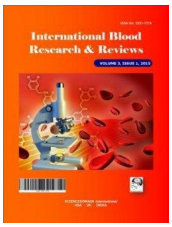

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Oral Busulfan and Cyclophosphamide (BU/CY) versus Cyclophosphamide, Melphalan and Vepsid (Etoposide) (CMV) with Autologous Stem Cell Transplant in Patients with Relapsed Non-Hodgkin Lymphomas (NHL)

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Authors' contributions

This work was carried out in collaboration between all authors. Author AZ designed the study, wrote the protocol and wrote the paper with other authors. Author RAEF supervised the clinical part of the study and wrote first draft of the paper. Author AI managed the literature searches and wrote the paper with other authors. Author AM carried out the clinical part, wrote the paper with other authors and performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Background: High dose chemotherapy with autologous stem cell transplantation (ASCT) is the standard of care and commonly used procedure for patients with relapsed non Hodgkin lymphomas (NHL). There is no clear evidence of superior conditioning regimen and studies that comparing different high dose regimens regarding the efficacy and toxicity profiles were little.
Objectives: To compare efficacy and toxicity profiles of BU/CY and CMV conditioning regimens in patients with relapsed NHL scheduled for ASCT.

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Patients and Methods: Between June 2013 and January 2017, a total of 50 patients were enrolled in the study, 25 patients received CMV and 25 patients received BU/CY followed by ASCT in Bone Marrow Transplantation Center, Nasser Institute and El Sheikh zayed Hospitals, Egypt.
Results: The median time for both neutrophil and platelet engraftment showed no significant difference between the two groups (p= .4) and (p=.3) respectively. Transplant related mortality (TRM) was less in CMV arm, but p value didn't reach the statistical difference (p= .1). The 3- year DFS and OS were slightly higher in CMV arm. However, they didn't show any significant statistical difference 72.8% and 66.5%, (p =.81) and (p= .07). The toxicities, Grade III / IV mucositis, nausea/vomiting and diarrhea occurred slightly higher in BU/CY than in the CMV (16%, 24%, 8% vs. 12%, 16%, 4% respectively).Pulmonary toxicity was higher in BU/CY (3 patients (12%) in BU/CY arm and 1 patient (4%) in CMV arm). However, the toxicities didn't reach the statistical difference.
Conclusion: We found that both BU/CY and CMV regimens are not significantly different in terms of efficacy and toxicity. Although, the small number of patients that were enrolled in our study, we recommend further trial with larger number of patients to confirm the results.

Keywords: BU/CY; CMV; autologous stem cell transplantation (ASCT); NHL.

1. INTRODUCTION

NHL is the third most common cancer in Egyptian men and the second most common cancer in women as reported by the National Cancer Institute (NCI), accounting for 10.9% of all cancers in Egypt diagnosed every year [1].

Patients with aggressive NHL treated with first line combination chemotherapy usually show higher response rate [2], but a large percent of these patients; reaching up to 50%; relapse with a dismal prognosis [3]. Although, a variety of salvage chemotherapy protocols have been developed, the reported long term survival rates ranged between 10-25% [4].

High dose chemotherapy (HDC) with autologous hematopoietic stem cell transplantation (HSCT) is the standard of care and commonly used procedure for patients with relapsed non Hodgkin lymphomas. It offers a chance for long-term disease control in many patients with relapsed or refractory NHL [5].

The purpose of the conditioning regimen is to eradicate the malignancy exploiting the dose response phenomena that most cancer cells exhibit. The most commonly used regimens are CBV (Cyclophosphamide, BCNU, etoposide), BEAM (BCNU + etoposide, cytarabine, melphalan) and BEAC (BCNU, etoposide, cytarabine, cyclophosphamide) [6].

Busulfan and cyclophosphamide (BU/CY) regimen has been described in several patient groups as a conditioning regimen for both autologous and allogeneic SCT for the treatment of hematologic malignancies [7].

Several studies using BU/CY as a conditioning regimen for autologous stem cell transplant (ASCT) in relapsed Non Hodgkin Lymphomas confirmed its efficacy in ASCT. For instance, a study by M. Ulrickson et al, reported 3 years DFS (disease free survival) was 48% and the 3 years OS (overall survival) was 65% [8].

CMV (cyclophosphamide, melphalan and etoposide (vepsid)) regimen also showed to be effective as ASCT conditioning regimen in NHL, with dose-limiting hematological toxicity. In one study by Schütt et al. the reported 5 years OS and event free survival (EFS) were 25% and 16% respectively [9]. This 5 year OS is usually comparable to other high dose conditioning regimens used in relapsed NHL patients like CBV and BEAM [10].

Previous studies didn't show clear evidence of a superior conditioning regimen [11]. So we conducted this study to compare efficacy and toxicity profiles of BU/CY and CMV conditioning regimens for autologous stem cell transplantation in patients with relapsed non-Hodgkin lymphomas scheduled for ASCT.

2. PATIENTS AND METHODS

The study was performed after obtaining approval from the local Institutional Review Board committee of our institute (No: 123/2013) and in accordance with the Declaration of Helsinki, the Good Clinical Practices, and local ethical and legal requirements. All patients signed informed consent. The study was prospective randomized phase II study on 50 relapsed NHL patients, where they randomized after CD34+ cell mobilization.

Between June 2013 and January 2017, a total of 50 patients, 25 patients received BU/CY (our institution standard of care arm) and 25 patients received CMV (comparative arm) followed by autologous stem cell transplantation in Bone Marrow Transplantation Center, Nasser Institute and El Sheikh zayed Hospitals, Cairo, Egypt, were recruited to participate in this study.

2.1 Inclusion Criteria

Patients of both genders, aged ≥16 years, with Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, and adequate liver and kidney functions, no medical contraindications for HSCT and cardiac ejection fraction > 60% were included in this study. Patients with relapsed NHL in complete remission were included only as it is the policy of our institute and this yields good results in contrast to patients with refractory or progressive disease.

2.2 Exclusion Criteria

Patients who have Evidence of uncontrolled infection, active hepatitis B, pregnant or lactating patients, seropositive human immunodeficiency virus (HIV), patients with partial response to salvage chemotherapy were excluded.

2.3 Hematopoietic Stem Cell Mobilization and Collection

All patients underwent transplantation with peripheral blood hematopoietic stem cells mobilized with a granulocyte colony-stimulating factor alone without using plerixafor and after 2-3 cycles of salvage chemotherapt till CR.The hematopoietic stem cells were collected from all patients using high-volume leukopheresis through a large-bore central venous catheter, with target cells of > 2 X 106 per kg of CD 34+ Cells. Most of patients had successful mobilization except 5 patients (3 in BU/CY arm and 2 in CMV arm) underwent a second mobilization procedure to reach the target level.

2.4 Conditioning Regimens

A- CMV Cyclophosphamide 3 gm/m^2i.v. over 2h on days –6 and – 5 , (etoposide) 150 mg/m2 i.v over 3 h on days -6 to -2 and Melphalan 100 mg/m2 over 30 min on day -2 .

B- BU/CY protocol that consisted of Cyclophosphamide: 60mg /Kg/ day 2 hr intravenous infusion (IVI) in 500 cm G 5% (D -3 and -2), Mesna: 20% of the Cy dose, IV / 4 hours to begin 4 hrs before the first Cy dose and continue until 16 hours after the last Cy dose, Phenytoin: 5 mg /Kg/d PO divided on 3 doses days (D-9 to D-3) and Busulfan 4 mg /Kg/ day divided / 6 hours (D -7 to -4).

Neutrophil engraftment was defined as first of three consecutive days with achievement of absolute neutrophil count of ≥ 500 /cm3 and no subsequent decline. Platelet engraftment was defined as first of three consecutive values of platelet count ≥ 20,000 /cm3 with transfusion independence.

DFS was defined as the time from stem cell infusion to progression, relapse or the date of death. OS was defined as the time from stem cell infusion to death from any cause.

Transplant related mortality (TRM) was taken as death from any cause other than disease relapse or progression occurring within the first 100 days after ASCT.

Relapse or progression was defined as worsening in the disease status from that at the time of transplant or the start of a new definitive therapy at any time after transplant. Regimen related organ toxicities were collected over a period of 100 days post-transplant and graded according to national cancer institute- common toxicity criteria (NCI-CTC) version 4.

2.5 Statistical Analysis

Statistical analyses were performed using SPSS v 16 for Windows. Differences between groups were assessed with the Mann–Whitney U-test. P-values less than 0.05 were considered significant. OS and DFS were estimated using the Kaplan and Meier method. Log-rank test was used to examine differences in survival curves.

3. RESULTS

Characteristics of patients receiving CMV or BUCY listed in Table 1. All patients have Eastern Cooperative Oncology Group performance status grade 1.

24 patients that received BU/CY regimen had high grad NHL (19 patients had diffuse large B-cell lymphoma (DLBCL), 4 patients had mantle cell lymphoma (MCL) that was transplanted at the time of relapse, 1 patient had T cell lymphoma (TCL) and one patient had low grade NHL (small lymphocytic lymphoma, SLL). All

patients that received CMV regimen had high grad NHL (22 patients had diffuse large B-cell lymphoma (DLBCL), 2 patients had mantle cell lymphoma (MCL), 1 patient had T cell lymphoma (TCL). Among the 50 patients, 25 received CMV and BU/CY regimen was given to 25 cases as conditioning regimen.

In Bu/Cy group, included 18 male patients (72%) and 7 female patients (28%) with median age of 45 years. On the other hand, in CMV arm, it included 13 male patients (52%) and 12 female patients (48%) with median age 43 years. This discrepancy in the gender could be related to the randomized nature of the study.

3.1 Transplant Outcomes and Toxicities

3.1.1 Engraftment

The median time to neutrophil engraftment was similar in both regimens (10 and 11 days for CMV and BU/CY respectively, p= .4).Also, the median time to platelet engraftment for both groups showed no significant difference (12 and 13 days for CMV and BU/CY respectively, p= .3). CD34 count was significantly higher in CMV arm than in BU/CY arm (p=.006), and this correlated with fewer blood product requirements, more rapid hospital discharge and slightly lower complications in CMV arm.Despite the fact it was aleatory, the CD34+ count can really be a bias in evaluating the toxicities of chemotherapy regimens.

3.1.2 Hospitalization

The median hospital stay of about 30 days (range 20-40) for CMV and 35 days (range 27-60) for BU/CY (p= .023). As the HSCT is considered a costly medical procedure and the transplant costs were closely associated with the length of hospital stay, so decreasing the period of hospital stay will reduce the overall costs.

3.1.3 Regimen related toxicities

The most common organ toxicities of both regimens were nausea and vomiting, mucositis and diarrhea. Grade III / IV mucositis, nausea/vomiting and diarrhea occurred with slightly higher incidence in BU/CY than in the CMV (16%, 24% and 8% vs. 12%, 16% and 4% for BU/CY and CMV respectively), but it didn't reach statistical significance (p value were .51, .48, .76 respectively). There were no cases of VOD in both regimens, 4 patients had pulmonary toxicity, 3 patients (12%) in BU/CY arm and 1 patient (4%) in CMV arm. Grade I-II renal toxicity was observed in 8 patients, 6 patients (24%) in BU/CY arm and 2 patients (8%) in CMV arm, with a comparable number of cases in both regimens for hepatic toxicity, septic shock and hemorrhagic cystitis. No patients in both arms developed veno-occlusive disease (VOD).

All patients developed febrile neutropenia. The febrile episodes were microbiologically documented in 6 patients (24%) for BU/CY regimen and in 4 patients (16%) for CMV regimen with no significant difference (p=.4). Moreover the duration of days of antibiotic use were also comparable between the 2 regimen as they were 16 days for BU/CY and 13 days for CMV(P= .18).

On the other hand, the median number of days with fever was significantly high in BU/CY regimen 8 days (2-15) compared to 3 days (2-8) for CMV regimen, (p=.006).The organisms that had been isolated from positive cultures in both conditioning regimens were mainly Gram +ve in comparison with Gram - ve organisms (16% vs. 8% for BU/CY and 12% vs. 4% for CMV), (P= .4).

3.1.4 Transplant related mortality (TRM)

Two patients (8%) died in the BU/CY arm at days 70 and 100 with no deaths in the CMV arm (p= .1). Cause of death was severe chest infection in the first case.On the other hand, the other case died at home with no identifiable etiology.

3.1.5 Relapse rate

Ten (10) cases were relapsed, 5 (20%) cases in CMV arm and 5 (20%) Cases in BU/CY arm (P=1).

3.1.6 Survival outcomes

- **Disease free survival (DFS):** There was no significant difference in the estimated 3 year DFS (BU/CY 66.5 +/- 13.4 vs. CMV 72.8 +/- 10.6 (p=.81).
- **Overall survival (OS):** There were 3 deaths in BU/CY arm with no deaths in CMV arm. Although, the 3 years OS was better in CMV than in BU/CY (86.1% vs. 100% +/- 7.5%) respectively, it didn't reach a statistical significance (p= .075).

Table 1. Patient characteristics of 50 patients underwent ASCT using BU/CY or CMV regimens for relapsed NHL

	CMV (n=25)	BU/CY (n=25)	P value
Median age years (range)	43 (19-57)	45(25-58)	.42
Sex			
Male	13(52%)	18 (72%)	.1
Female	12 (48%)	7 (28%)	
Histology			
DLBCL	22 (88%)	19 (76%)	.2
MCL	2 (8%)	4 (16%)	
TCL	1 (4%)	1 (4%)	
SLL	0	1 (4%)	
Stage at mobilization			
Early (I/II)	2 (8%)	2 (8%)	.16
Advanced (III/IV)	19 (76%)	23 (92%)	
Extra nodal	4 (16%)	0	
Number of prior chemotherapy lines			
1	20 (80%)	15 (60%)	
2	4 (16%)	7 (28%)	.1
≥ 3	1 (4%)	3 (12%)	
Median time Diagnosis to transplant (months) (range)	32 (11-108)	38 (19-132)	.2
Pre transplant disease status			
CR2	21 (84%)	19 (76%)	
CR3	3 (12%)	6 (24%)	.7
CR4	1 (4%)	0	
Median CD34+ cell dose infused (106 cells/kg recipient) (range)	4.1 (2-12)	2.6 (2-16)	.006

CMV: Cyclophosphamide melphalan vepsid; BU/CY: Busulfan, cyclophosphamide; DLBCL: Diffuse large B cell lymphoma; MCL: Mantle cell; TCL: Tcell; SLL: Small lymphocytic; CR: Complete remission

Table 2. Transplant outcomes difference between BU/CY or CMV arm

	CMV (n=25)	BU/CY (n=25)	P. value
Engraftment (days) Median (range)			
Neutrophil engraftment	10 (6-13)	11 (3-23)	.4
Platelet engraftment,	12 (7-30)	13 (2-60)	.3
Febrile neutropenia			
Fever without documented bacteremia	21 (84%)	19 (76%)	.4
Fever with microbiologically documented infection	4 (16%)	6 (24%)	
Number of Antibiotic days Median (range)	13 (9-24)	16 (2-34)	.182
Number of days with fever Median (range)	3 (2-8)	8 (2-15)	.006
Number of days with GCSF Median (range)	6 (4-9)	7 (4-18)	.17
100-day TRM, n (%)	0	2 (8%)	.1
Length of hospital stay (days) ,Median (range)	30 (20-40)	35 (27-60)	.023
3 year disease-free survival	72.8 +/- 10.6	66.5 +/- 13.4	.81
3 year overall survival	100%	86.1% +/- 7.5%	.075

GCSF: Granocyte colony stimulating factor; N: Number; VOD: Veno-occlusive disease; TRM: Transplant related mortality

4. DISCUSSION

High dose chemotherapy (HDC) with hematopoietic cell transplantation (HCT) is now considered the treatment of choice for patients with relapsed NHL. HCT has been shown to prolong relapse-free survival and even cure a proportion of patients with chemosensitive relapses compared to standard chemotherapy [12].

Since the early 1980s, most conditioning regimens for the treatment of lymphoma have included a combination of CY (±etoposide) with

either TBI or BCNU, resulting in excellent long-term survival. Moreover a significant proportion (22%) of patients treated with TBI experienced grades III to IV toxicities and treatment-related mortality rates of up to 12% have been reported [13].

The standard regimen for autologous stem cell transplant in relapsed NHL is BCNU containing regimen mostly (BEAM). However toxicities of BCNU namely the high incidence of interstitial non-infectious pneumonitis in 16-64%, being fatal in 9% of the patients [6].

Table 3. Transplant toxicities of 50 patients underwent ASCT using BU/CY or CMV regimens for relapsed NHL

	CMV (n=25)	BU/CY (n=25)	P. value
Mucositis			
Grade I/II	10 (40%)	13 (52%)	.51
Grade III/IV	3 (12%)	4 (16%)	
Nausea, vomiting			
Grade I/II	21 (84%)	19 (76%)	.48
Grade III/IV	4 (16%)	6 (24%)	
Diarrhea			
Grade I/II	11 (44%)	12 (48%)	.76
Grade III/IV	1 (4%)	2 (8%)	
Hepatic toxicity			
Grade I/II	2 (8%)	1 (4%)	.1
Grade III/IV	0	3 (12%)	
Renal toxicity			
Grade I/II	2 (8%)	6 (24%)	.25
Grade III/IV	0	0	
Hemorrhagic cystitis			
Grade I/II	4 (16%)	4 (16%)	1
Grade III/IV	0	0	
VOD	0	0	1
Pulmonary toxicity	1 (4%)	3 (12%)	.61
Septic shock	1 (4%)	1 (4%)	1

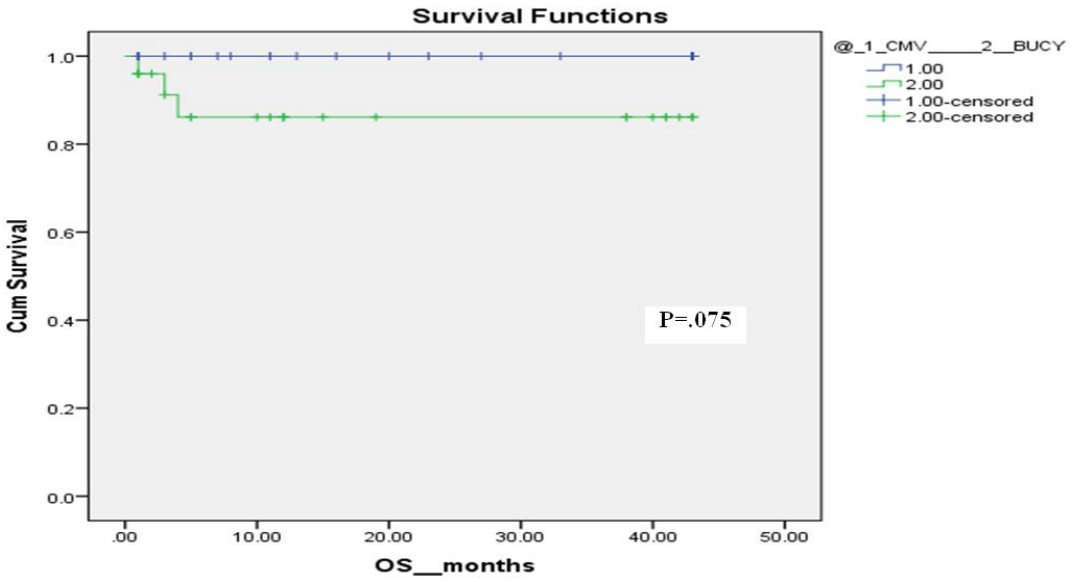

Fig. 1. Overall survival (OS) of 50 patients underwent ASCT using BU/CY or CMV regimens for relapsed NHL

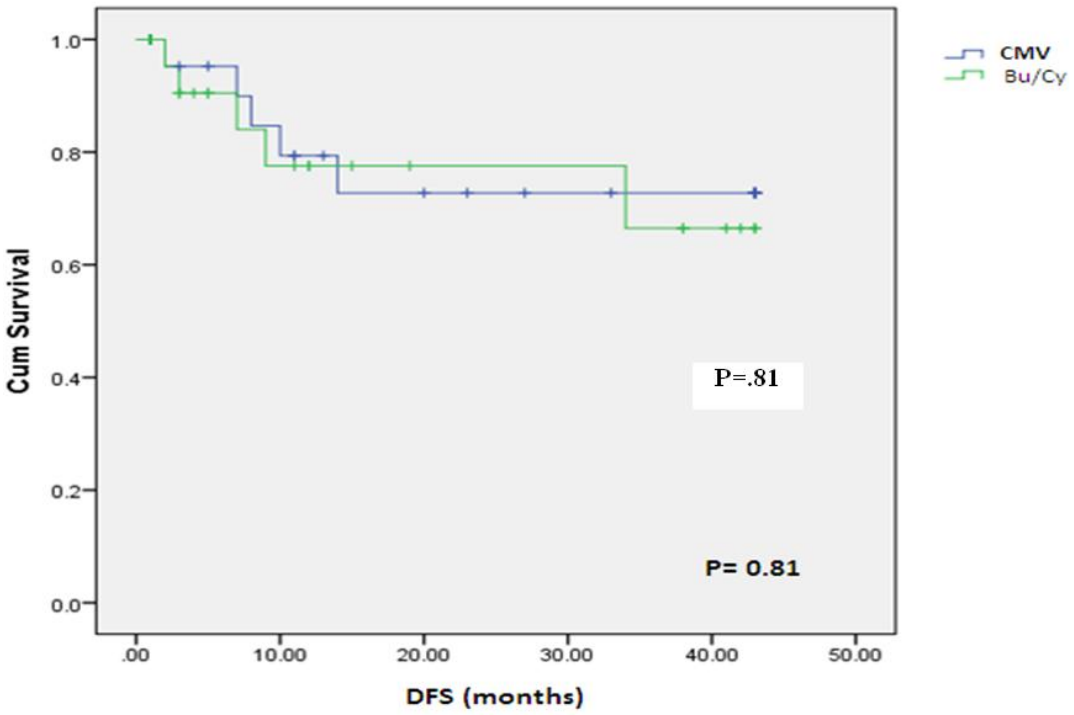

Fig. 2. Disease free survival (DFS) of 50 patients underwent ASCT using BU/CY or CMV regimens for relapsed NHL

So several trials were conducted to use other less toxic regimens, one of them is BU/CY which is the standard regimen in allogeneic stem cell transplant as it contains Busulfan which is an alkylating agent with profound toxic effect on non dividing marrow cells including early myeloid and lymphoid precursors [14].

BU/CY toxicities were mild in the form of mucositis, neutropenic fever and hepatotoxicity with no treatment related mortality but with 15% incidence of hepatic veno-occlusive disease (VOD) in one study [15]. Bu/Cy in addition to etoposide was compared with BEAM and the findings revealed that EFS, OS and toxicity profiles of both regimens were similar [16].

CMV regimen is one of the melphalan-based regimens. Melphalan is an alkylating agent that was used in both autologous and allogeneic transplantation.CMV regimen had been shown to be highly effective against lymphomas, in one study with dose-limiting hematological toxicities [17].

Our study compared the efficacy and toxicities of BU/CY and CMV as conditioning regimens in autologous stem cell transplant in relapsed NHL.

Regarding the engraftment, we found in our study that the median time of engraftment for both neutrophils and platelets was slightly shorter for CMV arm [median 10 days (range, 6–28) and 12 days (range, 7–65)] in comparison to BU/CY arm [median 11 days (3-23) and 13 days (range, 2-60)], but this was not statistically significant (p= .4 and .3, respectively).

Our results for neutrophils engraftment was matched the results of previous studies for both regimens. Regarding BU/CY a previous study by Weaver et al. who recruited 22 patients with relapsed NHL, the time to engraftment for both neutrophils and platelets 10 days (range, 8–14) and 12 days (range, 7–52), respectively which was comparable to our results [18].

Similarly regarding the CMV regimen the results of study conducted by Schutt et al. who recruited 59 patients with relapsed NHL, The median time to engraftment for both netrophils and platelets was comparable to our results for CMV arm {10 days (range, 6–28) and 12 days (range, 7–65) respectively} [9].

On the contrary, we found rapid and quicker time to platelet engraftment compared with previous

study which was done by DeMagalhaes-Silverman et al. [19] and conducted on 16 patients with relapsed NHL treated with BU/CY showed the median time for platelets engraftment was 18 days (9–39). Also, same findings were found in another study done by Matthew Ulrickson et al. [8] which conducted on 78 patients using BU/CY, Their median time to platelet engraftments was 17 days (6-576 days).

Regarding the toxicity, our results showed that gastrointestinal (GIT) toxicity was the most common organ toxicity in the form of nausea / vomiting, mucositis and diarrhea. Most of GIT toxicities were grade I/II and comparable between the two arms. On the other hand, grade III/IV nausea/vomiting, mucositis and diarrhea had occurred with a slightly higher incidence in BU/CY (24%, 16% and 8%) than in CMV (16%, 12% and 4%), but it didn't reach statistical significance (p= .51, .48 , .76) respectively.

Febrile neutropenia occurred in all cases with microbiologically documented infections in 16% of cases in CMV and 24% in BU/CY cases, mostly gram +ve organisms in most of cases for both regimens (12% vs. 16%, respectively).There was a slightly higher incidence of renal toxicity grade I/II in BU/CY arm 24% vs. 8% in CMV arm but didn't reach statistical significance. The pulmonary toxicity was slightly higher in BU/CY (12%) than in CMV (4%) but again was not statistically significant (p=.6).On the other hand, both regimens showed similar rates of hepatic toxicity, hemorrhagic cystitis, and septic shock cases and our results didn't report any cases of VOD in both arms.

The median duration of antibiotic use was comparable between the 2 regimens (13 days for CMV and 16 days for BU/CY, P: .18). On the other side, the median number of days with fever was significantly low (3 days, range: 2-8) for CMV regimen, while it was 8 days (range 2-15) for BU/CY regimen (p: 0.006).

Regarding our toxicity results of BU/CY arm were less than the other study results of DeMagalhaes-Silverman et al who reported higher incidence of VOD (15%) and one case developed interstitial pneumonitis. Also, the study by Chen et al. [20] reported 4% incidence of idiopathic pneumonia syndrome. Other spectrum of toxicity reported by Matthew Ulrickson et al. as 4 cases in their study (5%) developed engraftment syndrome, 3 cases (4%) of VOD, 6 cases (8%) cardiac toxicity and 2 cases (3%) of busulfan lung toxicity (interstitial pneumonitis).

On the other hand, our toxicity results for CMV arm compared to previous study by Schutt et al. These results of gastrointestinal toxicity were slightly lower than our results, but with comparable results of all other toxicity.

Regarding transplant related mortality (TRM), two patients (8%) died in the BU/CY arm at days 70 and 100 with no deaths in the CMV arm.

These results were comparable to 2 previous study used BU/CY as conditioning regimen, one of them is Weaver et al. who reported (9%) TRM rate. The other is Chen et al. [20] who reported 7% TRM rate. On the contrary, there are other studies reported lower TRM than in our study, for example a study by Matthew Ulrickson et al. had found that TRM was 1% with a lower relapse rate (2.5%). Another study conducted by DeMagalhaes-Silverman et al. reported a slightly lower TRM (5%).

Regarding, CMV arm, our results didn't report any transplant related mortality and this was different than previous study by Schutt et al who reported higher incidence of TRM of 10%.

Regarding relapse rate, Ten (10) cases were relapsed, 5 (20%) cases in CMV arm and 5 (20%) cases in BU/CY arm (P= 1).

Our results regarding BU/CY were lower in comparison with results of DeMagalhaes-Silverman et al study that reported a higher relapse rate of about 45%. On the contrary, our results are higher compared with results reported by Matthew Ulrickson et al. study that found a lower relapse rate of about 2.5%.

Concerning the disease free survival, There was no significant difference in the estimated 3 year DFS between BU/CY (66.5 +/- 13.4) and CMV (72.8 +/- 10.6), (p=.81). As regarding overall survival, we found that the estimated 3 years OS was better in CMV arm than in BU/CY (100% vs. 86.1% +/- 7.5%) respectively, but this difference was found to be statistically insignificant (p = .075) and this may be related to a small number of patients evaluated.

Our results regarding survival rates for both arms were better than other previous studies. Firstly concerning BU/CY arm, a study by Weaver et al. reported that the 3.6 year OS and DFS were

58% and 36% respectively. Also, Matthew Ulrickson et al. observed that the 3 years OS and DFS were 65% and 48% respectively. Chen et al had shown that the 3 years OS and DFS were 59% and 49% respectively.

Concerning the CMV arm, Schutt et al. had reported that the 5 years EFS and OS were 16% and 25% respectively. This could be due to development and availability of antifungal and supportive treatment which probably were not available at that time in nighties at the time of the conduction of the most of previous studies.

As the aim of our study is comparing the efficacy and toxicity of BU/CY versus CMV, We found no significant differences between the 2 conditioning regimens in terms of engraftment, toxicity profile, episodes of febrile neutropenia and days of antibiotics. Also, no significant differences in both groups regarding relapse rate and DFS. Although there is a slight improvement in 3 years OS for CMV arm compared to BU/CY arm, it didn't reach statistical significance. Similarly TRM in CMV arm was less than the BU/CY arm but it didn't also reach statistical significance (p = .1). We recommend further studies with large sample size to explore this survival difference.

5. CONCLUSION

We found that both BU/CY and CMV regimens are not significantly different in terms of efficacy and toxicity.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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