transplant related mortality rate.

2. Patients and Methods

Our hospital is a tertiary care center and JCI accredited with a bed capacity of more than 900 beds. After obtaining the approval from the institutional review board, all adult patients (older than 14 years who received AHSCT in the period of February 2010 until October 2013 and completed 36 months of follow up were included.

The transplantation process was conducted in five phases: stem cell collection, conditioning, stem cell infusion, engraftment, and immunoreconstitution. Stem cells were acquired byperipheral blood apharesis processes, and then cryopreserved after giving the patients a mobilizingregimen consisting of chemotherapy and granulocyte colony stimulating factor (G-CSF).In case of Multiple Myeloma, the mobilization regimen was cyclophosphamide followed by G-CSF and for lymphoma, the G-CSF was given after the first or second cycle of salvage chemotherapy such as ESHAP. Plerixafor, which is CXCR4 antagonist was used in cases of previously failed mobilization attempt or as pre-emptive therapy in case of poor mobilization or high risk patients for poor mobilization. If the bone marrow was involved by disease it was mandatory to repeat the BM biopsy prior to mobilization attempt to make sure it is in remission.

The second phase was conditioning where the patients received a myeloablative regimen that included a high dose of chemotherapy and/or radiotherapy to eliminate the malignant disease. In cases of Multiple Myeloma,the high dose melphalan 200 mg/m2 was used and in cases of HL and NHL,BEAM (BCNU, Etoposide, Cytarabine and Melphalan)

regimen was commonly used.The stem cells wereinfused via a central venous catheter on day 0. The transplantation procedure was done in an isolated room with positive-pressure and high-efficiency particulate air (HEPA) filters.

Engraftment is defined by the first day of neutrophils count above 0.5×10^9/L for three consecutive days or platelet count more than $20x10^9$/L for three days unsupported by platelet transfusion.

Through approved access to the medical records department, data were collected and entered to a data collection sheet which includes age, gender, diagnosis, disease status pre-transplant, chemotherapy, transplant details, disease assessment at day 100, and follow up post-transplant. The patients were analyzed in Table I according to their characteristics including age, gender, diagnosis, radiation, indication of transplant, pre-transplantation status, conditioning regimens, death, and disease relapse. Data were entered into excel spreadsheets and then managed with SPSS using descriptive methods: meanand standard deviation for numerical variables; percentages and frequencies for categorical variables. OS and DFS curves were calculated by the Kaplan-Meier method. The level of significance was set to 0.05. The analyses were performed using The SAS© System, Second Edition.

3. Results

The clinical characteristics are shown in Table 1 of 38 patients who received autologous stem cell transplantation between February 2010 and October 2013, including 25males and 13females. The mean age at transplantation was 37 years. The underlying disease was HL in 23 cases, MM in 7 cases, three cases with DLBCL, threecases with central nervous system lymphoma, one case of Non-Hodgkin's lymphoma and one case with relapsed acute promyelocytic leukemia. Peripheral blood stem cells apheresis was the source of stem cells in all cases. In 28 cases, diseaserelapse was the indication for transplant and the other indications were part of first line therapy (MM and primary CNS lymphoma) n=8; primary refractory n=1; and plasma cell leukemia n=1. The conditioning regimen consisted of BEAM in 27 cases, high dose Melphalan in 7 cases, TBC(thiotepa, busulfan, and cyclophosphamide) in 3 cases of primary CNS lymphoma, and finally Bu/CY in 1 case of relapsed acute promyelocytic leukemia. A total of 15 patients received radiation therapy in addition to salvage chemotherapy before the transplantation.

Disease status before transplantation was as the following: 47% were in partial remission, 42% had complete remission and 11% were in very good partial remission. After stem cell transplantation, disease status in the last follow up was complete remission in 77% of the cases and 23% were in relapse or disease progression. The median time for neutrophils and platelets engraftment was 12 days and 10 days respectively for all patients.

The 3-year OS was 79% and the DFS was 76% (Figure 1). Eight (21%) patients died after transplantation and 30 (79%) are still alive. The 3-year OS for the HL patients (n=23) was 87%, and the DFS was 87% (Figure 2). The 3-year OS for the MM patients (n=7) was 86% and the DFS was 57% (Figure 3). Three patients died with HL, two with DLBCL, one patient with NHL, one with MM, and one patient with primary CNS lymphoma. Majority of cases died secondary to disease relapse or progression post-transplant. The none relapsemortality (NRM) was 3 percent and 18% at one and three years, respectively (Figure 4).

4. Discussion

The aim of this study was to report the outcome of AHSCT in adult patients who were transplanted at our center. The commonest indication for AHSCT in our patient series was Hodgkin's lymphoma (61%) followed by MM (18%) then DLBCL and CNS lymphoma in 8% only. These findings differ from international figures where number one indication is plasma cell disorder, mainly MM, followed by NHL then HL as the third commonest indication for AHSCT.[6]The prevalence of Hodgkin's lymphoma among all lymphoma cases in the western world is less than 10% while it represents around 30% of total cases of lymphoma in Saudi Arabia.[7],[8]The epidemiologic difference in distribution of lymphoma in our country might explain partly the increased number of cases of HL in our transplant series.

The three-year OS and DFS rates were similar to international results; however, the short follow-up time of the patients limits our interpretations. In HL cases the results are very encouraging where the 3-year OS and DFS exceeded 80%. Report of using AHSCT in relapsed or refractory HL indicated 3-year progression-free survival(PFS)of 62% and OS of 78% in an American study.[5]

The limitations of this study are the retrospective nature and the single center experience. Other limitations include the short term follow up of 36monthsand the heterogenous population. However, this is meant to report an encouraging experience at its early stage and the types of diseases that constitutes our transplanted population. These results will certainly need to be confirmed in a large prospective study. We are planning to report our outcome after 5 years from establishing the transplant activity in our center. In conclusion, the results reported here indicate that the clinical outcomes of our autologous stem cell transplantation program are comparable to those reported from other centers of longer experience with some epidemiological differences in the disease distribution of our transplant series.[9],[10]

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Tables and Graphs

Table I: Clinical Characteristics of The 38 Patients Undergoing Autologous Stem Cell Transplantation

Age [mean ± SE]	37 ± 3 Years
Gender (N (%))	
Male	25 (65.79)
Female	13 (34.21)
Diagnosis (N (%))	
Hodgkin'sLymphoma	23 (60.53)
Multiple Myeloma	7 (18.42)
Non-Hodgkin Lymphoma	1 (2.63)
Diffuse Large B-cell Lymphoma	3 (7.89)
Central Nervous System Lymphoma	3 (7.89)
Acute Promyelocytic Leukemia	1 (2.63)
Radiation (N (%))	
No	23 (60.53)
Yes	15 (39.47)
Indication for Transplant (N (%))	
Front Line	8 (21.05)
Relapse	28 (73.68)
Primary Refractory	1 (2.63)
Plasma Cell Leukemia	1 (2.63)
Pre-Transplantation Disease Status (N (%))	
Complete Remission	16 (42.11)
Very Good Partial Remission	4 (10.53)
Partial Remission	18 (47.37)
Conditioning (N (%))	
MELPH	7 (18.42)
BEAM	27 (71.05)
Bu/CY	1 (2.63)
TBC	3 (7.89)
Death (N (%))	
No	30 (78.95)
Yes	8 (21.05)
Disease Status (N (%))	
Remission	29 (76.32)
Relapse	9 (23.68)

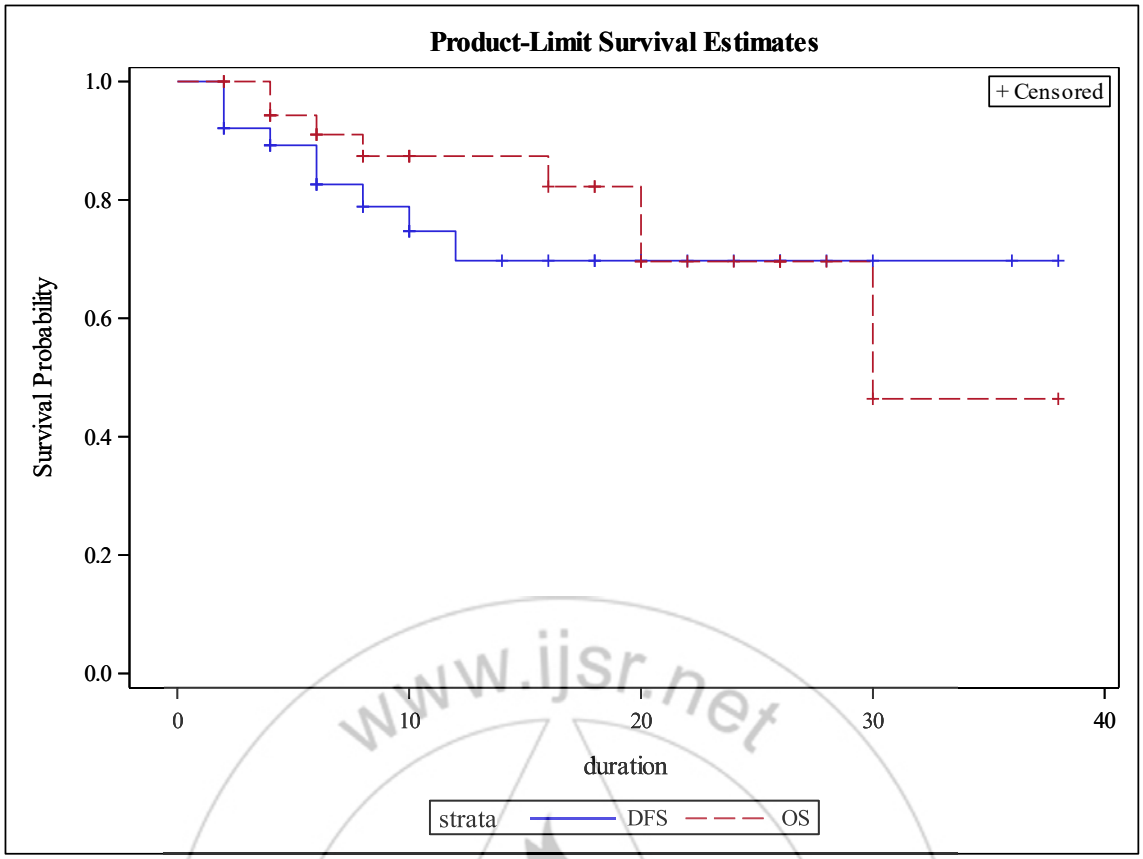

Figure 1: Disease Free Survival Curve (DFS) and Overall Survival (OS) Among Patients Post Stem Cell Transplantation

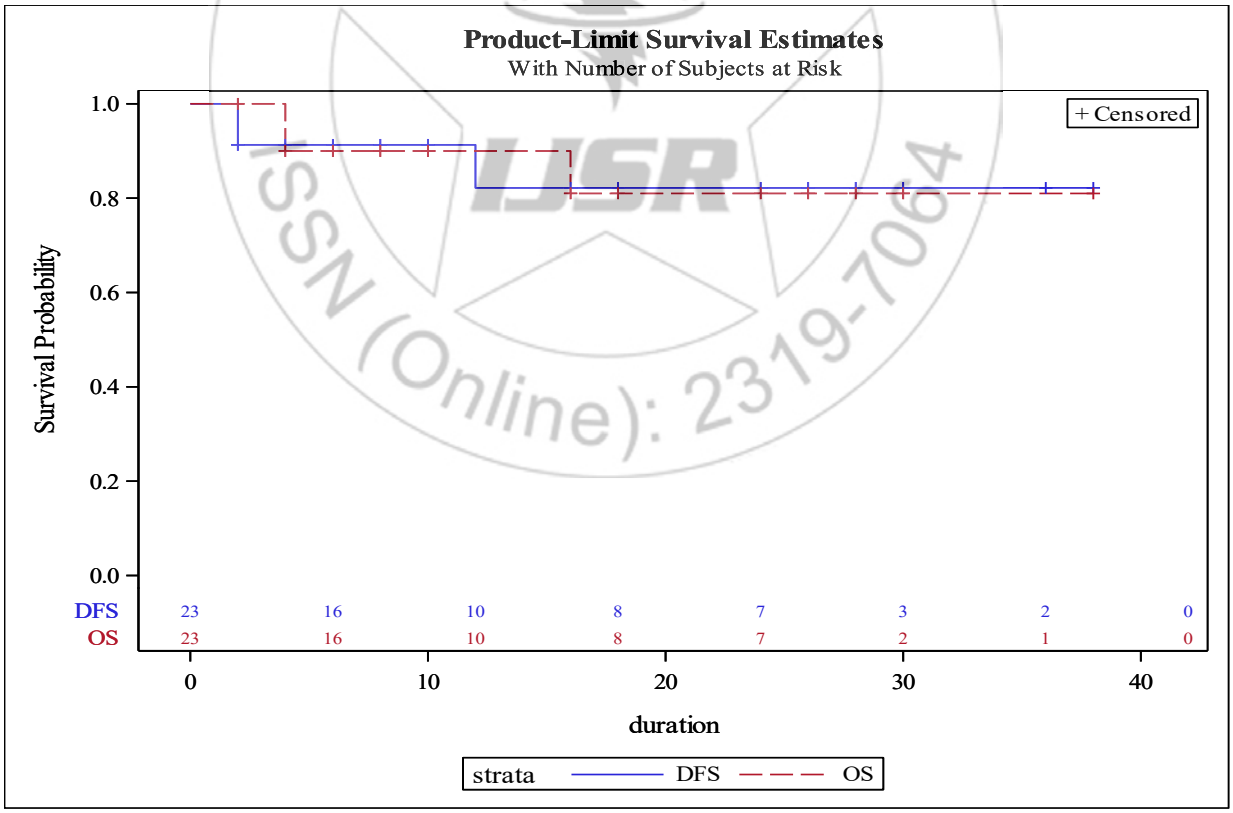

Figure 2: Disease Free Survival Curve (DFS) and Overall Survival (OS) Among Patients Post Stem Cell Transplantation and Diagnosed with Hodgkin's Lymphoma

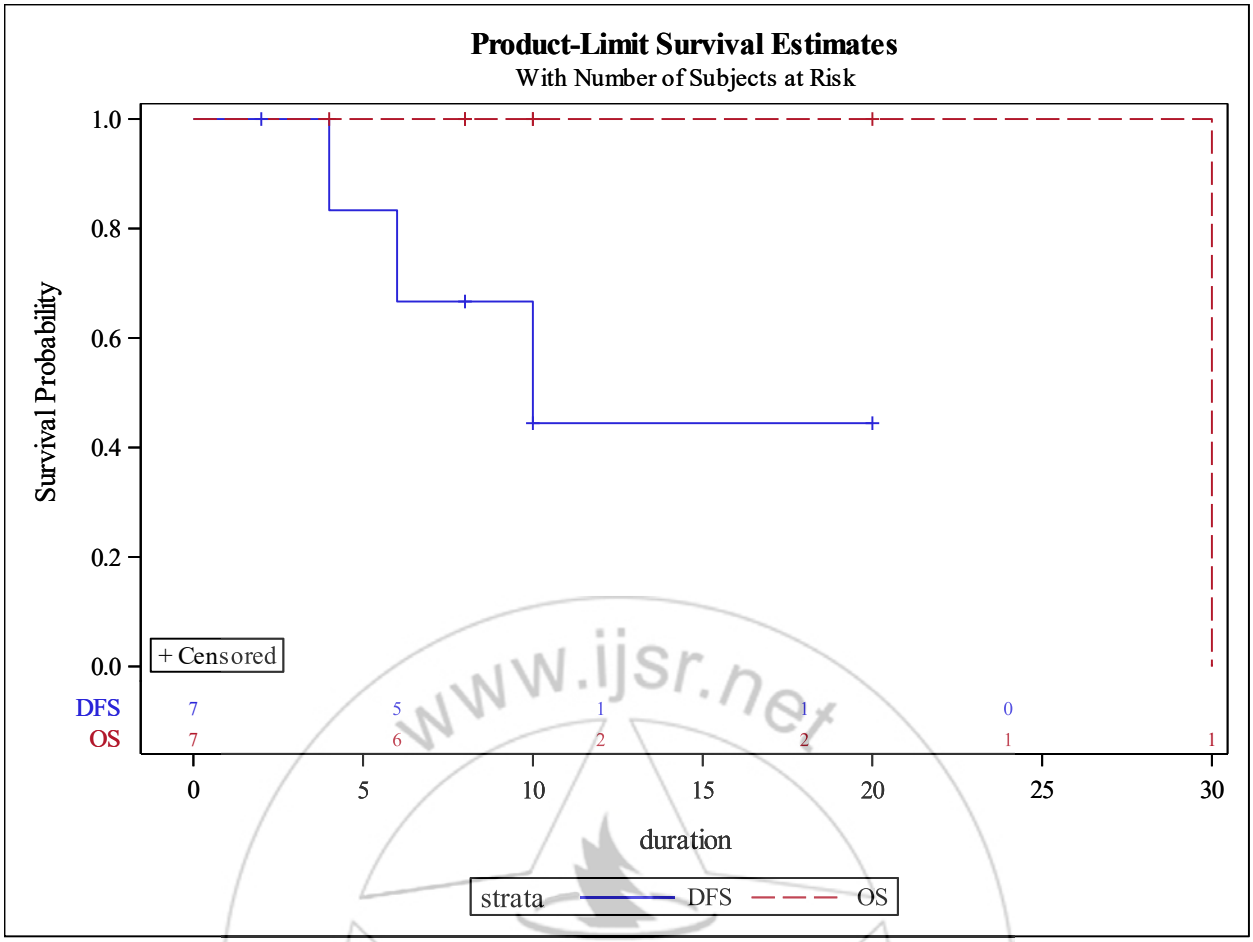

Figure 3: Disease Free Survival Curve (DFS) and Overall Survival (OS) Among Patients Post Stem Cell Transplantation and Diagnosed with Multiple Myeloma

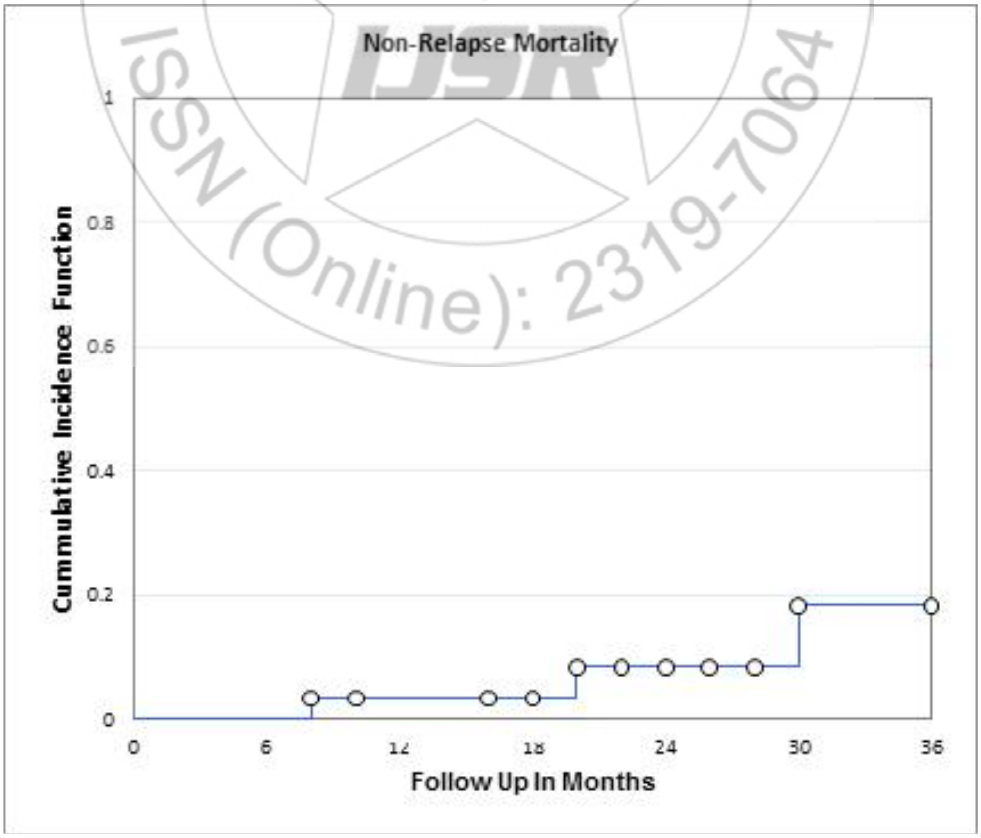

Figure 4: Non-Relapse Mortality (NRM) Among Patients Post Stem Cell Transplantation