RESEARCH ARTICLE

Impact of Inadequate Doses of Rituximab in the Treatment of Diffuse Large B Cell Lymphoma in Malaysian Patients

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Abstract

Background: The current standard treatment for patients with newly diagnosed diffuse large B cell lymphoma (DLBCL) is rituximab combined with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). A significant number of patients were not treated with recommended dose of rituximab due to limited financial resources in Malaysia. This study evaluates the efficacy of R-CHOP like chemotherapy in Malaysian patients with DLBCL. Materials and Methods: The study comprised a retrospective analysis of patients with DLBCL treated at a single centre. The outcome was compared with patients who were treated with R-CHOP like and CHOP like chemotherapy. Patients who were treated with lower dose of rituximab was subanalysed for outcome. Results: A total of 86 patients who had CHOP-like chemotherapy were included. Only 39 (45%) patients had rituximab and only 12 (29%) patients had the recommended dose. The overall response (OR) and complete response (CR) rates were 88% and 81% respectively. There was no significant difference in OR and CR in patients who had rituximab and those without rituxmab. Those with International Prognostic Index (IPI) score of ≤2 had significant higher CR rate, progression free survival (PFS) and overall survival (p<0.001). Conclusions: The lack of significant improvement in CR and DFS in our patients may be due to an inadequate dose of rituximab.

Keywords: Diffuse large B cell lymphoma - rituximab - CHOP

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Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of aggressive B-cell non-Hodgkin Lymphoma (NHL), accounting for 30-35% of the newly diagnosed adult NHL (Armitage, 2012). There has been a gradual increase in the incidence of DLBCL both in US and Japan (Chihara et al., 2013). Other countries within the East Asia region with great economic growth have also shown increase in the incidence of DLBCL (Huh et al., 2012; Teoh et al., 2013).

The current treatment approach for DLBCL is rituximab in combination with chemotherapy, mainly CHOP. Rituximab is a chimeric anti-CD20 monoclonal antibody which binds specifically to CD20 antigens expressed mainly in the B lymphocytes. The results from European Groupe D'Estude des Lymphomes des L'Adulte LNH-98-5 study (GELA) study demonstrated that 5 year overall survival (OS) is significantly higher in elderly patients with rituximab combination chemotherapy (Coiffer et al., 2002). In younger patients who had R-CHOP like chemotherapy had an increased 3-year event-free survival and OS compared to those without rituximab; 79% vs 59% and 93% vs 84% respectively (Pfreundschuh et al., 2006) More recently, the Asia groups including the Japanese, Korean, Chinese and Singaporean had also confirmed similar findings in patients with DLBCL (Park et al., 2006; Li et al., 2007; Ngo et al., 2008; Nishimori et al., 2009; Seiki et al., 2010). However, within the Asian countries, there are many which have limited health care resources in treating patients with lymphoma. There is limited published data on the survival of patients with DLBCL in these developing countries except for one report from Thailand where inferior progression free survival is documented when patients are not treated with rituximab (Intragumthornchai et al., 2013).

In Malaysia, rituximab is currently widely used in patients with follicular lymphoma and DLBCL but due to the relative high cost, there are still a group of patients who are unable to afford this treatment. The available rituximab injection comes in a vial of 500mg and it is only in the last 4 years that 100mg vial was made available. Due to the high cost of rituximab, many clinicians had opted for a flat dose of 500mg rituximab rather than the recommended 375mg/m^2 in the past years.

This study aimed to determine the response as well as overall survival of patients with DLBCL who had been treated with a flat dose of 500mg rituximab containing chemotherapy and those without any administration of this drug.

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Materials and Methods

Patients

This is a retrospective study with approval from local institution ethic committee. All DLBCL patients attending the adult hematology unit at UMMC were recruited from the period of April 2007 to October 2009. Disease staging was assessed according to Ann Arbor classification. Staging of all patients would include unilateral bone marrow examination and CT scan of neck, thorax, abdomen and pelvis. Clinical information collected were age at diagnosis, gender, stage of disease, LDH level, performance status, and chemotherapy regimen. Remission status in response to chemotherapy was assessed using the International Working Group criteria. Patients were followed up until February 2010 for incidence of relapse and death.

Previous unpublished study on similar group of patients data without rituximab containing chemotherapy were used as historical control. These patients were diagnosed of DLBCL in the same institution from year 1996 to 2001.

International prognostic index (IPI) i.e. age, performance status, stage, extranodal involvement and LDH level were used as clinical prognostic factors. Index values of 0 and 1 are classified as low risk (L), 2 as low-intermediate risk (L/I), 3 as high-intermediate risk (H/I) and 4 and 5 factors as high risk (H). Patients who had risk score of 0-2 is categorized into low risk and those with score of >2 is categorized as high risk.

CHOP based chemotherapy includes CHOP and CEOP. The CHOP regimen comprised of intravenous (iv) cyclophosphamide 750mg/m^2, iv doxorubicin 50 mg/m^2, iv vincristine 1.4mg/m^2 (maximum 2mg) on day1 administration and 5 days of oral prednisolone 60mg/m^2; CEOP was similar to CHOP except doxorubicin is replaced by epirubicin 75mg/m^2. A flat dose of 500mg of rituximab was given in patients who were not able to afford. Patients with BSA of <1.4 were given the recommended dose of rituximab at 375mg/m^2.

Disease free survival (DFS) was defined as time of diagnosis to relapse or death or last known follow up. Overall survival (OS) was defined as time of diagnosis to death or last follows up.

Statistic analysis

Patients' characteristics in the historical cohort were compared with the current patients' cohort. Patients who did not have rituximab containing CHOP-like chemotherapy were included together with the historical group for treatment outcome analysis. The treatment outcome of both groups was compared using chi-square analysis.

Overall survival and disease free survival was analysed using Kaplan Meier survival curve and compared between groups using the log rank test. p value of <0.05 is considered as statistical significant.

Results

A total of 59 patients were included in this present study. There were a total of 31 male and 28 female. The median age of the patients studied was 56 years (ranges 16-81 years).There were a total of 45 patients in the historical control group. The median duration of follow up for the historical patients were 23 months (ranges 0.25-201) and for the current patients' cohort, the median duration of follow up was 51 months (ranges, 1-200). The patients' characteristics of both groups are shown in Table 1. 14 patients in the current study were unable to be classified into any of the IPI risk groups due to inadequate clinical information.

In this current patients cohort, the types of first line chemotherapy used in combination with rituximab are CHOP regimens (39 patients), CVP (2 patients) and ICE (3 patients). There were 14 patients who had CHOP-like chemotherapy without rituximab as first line therapy. In the historical control patients, none of the patients had rituximab containing chemotherapy as first line treatment. The majority of patients (37) had CHOP-like chemotherapy; 24 patients had CEOP, 6 patients had CHOP and the remaining patients had CVP (7). Characteristics of patients who had CHOP-like chemotherapy with or without rituximab are showed in Table 2.

The overall response (OR) and CR rate in these 104 patients irrespective of the treatment regimen was 88% and 73% respectively. The OR rate was 86% in the current patient cohort and 82% in the historical patients. There was a significant better CR rate in this cohort of patients compared to the historical control patients, 81% vs 56% respectively, p<0.01. However, there was no significant difference in CR rate in patients who had R-CHOP like chemotherapy compared with patients who had CHOP-like chemotherapy without rituximab, 82% vs 70 % respectively.

45.2% of patients were categorized into the lower risk group (IPI≤2) and CR rate was significantly higher in patients with IPI score of ≤2, p<0.0005. Patients in the historical cohort had a worse IPI score compared to the present patients cohort, p<0.0001. Patients who had R-CHOP like chemotherapy had significantly lower IPI score compared to those who were treated with CHOP-like therapy, p<0.001.

Table 1. Characteristics of Patients

		Current patients cohort N=59 (%)	Historical patients cohort N=45 (%)	Total N=104 (%)
Median Age, years (range)		56 (16-81)	52 (22-86)	55(16-86)
Gender	Male	31(52.5)	20(55.6)	56(53.8)
	Female	28(47.5)	25(44.4)	48(46.2)
Race	Malays	23(39)	22(48.9)	45(43.3)
	Chinese	26(44.1)	19(42.2)	45(43.3)
	Indians	10(16.9)	4(8.9)	14(13.5)
Stage at presentation	I-II	29(49.2)	16(35.6)	45(43.3)
	III-V	27(45.8)	29(64.4)	56(53.8)
	Indetermine	3(5.1)	--	3(2.9)
IPI score*	0 to 2	34(57.6)	13(28.9)	47(45.2)
	3 to 5	11(18.6)	32(71.1)	43(41.3)
	Unevaluable	14(23.7)	--	14(13.5)
CHOP-like chemotherapy		14(23.7)	39(86.7)	53(51)
RCHOP-like chemotherapy		41(69.5)	--	41(39.4)
Others		4(6.8)	6(13.3)	10(9.6)

*p<0.05

Table 2. Characteristics of Patients Treated with CHOP-like Chemotherapy With and Without Rituximab

			CHOP-like chemotherapy N=47 (%)	RCHOP-like chemotherapy N=39 (%)	Total N=86 (%)
Median age, years (range)			56 (21-77)	55 (16-79)	55.5 (16-79)
Gender	Male		24(50.9)	19(48.8)	43(50)
	Female		23(49.1)	20(51.2)	43(50)
Race	Malays		21(44.6)	13(33.3)	34(41.5)
	Chinese		24(51)	18(46.1)	42(44.7)
	Indians		2 (4.4)	8(20.5)	10(13.8)
Stage at presentation		I-II	24(51)	20(51)	44(51)
		III-V	23(49)	19(49)	42(49)
IPI score*	0 to 2		21(44.5)	24(61.5)	45(52)
	3 to 5		24(51)	6(15)	30(35)
	Unevaluable		2 (4.5)	9(23.5)	11(13)
Follow up duration Median, months (range)			45 (0-201)	46 (4-125)	45.5 (0-201)

*p<0.05

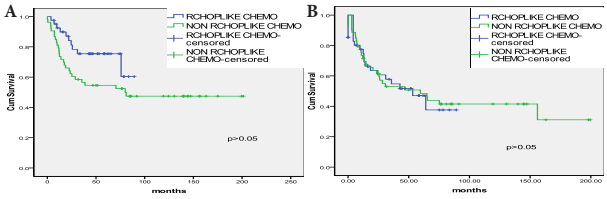

Figure 1. A) Overall Survival and B) Progression free survival, of Patients Treated with R-CHOP Like Chemotherapy and CHOP-like Chemotherapy

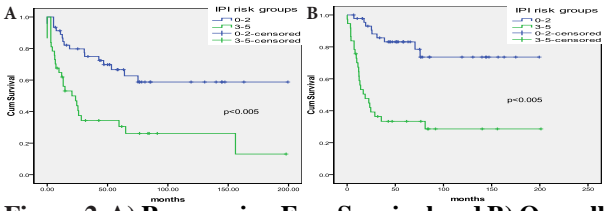

Figure 2. A) Progression Free Survival and B) Overall Survival, of Patients According to IPI Risk Groups

In the current patient cohort, 57 patients had documented BSA readings. 12 patients had the recommended dose of rituximab and the remaining 29 patients were not given the recommended dose. There was no significant difference in the OR and CR rate of these groups of patients.

The estimated OS at 3 years of the R-CHOP group (80%) was superior to that of CHOP group (55%), however, this was not statistically significant (Figure 1A). The DFS at 3 years was 50% for both groups (Figure 1B). Patients with IPI score of <2 had significant better OS and PFS compared to those with higher score, p<0.0005 (Figure 2).

Discussion

For most patients, R-CHOP remains the choice of treatment for DLBCL. R-CHOP or CHOP like chemotherapy has proven to improve overall survival of patients with aggressive NHL (Coiffer et al., 2002; Feugier et al., 2005; Sehn et al., 2005; Pfreundschuh et al., 2006). The results are indisputable and many studies done within Asia region had also proven so (Park et al., 2006; Li et al., 2007; Nishimori et al., 2009). A study which evaluated the outcomes of Western and Asian patients with DLBCL treated with R-CHOP found no difference in OS and progression free survival (PFS) (Castillo et al., 2013). The Asian population of this study was mainly from Japan, Korea and China. There is not many published data in South East Asia (SEA) region where the populations are generally more heterogenous and resources are often limited in certain countries within SEA region (Intragumthornchai et al., 2013). This study demonstrated that OR and CR rates were comparable to other studies, 88% and 73% respectively. The significant better CR rate of the current patient cohorts compared to the historical control patients (81% vs 56%) were likely due to the higher IPI risk group of the historical control patients. There was no significant difference in patients who had been treated with R-CHOP like therapy compared to those who were treated with CHOP-like chemotherapy without rituximab. These results are in contrary to many other published results (Coiffer et al., 2002; Feugier et al., 2005; Sehn et al., 2005; Pfreundschuh et al., 2006; Nishimori et al., 2009). The most likely explanation for this would be the inadequate dose of rituximab. Rituximab is widely used in Malaysia and although it is available to most patients, there are still a small number of patients who are not able to afford the treatment. The 100mg vial of rituximab was not available in Malaysia until years ago. Many patients were given a flat dose of 500mg rather than recommended dose of 375mg/m^2 as a mean to save cost.

In this patient's cohort, only 45% (39) of the patients treated with CHOP-like chemotherapy had rituximab infusion. 30% of these patients had adequate dose of rituximab. The OR and CR rates in these patients were not significant better. Although the 3-year OS of patients treated with R-CHOP like chemotherapy was better than those who did not have rituximab, this was not significant. One of the possible reasons could be the numbers of patients are too small to make any significant conclusion. Another possible explanation could also be due to the inadequate dose of rituximab given.

IPI has been used as a predictive model for outcome of aggressive lymphoma. It remained as one of the most useful clinical prognostic tool. Patients with IPI score of ≤2 had significant better CR rate and PFS compared to patients with higher IPI score (Blay et al., 1998; Vose et al., 2001; Li et al., 2007). In the era of rituximab, the improvement of treatment response seems to alter the survival of the different IPI risk groups. It is reported that the 4-year survival rate of patients with revised IPI score of ≤2 was more than 80% compared to those with higher score, 4-year survival of 58% (Vose et al., 2001). In this study, IPI remained the significant clinical prognostic factor irrespective of choice of therapy given. Patients presenting with high IPI score >2 had a significant poorer PFS and OS. This is also consistently demonstrated in many studies (Blay et al., 1998; Vose et al., 2001; Li et al., 2007).

There are important limitations to this study. This is a retrospective study and is not randomized; hence there may be other confounding factors. It is well established that different genetic subgroups of DLBCL confers different prognosis; where germinal centre B-cell (GCB)

lymphoma had a better prognosis than activated B cell (ABC) lymphoma (Rosenwald et al., 2002). There are evidences which demonstrated that, ABC lymphoma is associated with poorer outcome even with addition of rituximab (Lenz et al., 2007; Fu et al., 2008; Visco et al., 2013). It has also been suggested that Asian have higher rate of non-GC lymphoma compared to Western patients (Shia et al., 2005; Shiozawa et al., 2007). A study by Li et al. (2014) reported that there is no survival benefit in patients with GCB lymphoma treated with R-CEOP and those with CEOP (Li et al., 2014). In this study, we did not sub-classify the lymphoma. Therefore it is difficult to determine the lack of significant survival benefit in this study is due to the inadequate dose of rituximab and not the different rates of ABC or GCB lymphoma compared to the other studies. It is therefore important for future studies to establish if indeed the non-superior outcome of our patients is due to the inadequate dose of rituximab rather than the possible difference in the subtypes of DLBCL lymphoma.

In conclusion, there was no demonstrable significant improvement of our patients with DLBCL who were treated with R-CHOP like chemotherapy and this is most likely due to the inadequate dose of rituximab. Therefore, it is important for treating physicians to ensure that patients are given the recommended dose of rituximab. A follow up study which includes the various biologic markers and further subclassification would be helpful to determine and to confirm the role of rituximab in our patients.

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