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Outcome of autologous bone marrow transplant in patients with relapsed and refractory diffuse large B-cell lymphoma in relation with prognostic factor: A single-center experience

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Abstract:

BACKGROUND: Currently, about 50% of diffuse large B-cell lymphoma patients are relapsed following their complete response to first-line therapy. The treatment strategy for fit patients with relapsed refractory diffuse large B-cell lymphoma (R/R DLBCL) has been done with salvage therapy with non-cross resistant combination chemo-immunotherapy regimens followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT).

OBJECTIVES: The aim of study was to evaluate the outcome of ASCT for R/R DLBCL in relation to certain prognostic parameters.

PATIENTS, MATERIALS AND METHODS: This is retrospective study, conducted from May 2014 to December 2022, at Hematology and BMT Center of Medical City Complex in Baghdad. Thirty-six patients with R/R DLBCL were investigated pre- and post-ASCT; the recorded data included patient disease status pre-transplant, early mortality rate, and type of response at day 100 post-transplant and, survival rate, relapsed rate, and mortality at the end of the study were documented accordingly.

RESULTS: The mean age of DLBCL patients in this study was 41.3 (14–65) years, post-ASCT at day 100; there were 33 (91.6%), 2 (5.5%), and 1 (2.7%) patients in complete remission, relapsed progressive disease, and death, respectively, At 3-year posttransplant, the overall survival (OS) was 71%, whereas the event-free survival (EFS) was 59%. According to disease status pre-ASCT, the OS was 62%, 80%, and 66% with $P = 0.7$, whereas the EFS was 66%, 60%, and 50% with $P = 0.5$ for CR, UCR, and PR, respectively.

CONCLUSION: Iraqi bone marrow transplant center data showed acceptable OS and EFS results in the treatment of R/R DLBCL patients in areas where there is no more option in terms of better OS and EFS but with insignificant relation to the available prognostic factor.

Keywords:

Autologous bone marrow transplant, prognostic factor, relapsed and refractory diffuse large B-cell lymphoma

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Introduction

The most common type of adult non–Hodgkin's lymphoma (NHL) is the diffuse large B-cell lymphoma (DLBCL), which represents about 35%–40% of NHL,[1-3] while in pediatrics, it represents the second most common type of NHL and

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the incidence increases with age.[4] The conventional chemotherapy cyclophosphamid, vincristine, doxorubicin, and prednisolone protocol with the addition of rituximab (anti-CD20 monoclonal antibody) for treatment of DLBCL has improved over the past years, still approximately 50% of the patients are not cured of their disease and need further treatments.[5]

The autologous bone marrow transplant (auto-BMT) in DLBCL is the standard treatment for relapsed case with a salvage chemosensitive therapy with partial or complete response or cases who demonstrated induction failure to front-line therapy. While the benefit of auto-BMT is only well proven in cases that showed chemosensitivity to salvaged therapy before transplant (partial response [PR] or complete response [CR]),[3,6,7] still the relapses frequently occur in areas of previous disease sites which may be related to the fact that the conditioning regimen was not adequate or that the tumor cells contaminating the infused hematopoietic product tracked to the site of previous disease. These cases of DLBCL need further investigations pre- and posttransplant to improve the long-term, disease-free survival.[8]

In a review of 938 auto-BMT and 122 allogeneic BMT (allo-BMT) for relapsed aggressive NHL from the European-BMT registry, progression-free survival (PFS) between auto-BMT and allo-BMT was equivalent and the incidence of relapse was also similar. Of these patients, 23% relapsed or progressed after allo-BMT compared with 38% of patients after auto-BMT, while the mortality rate related to the treatment was higher after allo-BMT.[9]

There are many salvage chemotherapy protocols based on either platinum or ifosfamide therapy used before autologous stem cell transplantation (ASCT), and no one is preferred to other regimens.[3,5,6] In auto-BMT, a lesser transplant morbidity, a shorter hospital stay, and a reduction of costs are usually related to the faster recovery of cell counts posttransplant, specially when the peripheral blood stem cell used instead of stem cell harvested from bone marrow in terms of hematopoietic recognition.[10,11]

An essential component of BMT is the conditioning regimen administered before the hematopoietic cell infusion. In DLBCL, there is no total consensus reached among different BMT centers; however, the most preferred conditioning regimen used for auto-SCT is the BEAM protocol which consists of BCNU (300 mg/m^2 × 1, day 6), VP (200 mg/m^2, days 5–2), Ara-C (200 mg/m^2 bid, days 5–2), and MEL (140 mg/kg/day ×1, day 1).[10,12] Against initial treatment of DLBCL at diagnosis, the addition of rituximab to BEAM had no impact on the outcomes of transplant.[13]

Many studies included many parameters in patients with DLBCL posttransplant: time of relapse from the first remission, prior exposure to rituximab, age at relapse, performance status, and involvement of extranodal site, in trying to identify the most important prognostic factor for the best outcome.[5,10] The aim of the study was to evaluate the outcome of ASCT for R/R DLBCL and in relation to available different prognostic parameters such as pretransplant disease status, number of chemotherapy line before transplant, age, and gender.

Patients, Materials and Methods

This study was a hospital-based, retrospective study, conducted from May 2014 to December 2022, at Hematology and BMT Center of Medical City Complex. Thirty-six patients with relapsed or refractory NHL/DLBCL type were enrolled in this present study. The patient's age was ranged between 14 and 65 years. All patients were grouped according to the disease status pretransplant into complete remission confirmed by positron emission tomography (PET) scan study, and uncertain complete response for patients with negative and normal computed tomography (CT)-can result, while partial remission and stable disease response depend on either PET or CT scan result according the Lugano criteria response,[14] patients who failed to collect stem cell, or patients who relapsed after stem cell collection with failure to respond to other salvage therapy was excluded from study.

Patients with relapsed DLBCL categorized according to the number of chemotherapy protocol lines given pretransplant to 2 or more protocol lines and whether patient received radiotherapy or not.

In almost all patients of R/R DLBCL, their stem cells mobilization was done by chemomobilization (its mean use chemotherapy plus cytokine granulocyte colony-stimulating factor [GCSF] like filgrastim which started postchemotherapy in a dose 10 μg/kg/day and this way more preferred than usage of GCSF alone because it expect to yield more stem cell with fewer apheresis sessions and useful for more decrease in tumor burden) and only one patient stem cell mobilization done with only GCSF in dose 10 μg/kg/day for 5 days. Reinfusion of stem cells was done within 1 month of mobilization. As a conditioning regimen, all cases received either BEAM consisting of BCNU (carmustine) [300 mg/m2 × 1, day 6], VP [200 mg/m2, days 5–2], Ara-C [200 mg/m2 bid, days 5–2], and MEL [140 mg/kg/day × 1, days 1]) or LEAM protocol (same as BEAM but instead of BCNU we use CCNU [lomustine]) in dose 200 mg/m^2 × 1, day 6) according to the drug availability in the center (27 patients for LEAM and 9 patients for

BEAM protocol), and there is no difference in safety, effectiveness, and overall survival (OS) for R/R NHL;[15] on day 5 of the transplant date, patients started to receive GCSF in dose 5 µg/kg/day. Patients were discharged once peripheral blood indices recovered and then followed weekly in the 1st month. All patients received prophylaxis with antibacterial and antifungal from the date of transplant till 100 days.

Recording data include: response and early mortality rate or transplant related mortality (which mean mortality that happened in the 1st 100 days post transplant), then we also record date regarding survival, relapse rate and mortality rate at the end of study were documented accordingly.

Ethical approval

This study was approved by the review ethical and scientific committee in BMT Center in Medical City in Baghdad. The nature of the study design as retrospective so no patient consent was obtained yet all patient were agreed to used their data for reseach purposes.

Statistical analysis

The data gathered were retrospectively collected and subjected to statistical analysis using the Statistical Package for the Social Sciences (SPSS Version 23, IBM; Chicago, Illinois, USA). When applicable, the data were characterized in terms of mean, range, frequencies, and percentages. Survival analysis was conducted utilizing the Kaplan–Meier method. We assessed potential prognostic factors (status of disease before transplant, number of chemotherapy line given from the date of diagnosis, age, and gender) for both OS and event-free survival (EFS) by employing the two-sided log-rank test. OS was calculated from the date of transplant to the date of the last follow-up or the date of death from any cause. EFS was determined from the date of transplant to the date of relapse, disease progression, or death due to any cause. $P < 0.05$ was considered to indicate statistical significance.

Results

The mean age of DLBCL patients in this study was 41.3 ± 13.9 (14–65) years with 52.77% of patients ≥ 45 years and male to female ratio of 1.4:1; the mean disease duration since diagnosis was 63 ± 32.3 (13–151) months.

All included patients was received many salvage therapy before transplant in which 72.2% received 2 lines while the other received more than 2 lines; at the date of ASCT, 55.6% of patients were in complete response (CR) and uncertain complete response (UCR), while 41.7% of patients were with PR, and 2.8% were stable disease as shown in Table 1.

Table 1: The diffuse large B-cell lymphoma patients' characteristics

Characteristics	*n* (%)
Total number of patients	36 (100)
Age (years), mean±SD	41.3±13.9
<45	17 (47.22)
≥45	19 (52.77)
<60	34 (94.4)
≥60	2 (5.5)
Gender	
Male	21 (58.33)
Female	15 (41.66)
Disease status pre-ASCT	
CR	9 (25)
UCR	11 (30.6)
PR	15 (41.7)
Stable	1 (2.8)
Number of chemotherapy line	
2 lines	26 (72.2)
2 lines + RT	1 (2.8)
>2 lines	8 (22.2)
>2 lines + RT	1 (2.8)
Disease follow-up duration in month	
Mean	63.31
Maximum	151
Minimum	13

ASCT=Autologous stem cell transplantation, SD=Standard deviation, RT=Radiotherapy, CR=Compete response, PR=Partial response, UCR=Uncertain complete response

Table 2: The 100-day posttransplant outcome

Patient status at 100-day posttransplant	Patients' number (%)
CR	33 (91.6)
Relapsed and progressive disease	2 (5.5)
Died	1 (2.7)
Total number	36 (100)

CR=Complete response

Post-ASCT at 100 days, 33 (91.6%), 2 (5.5%), and 1 (2.7%) patient were in CR, relapsed progressive disease, and died, respectively, as shown in Table 2.

At 3-year posttransplant, the OS was 71% while the EFS was 59% as shown in Figures 1 and 2.

The OS and EFS in relation to different parameters included in this study pre-ASCT, are shown below including disease status pretransplant, number of chemotherapy protocol lines, age of patients, and gender.

According to disease status pre-ASCT, the OS was 62%, 80%, and 66% with $P = 0.7$, while the EFS was 66%, 60%, and 50% with $P = 0.5$ for CR, UCR, and PR, respectively [Figures 3 and 4].

The 3 years OS in relation to pre ASCT number of chemotherapy protocol lines was 63% and 80% for patients with 2 line and more than 2 lines respectively with $P = 0.09$, while the EFS was 44% and 88% for patient

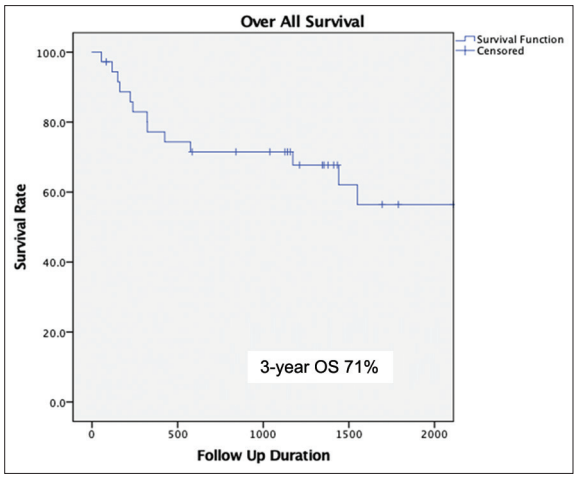

Figure 1: Overall survival of transplanted diffuse large B-cell lymphoma patients since the day of transplant. OS = Overall survival

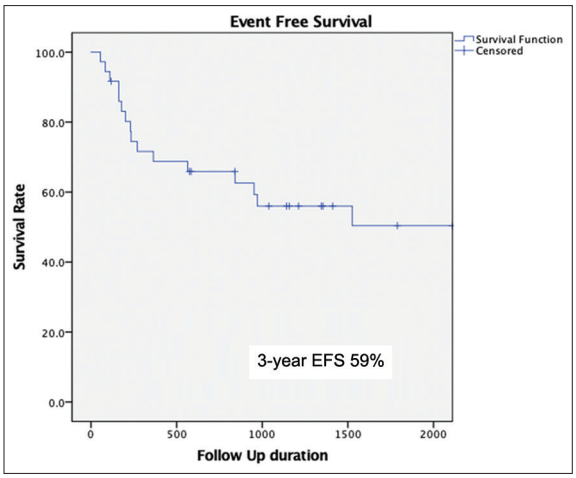

Figure 2: Event-free survival of transplanted diffuse large B-cell lymphoma patients since the day of transplant. EFS = Event-free survival

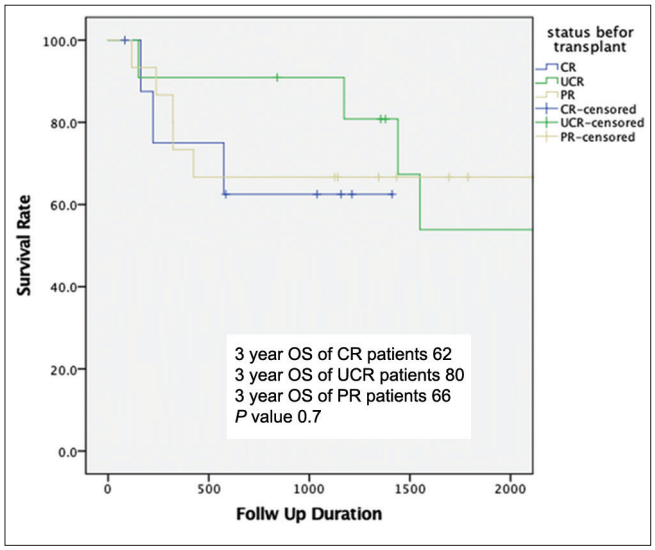

Figure 3: The overall survival according to the pretransplant disease status for diffuse large B-cell lymphoma patients. CR = Complete response, PR = Partial response, UCR = Uncertain complete response

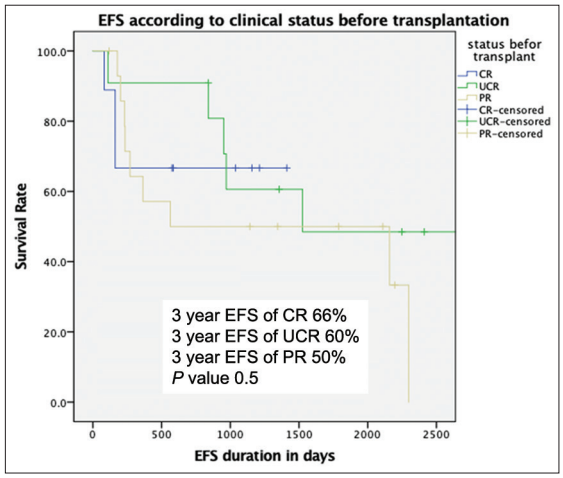

Figure 4: The event-free survival according to the disease status for diffuse large B-cell lymphoma patients. EFS = Event-free survival, CR = Complete response, PR = Partial response, UCR = Uncertain complete response

with 2 lines and more than 2 lines respectively with P = 0.1 as showen in Figures 5 and 6.

The 3-year OS according to the age of DLBCL patients showed 88% and 55% for age <45 and ≥45 years subsequently with P = 0.012, while the 3-year EFS showed 70% and 41% for age <45 years and ≥45 years, respectively, with P = 0.018, as shown in Figures 7 and 8.

According to the gender of DLBCL patients, the 3-year OS was 66% and 67% with P = 0.9, whereas the 3-year EFS was 51% and 61% with P = 0.4 for males and females, respectively, as shown in Figures 9 and 10.

Discussion

Among the relapsed DLBCL patients, the ASCT stays the standard of care for those who are sensitive to the salvage chemotherapy, but not the refractory disease. Several studies to date have attempted to describe the outcomes of ASCT in DLBCL; here, we analyzed our center data trying to identify the best outcome to ASCT for 3-year duration.

In this study, we enrolled 36 cases with R/R DLBCL. It is well known that the incidence risk of DLBCL increases with age;[16,17] here, the mean age of our studied group was 41.3 ± 13.9, about 94% of patient <60 years of age with male predominance, a male-to-female ratio of 1.4:1. Generally, the overall most common age at diagnosis of DLBCL is between 65 and 75 years; almost all our patients were of young age below 60 years; this may be related to the rules of the center to rescind those cases above the age of 60 years with comorbidities. A study by Haeno *et al*. showed median age at transplant was 59 (20–76) years with 54% ≤60 years, with female predominance (63%).[18]

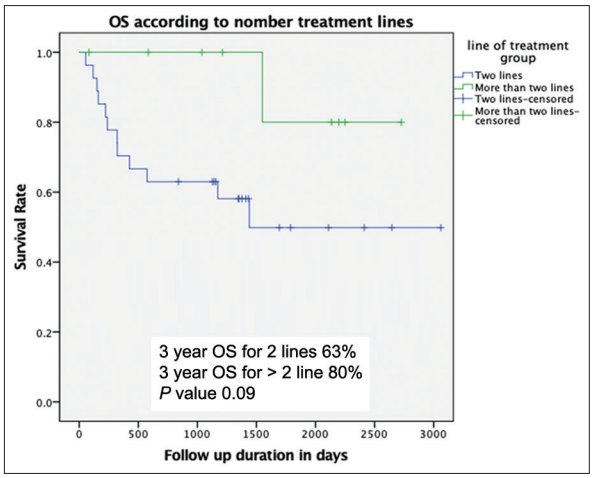

Figure 5: The overall survival according to the number of chemotherapy lines received. OS = Overall survival

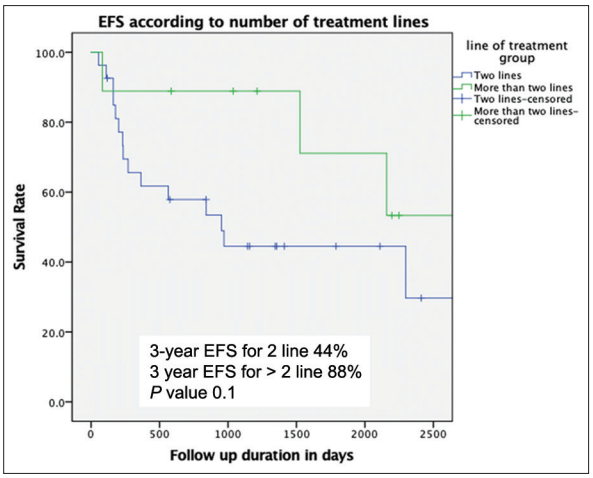

Figure 6: The event-free survival according to the numbers of chemotherapy lines received. EFS = Event-free survival

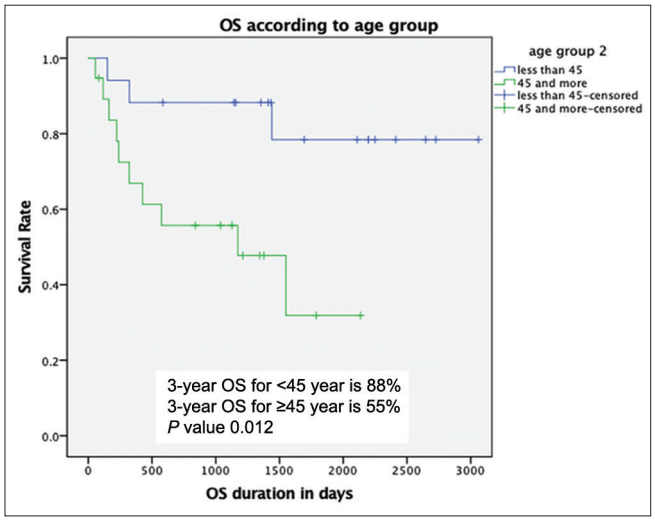

Figure 7: The overall survival according to the age of diffuse large B-cell lymphoma patients. OS = Overall survival

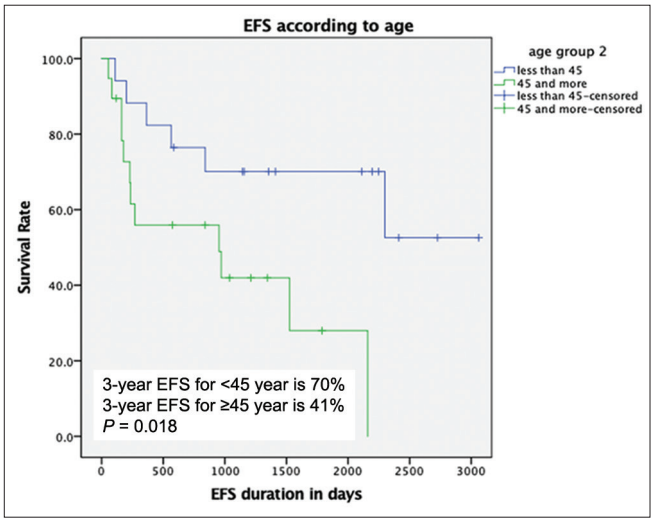

Figure 8: The event-free survival according to the age of diffuse large B-cell lymphoma patients

At the time of transplant, a higher percentage of patients (55.6%) were in CR and UCR by current salvage therapy options, compared to 44% of patients who could not achieve good response (PR and stable disease), as there were no more therapeutic options after failure of more than 2 salvage lines.

Among the 36 patients included in our study, at 100-day post-ASCT, 92% of patients had CR confirmed by PET scan or pan CT scan, 6% of patients had relapse/progressive disease as they had stable disease before transplant, while only 1 (2%) patient was died. In comparison to other study by Philip *et al*., from 49 patients who received high-dose chemotherapy and ASCT, 3 (6%) patients died from toxic effects due to infections and cardiac toxicity which is transplant related mortality.[19]

There was good response rate of our patient with DLBCL post ASCT with mean follow up 63.31 month, in which the OS and EFS at 3 year was 71% and 59% subsequently, which is higher than the results of Bal *et al*. which showed OS and EFS at 3 years was 52.7% and 46.8% subsequently.[20] Other study by Haeno *et al*. showed EFS for R/R DLBCL patients at 5 years was 57.8% and OS was 62.6%.[18]

Pretransplant differences in response type to salvage therapy, number of salvage lines, and sex, were failed to establish a better prognostic marker for both better PFS and OS in DLBCL post-ASCT. As showed in our study statically there was no significant difference in OS and EFS regarding disease status before transplant and for those with PR status still had acceptable response post ASCT with 66% and 50% for OS and EFS subsequently. Bal *et al*. study showed that OS at 3 years for CR and PR patients was 58.9% and 49.3% respectively with $P = 0.2$, whereas the EFS at 3 years for CR and PR patients was 52.4% and 43.8% respectively with $P = 0.2$,[20] and this is

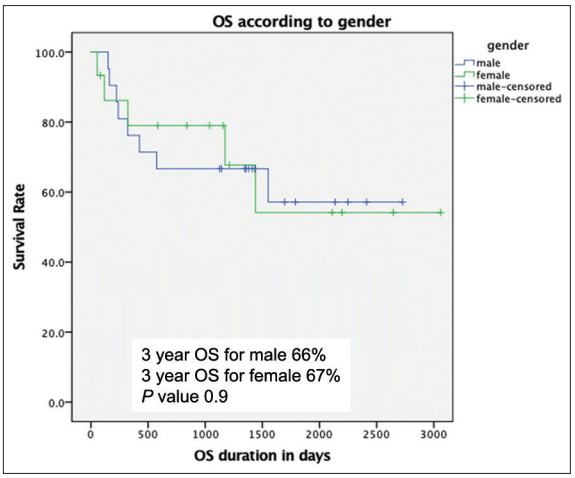

Figure 9: The overall survival according to the gender of diffuse large B-cell lymphoma patients

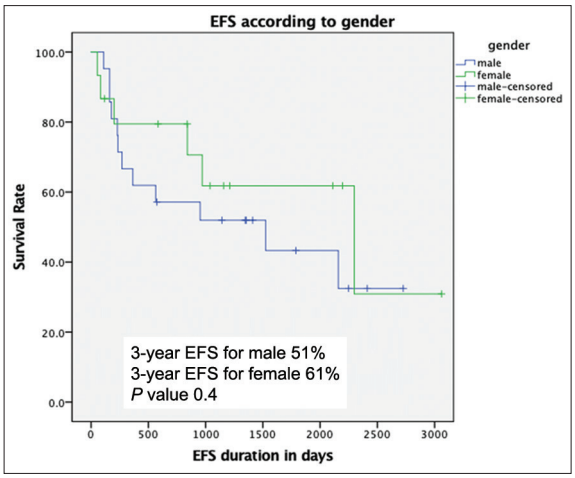

Figure 10: The event-free survival according to the gender of diffuse large B-cell lymphoma patients

comparable to our study. Haeno *et al*.'s study showed that the remission status before ASCT was an independent poor prognostic factor for PFS (hazard ratio = 10.9; 95% confidence interval = 1.94–61.9; P = 0.00680).[18] Conversely, several studies have identified response to salvage therapy as the single most important prognostic factor for better OS and EFS among R/R DLBCL as shown in studies by Rauf *et al*.,[21] Armand *et al*.,[22] and Lekakis and Moskowitz.[23]

Here, regarding the depth of response, more salvage lines pretransplant showed better OS (80%) and PFS (88%) at 3-year follow-up than those with 2 lines of salvage therapy but without significance differences. These subset of patients in PR and difficult to induce good response from following many salvage therapy could be considered for ASCT to lower their risk of relapse and for better survival.

Although the gender differences did not show significant results in terms of OS and EFS at 3 years, the age differences of <45 years showed better OS (88% vs. 55%) and EFS (70% vs. 41%) than those of 45 years and older.

Conclusion

Despite several limitations including the number of cases and lack of initial data of patients at the time of diagnosis, Iraqi BMT Center data showed acceptable OS and EFS results in the treatment of R/R DLBCL patients in areas where there is no more option in terms of better OS and EFS, but with insignificant relation to the available prognostic factors such as disease status before transplant, number of chemotherapy lines, gender, and age.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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