Outcome of Relapsed or Refractory Diffuse Large B-cell Lymphoma with Second-line Chemotherapy Ifosfamide-Carboplatin-Etoposide with or without Rituximab

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Treatment of relapsed or refractory diffuse large B-cell lymphoma is difficult. The de novo diffuse large B-cell lymphoma has better prognosis than the transformed diffuse large B-cell lymphoma. The response of CHOP or a similar regimen has an important role in determining response to salvage therapy, in relapse or refractory diffuse large B-cell lymphoma patients. Patients who are non-responder to initial treatment have a very poor chance of responding to therapy for relapse. This was a small scale observational study and was conducted from January 2017 to December 2020 in National Institute of Cancer Research and Hospital, Bangladesh. A total of 34 patients with relapsed or refractory diffuse large B-cell lymphoma were identified at hematology department in National Institute of Cancer Research and Hospital, 28 of them were treated with ICE chemotherapy and 6 with R-ICE chemotherapy as second line regimen. Overall response rate to 2nd line chemotherapy was 64.8%, with 32.4% (11 patients) complete remission and 32.4% (11 patients) partial remission. Median overall survival to second line regimen was 10 months, corresponding to a 4 year overall survival of 32.4% and a 4 year progression free survival was 17.6%. Patient with stable disease/progressive disease median overall survival was 7 months compared with 15 months for complete remission and 9 months for partial remission (p<0.001). Median overall survival was significantly better in patients with international prognostic index 0-2 compared in those with international prognostic index >2 (p=0.010). However improvement of salvage efficacy is an urgent need with new drugs. Further studies are necessary to determine whether this regimen will improve outcomes of relapsed or refractory diffuse large B-cell lymphoma patients.

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Key words: Relapsed Diffuse Large B-cell Lymphoma, Outcome, Stable disease, second-line Chemotherapy

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of lymphoma and constitutes about 30-40% of adult non-Hodgkin lymphoma (NHL) cases[1]. Rituximab administered with cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) is the current standard therapy for newly diagnosed DLBCL patients. With R-CHOP complete response rate is approximately 75.0% and long term disease free survival is approximately 50.0-60.0%[2,3,4,5]. Unfortunately half of all diffuse large B cell lymphoma patients will have either persistence of tumor following initial therapy (primary refractory disease) or a relapse after a complete remission (CR)[6,7]. Salvage chemotherapy followed by high dose therapy and autologous stem cell transplantation (ASCT) has become the standard second line treatment in chemo-sensitive diffuse large B-cell lymphoma patients[8,9,10]. Although there is no gold standard for salvage chemotherapy, ifosfamide-carboplatin-etoposide (ICE) regimen is an effective, cytoreductive regimen for chemosensitive

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relapse and refractory DLBCL patients[11,12]. The overall response rate (ORR) to ICE in patients with relapsed or refractory DLBCL is approximately 70.0%, with a CR rate of 25.0 to 30.0%[12,13]. Disease status-that is, whether the patient has relapsed or primary refractory disease and the second line age adjusted international prognostic index ($_S$AAIPI) are the primary determinants of the response to ICE[13,14]. Among the evolving therapies for NHL, anti-CD20 monoclonal antibodies (mAb) have shown significant promise[15,16]. Rituximab is a chimeric anti-CD20 IgG1K mAb, which is comprised of murine variable regions and human constant regions[17]. Recent studies suggest that adding rituximab to CHOP significantly improves the CR rate and survival in patients with untreated DLBCL[3,18]. Patients who are responders to second line therapy were less likely to receive rituximab with their initial therapy than those in the non-responder group[19,20]. This study was designed to determine overall survival (OS), progression free survival and ORR of relapsed or primary refractory DLBCL patients who received ICE or R-ICE therapy as second line regimen. The study results will enrich the hematologist.

Methods

This is a small scale observational study and was conducted from January 2017 to December 2020 in National Institute of Cancer Research and Hospital, Bangladesh. Patients were included if they manifested de novo DLBCL that relapsed after, or was refractory to, initial chemotherapy and who had adequate records available like the nature of the treatment, the response to therapy, dates of initial diagnosis and treatment, the date of recurrence, dates of second-line treatment. A total of 34 patients aged 15 to 70 years were included in this study. Preformed data collection sheet was used for data collection. OS of the patients who had received at least one subsequent therapy including ICE, R-ICE was estimated. OS was defined as the time from the date the patient was declared as having failed initial therapy until death and was estimated according to the Kaplan-Meier method. All patients with survival data available were taken into the study and the time of follow up was 48 months.

ICE/R-ICE second line chemotherapy treatment program:

Three cycles of ICE/R-ICE chemotherapy were planned to be administered at 2 weeks intervals. A brief summary of the treatment program is as follows; patients were treated as inpatients. On admission 12-h creatinine clearance was measured for subsequent carboplatin dosing. Chemotherapy was administered as follows: etoposide 100mg/m^2 by intravenous bolus from day 1-3; carboplatin (area under the curve (AUC) 5; dose=5 x [25+CI$_{CR}$]) was administered as a bolus infusion on day 2, ifosfamide (5000 mg/m^2) mixed with an equal amount of mesna on day 2, granulocyte-colony stimulating factor (G-CSF) was administered for 2 days and was given after completion of chemotherapy. In R-ICE chemotherapy, rituximab (375mg/m^2) was administered on day 1 of each cycle according to standard prescribing guidelines.

Results

A total of 34 patients with relapsed or refractory DLBCL who underwent second line chemotherapy from 2017 to 2020 were included in this study. Among them 28 patients received ICE therapy and 6 patients received R-ICE therapy. Patient's characteristics are outlined in Table I. The mean age was 45±14 years. Immuno-histochemical expression of Ki67 was observed in 18 patients (mentioned in Table II). Mean of Ki67 % was 67 in ICE group and 68 in R-ICE group (not shown in the table). There was no statistically significant difference in these groups. Types of initial treatment are listed in Table II. Twenty nine (29) patients received CHOP therapy and 5 patients received R-CHOP therapy as 1st line chemotherapy. Response to 1st line regimen. ORR to 1st line chemotherapy was 70.6% with 47.1% CR and 23.5% partial remission (PR) as shown in table 2.29.4% was primary refractory as they did not response to 1st line chemotherapy. Mean duration of 1st remission was 7.0±8.0 months. Response to 2nd line regimen. ORR to 2nd line chemotherapy was 64.8%, with 32.4% (11 patients) CR and 32.4% (11 patients) PR as shown in table 3.9 patients (26.5%) were refractory to 2nd line regimen. Death occurred in 3 (8.8%) cases. Median overall survival was significantly better in patients with IPI 0-2 compared in those with IPI >2 as shown in Table IV (p= 0.010). Survival Median OS of the entire population was 10

months after receiving second line chemotherapy (Table IV), corresponding to a4 year OS of 32.4% (Figure 2) and a 4 year progression free survival was 17.6% (Figure 1). Median OS for patients who achieved CR, PR and for those who did not respond (SD/PD) to 2nd line regimens were significantly different (Table IV). Patient with stable disease/progressive disease (SD/PD) median OS was 7 months compared with 15 months for CR and 9 months for PR ($p<0.001$). Median overall survival of DLBCL patients from diagnosis was 24 months (Table IV).

Table I: Demographic and General findings of study subjects (N=34)

Demographics and General findings	ICE Group		R-ICE Group		Total	
	Mean±SD	n (%)	Mean±SD	n (%)	Mean±SD	n (%)
Age in years	44±14	28 (82.0)	51±11	06 (18.0)	45±14	34 (100.0)
Gender						
Male		20 (59.0)		03 (09.0)		23 (68.0)
Female		08 (23.0)		03 (09.0)		11 (32.0)
Stage						
I		06 (17.6)		00 (0.0)		06 (17.6)
II		10 (29.4)		04 (11.8)		14 (41.2)
III		11 (32.4)		02 (05.9)		13 (38.2)
IV		01 (02.9)		00 (00.0)		01 (02.9)
B symptoms		16 (47.1)		04 (11.8)		20 (58.8)
Extra nodal involvement		07 (20.6)		05 (14.7)		12 (35.3)
International prognostic index						
Low		12 (35.3)		00 (0.0)		12 (35.3)
Low-Intermediate		10 (29.4)		05 (14.7)		15 (44.1)
High -intermediate		04 (11.8)		00 (00.0)		04 (11.8)
High		02 (05.9)		01 (02.9)		03 (08.8)
Performance status						
0		07 (20.6)		00 (00.0)		07 (20.6)
1		15 (44.1)		03 (08.8)		18 (52.9)
2		04 (11.8)		02 (05.9)		06 (17.6)
3		02(05.9)		00 (00.0)		02 (05.9)
4		00 (00.0)		01 (02.9)		01 (02.9)

Table II: Diagnostic markers and response to first-line regimen (N=34)

Diagnostic markers, response to1st line regimen	n (%)
Ki67; [mean±SD]	68.0±15.0
1st line chemotherapy used	
CHOP	29 (85.3)
R-CHOP	05 (14.7)
Response to 1st line regimen	
Complete remission	16 (47.1)
Partial remission	08 (23.5)
Progressive/Stable disease	10 (29.4)
Duration of 1st remission in months; mean±SD	7.0±8.0

Table III: Median OS according to response to 2nd line regimen

Response to 2nd- line regimen	n (%)	Median overall survival (months)
complete remission	11 (32.4)	15
Partial remission	11 (32.4)	09
Stable disease/Progressive disease	09 (26.5)	07
Death	03 (08.8)	

Table IV: Survival- medians for survival time in months

Median survival		95% Confidence interval	p value
Median overall survival from relapse	10.000	8.042-11.958	
Median overall survival from diagnosis	24.000	20.887-27.113	
Median survival according to initial International prognostic index			
Low	24.000	17.828-30.172	0.010
Low intermediate	27.000	22.756-31.244	
High intermediate	16.000		
High	15.000	6.998-23.002	
Median survival according to response of second line chemotherapy			
Complete remission	15.000	12.608-17.392	<0.001
Partial remission	9.000	6.580-11.420	
Refractory (Stable disease/Progressive disease)	7.000	5.539-8.461	

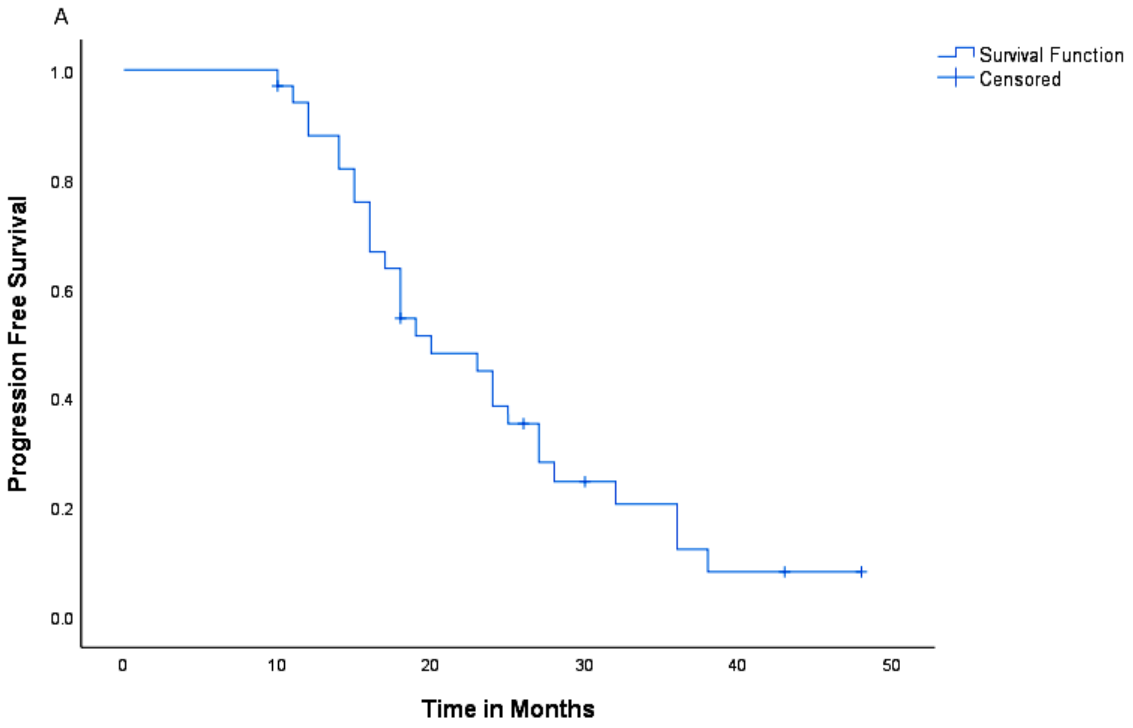

Figure 1: Progression free survival of 34 patients from time of relapse

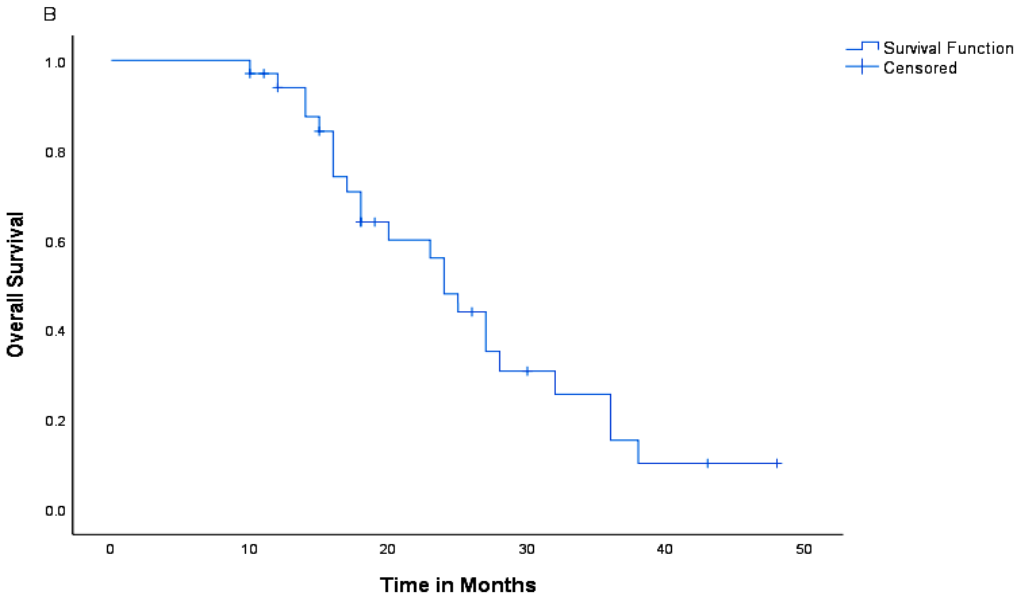

Figure 2: Overall survival of 34 patients from time of relapse

Discussion

Patients with relapsed or refractory DLBCL have a life expectancy of 3 to 4 months if they are not treated.[5]In chemo-sensitive DLBCL patients the response to high-dose chemotherapy is usually determined by tumor burden[21]. The type of initial response is essential in assessing response to second line therapy in patients who have relapsed after CHOP or a similar regimen[22]. Lower IPI is independently related with better outcome in DLBCL. Neste EVD et al. demonstrate that the IPI is effective in third line therapy, as it has been in second-line therapy and in patients who have relapsed after ASCT[23]. In this study, median overall survival was significantly better in patients with IPI 0-2 compared in those with IPI >2 (p=0.010). The result is similar to the result of an International CORAL study, where the OS was significantly better in patients with tertiary IPI 0-2 compared in those with tertiary IPI >2[8]. In this study, ORR to 1st line chemotherapy was 70.6% with 47.1% CR and 23.5% PR. Patients with partial response to initial therapy have a better chance of responding to relapse therapy than the refractory patients. Patients who had a complete response to initial therapy, especially those who had a complete response for more than one year, had a good likelihood of responding to relapse therapy[22]. In this study 29.4% patient was primary refractory. Primary refractory patients have lower overall response than relapsed patients[11]. In this study, ORR to 2nd line regimen was 64.8%, with 32.4% (11 patients) CR and 32.4% (11 patients) PR. Nine (9) patients (26.5%) were refractory to 2nd line regimen and death occurred in 3(8.8%) cases. ORR to ICE was found to be 71.6%, with 28.4% CR and 43.2% PR by Zelenetz, Hamlin and Kewalramani[6] and ORR to ICE was found to be approximately 70.0%, with a CR rate of 25.0 to 30.0% by Moskowitz, Bertino and Glassman[12,13]. This analysis based on OS after 2nd line chemotherapy. Median OS of the entire population (who received 2nd line chemotherapy) was 10 months, corresponding to a 4 year OS of 32.4%. In the international CORAL study, median OS of the patients who received ICE as third line therapy was 4.4 months, corresponding to a 1 year OS of 23%[8]. In relapsed aggressive lymphoma OS of 47.0% at 1 year was reported in the study of Glass, Hasenkamp and Wulf[24] and OS of 38.4% at 5 years was found in the study of Zelenetz, Hamlin and Kewalramani. In this study, progression free survival was 17.6% at 4 years. In other study, progression free survival was 29.2% at 5 year[6] and in the study of Kewalramani, Zelenetz and Nimer, progression free survival was 43.0% at 2 year in patients who underwent ASCT after receiving ICE as second line therapy[11]. Median OS for patients who achieved CR, PR and for those SD/PD to 2nd line regimen was significantly different in this study. Patient who did not respond to ICE/R-ICE median OS was 7

months compared with 15 months for CR and 9 months for PR ($p<0.001$). In the International CORAL study, median OS was 63.6 months for CR, 11.7 months for PR and 3.7 months for SD[8]. One study showed that patient who did not respond to ICE had a median survival of only 4.8 months[6]and it was 4 months in the study of Elstrom, Martin and Ostrow[2]. Median overall survival of DLBCL patients from diagnosis was 24 months in this study. Adding rituximab to ICE appears to significantly improve the CR rate of patients with relapsed or primary refractory DLBCL, with more than 50.0% of patients achieving CR[11]. As the cases of R-ICE was very low than ICE so the comparison of ORR to ICE with R-ICE could not done. It is clear from this result that there are substantial needs for improvement in salvage regimens. Our limitations for second line therapy include age greater than 70 years and patients with significant renal or cardiac disease. For these reasons, there will always be a demand for newer treatment programs. We are also looking at the accuracy of prognostic models that can distinguish between different risk groups that require new therapeutic approaches. Small sample size and the inability to perform ASCT are the limitations of the study.

Conclusion

If IPI is low, a fraction of DLBCL patients who fail first line therapy have a better response to second line therapy. Median OS for patients who achieved CR, PR and for that SD/PD to 2nd line regimen was significantly different. Patients who do not respond to 2nd line regimen, outcome and survival rate of them are not satisfactory. Novel therapeutic strategies and clinical trials should be prioritized for these patients. Further large scale, multi-centric study with a longer follow-up period for responding cases is recommended.

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