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Treatment Outcomes of Rituximab Plus Hyper-CVAD in Korean Patients with Sporadic Burkitt or Burkitt-like Lymphoma: Results of a Multicenter Analysis

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Purpose

This study was conducted to evaluate outcomes in adult patients with Burkitt lymphoma (BL) or Burkitt-like lymphoma treated with an rituximab plus hyper-CVAD (R-hyper-CVAD) regimen by focusing on tolerability and actual delivered relative dose intensity (RDI).

Materials and Methods

Patients ≥ 20 years of age and pathologically diagnosed with BL or Burkitt-like lymphoma were treated with at least one cycle of R-hyper-CVAD as the first-line treatment in this study. Eligible patients' case report forms were requested from their physicians to obtain clinical and laboratory data for this retrospective study.

Results

Forty-three patients (median age, 51 years) from 14 medical centers in Korea were analyzed, none of which were infected with human immunodeficiency virus. The majority of patients had advanced diseases, and 24 patients achieved a complete response (75.0%). After a median follow-up period of 20.0 months, 2-year event-free and overall survival rates were 70.9% and 81.4%, respectively. Eleven patients (25.6%) were unable to complete the R-hyper-CVAD regimen, including six patients due to early death. The RDIs of adriamycin, vincristine, methotrexate, and cytarabine were between 60% and 65%, which means less than 25% of patients received greater than 80% of the planned dose of each drug. Poor performance status was related to the lower RDIs of doxorubicin and methotrexate.

Conclusion

R-hyper-CVAD showed excellent treatment outcomes in patients who were suitable for dose-intense chemotherapy. However, management of patients who are intolerant to a dose-intense regimen remains problematic due to the frequent occurrence of treatment-related complications.

Key words
Burkitt lymphoma, Rituximab, CVAD protocol

Introduction

Burkitt lymphoma (BL) is a highly aggressive B-cell lymphoma accounting for 1%-5% of all non-Hodgkin lymphomas (NHL) in adults [1,2]. BL was first identified as a childhood endemic tumor with a geographical distribution [3]. Since then, worldwide and sporadic occurrence of BL has been reported, and BL has become a well-known human immunodeficiency virus (HIV)–associated malignancy [3]. As BL tumor cells are characterized by rapid cellular growth, conventional regimens for NHL have shown disappointing results [4]. On the other hand, dose-intense, multi-fractionated chemotherapeutic regimens have been shown to improve treatment outcomes [5-7]. A recent population-based study [8] demonstrated the impact of regimen intensity on treatment outcome of adult BL patients, reporting a 2-year overall survival (OS) rate of only 38.8% for cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) or CHOP-like regimens, whereas survival rates of 68.6% to 82.8% were achieved for dose-intense regimens.

In addition to BL, other lymphomas morphologically resembling BL were classified as "atypical BL/Burkitt-like lymphoma" by the 2001 World Health Organization (WHO) classification, and these morphologically similar lymphomas are thought to lie on a continuum between BL and diffuse large B-cell lymphoma (DLBCL) [9]. In the 2008 WHO classfication, classification of these atypical BL/Burkitt-like lymphomas was more refined, including a new provisional entity, "B-cell lymphoma, unclassifiable, with features intermediate between BL and DLBCL," which we define as BL-U in this report [9]. Despite these changes in classification, there are no established treatment guidelines for these lymphomas. Thus, dose-intense treatment strategies similar to those used for BL are typically used for aggressive lymphomas with overlapping features of BL and DLBCL [10].

Among dose-intense treatment regimens, hyper-CVAD regimen (hyper-fractionated cyclophosphamide, adriamycin, vincristine, and dexamethasone alternated with methotrexate plus cytarabine) has been proposed for treatment of highly aggressive lymphoid malignancies by the MD Anderson Cancer Center [6].

Since addition of rituximab to hyper-CVAD regimen (R-hyper-CVAD) has been shown to improve treatment outcomes [11], R-hyper-CVAD has been used as a primary treatment option for BL. Using this approach, a complete remission (CR) rate of 86% and 3-year OS rate of 89% without any induction death were observed [11]. However, significant toxicity, delayed treatment, and treatment-related early death are not uncommon in actual clinical practice since patient characteristics often differ from those in clinical trials. As elderly and frail patients are commonly treated in clinical practice, information on real-life outcomes of the regimen could be a useful reference for physicians who treat BL. In addition, although ethnic differences might affect drug tolerability and efficacy, outcomes of R-hyper-CVAD in Asian patients have never been reported. Thus, we analyzed the outcomes of adult Korean patients with sporadic BL or BL-U treated with R-hyper-CVAD regimen [11] by focusing on tolerability and delivered dose intensity.

Materials and Methods

1. Patients

We reviewed the medical records of 14 hospitals belonging to the Consortium for Improving Survival of Lymphoma (CISL) [12] and selected patients who fulfilled the following inclusion criteria: 1) age ≥ 20 years, 2) pathologically diagnosed as BL or BL-U according to the 2008 WHO criteria, and 3) treated with at least one cycle of R-hyper-CVAD as the first-line systemic treatment. The Institutional Review Boards of each participating center approved this study and waived informed consent since no actual intervention was performed due to its retrospective nature.

2. Case report forms

Case report forms (CRF) for eligible patients were requested from physicians who treated the patients in this retrospective study (CISL-1201) from March 2012 to March 2013. The CRF contained a fill-in section on patient characteristics such as gender, age at diagnosis, anti-HIV antibody status, the International Prognostic Index (IPI) factors, bone marrow involvement, and crucial laboratory data, including complete blood cell counts and serum lactate dehydrogenase, among other values. Patient height, weight, accurate dose of each administered drug, and date of drug administration were obtained in order to calculate relative dose intensity (RDI). Hematologic toxicity and grade 3 or greater non-hematologic toxicity was reviewed for each cycle in the CRF. Special events during immunochemotherapy, such as tumor lysis syndrome, cerebellar ataxia due to cytarabine, and infectious episodes, were investigated in detail. The results of the interim and final treatments according to the revised response criteria for malignant lymphomas [13] were collected along with data on relapse, progression, or death of patients.

Table 1. Patient characteristics

Parameter	No. (%) (n=43)
Gender	
Male	29 (67.4)
Age (yr)	
Median (range)	51 (20-83)
20-40	14 (32.6)
41-60	17 (39.5)
> 60	12 (27.9)
Ann Arbor stage	
I	3 (7.0)
II	7 (16.3)
III	4 (9.3)
IV	29 (67.4)
ECOG performance status	
≥ 2	13 (30.2)
≥ 3	4 (9.3)
Lactate dehydrogenase	
Elevated	32 (74.4)
Extranodal lesion	
≥ 2 sites	23 (53.5)
Standard international prognostic index	
Low risk	9 (20.9)
Low-intermediate risk	9 (20.9)
High-intermediate risk	12 (27.9)
High risk	13 (30.2)
B Symptoms	
Present	16 (37.2)
Bone marrow involvement	
Involved	9 (20.9)
Bulky lesion	
Present	10 (23.3)

ECOG, Eastern Cooperative Oncology Group.

3. Statistical analysis

Event-free survival (EFS) denotes survival free from progressive disease or discontinuation of therapy for any reason. To eliminate the impact of early death on overall treatment outcomes, we also used disease-free survival (DFS), which is the same parameter as EFS except that death by any cause other than progression of lymphoma is not considered. OS denotes survival free from death by any cause. The Kaplan-Meier method and log-rank test were used for survival analysis. Univariate and multivariate analyses were performed by using a backward Cox regression model with variables of $p < 0.1$ in the univariate analysis. Mann-Whitney tests were used to compare means between the two groups. All values were two-sided, and statistical significance was accepted at a level of $p < 0.05$.

Results

1. Patient characteristics

Data on 43 patients from 14 medical centers were collected and analyzed. All patients had sporadic BL or BL-U (i.e., no patients had HIV-associated lymphoma) and were of a median age of 51 years. Dates of initial diagnosis ranged from February 2006 to March 2013, and the majority of patients had advanced diseases at the time of diagnosis. More than half of patients were in Ann Arbor stage IV (n=29, 67.4%), had two or more extranodal sites (n=23, 53.5%), and were at high or high-intermediate risk (n=25, 58.1%) according to the standard IPI. A summary of patients' characteristics is shown in Table 1.

2. Treatment and tumor response

Prophylactic measures, doses and intervals of cytotoxic drugs, number of planned cycles, central nervous system (CNS) prophylaxis, and overall schedule of the regimen were as those in a previous study [11], except for administration of rituximab (two patients received 375 mg/m^2 of rituximab on the first and eighth days of each cycle, whereas others received the same dose of rituximab on the first day of each cycle only). According to the recommendations of the Korean National Health Insurance Guideline, granulocyte-colony stimulating factor (G-CSF) was administered daily starting the first day patients showed an absolute neutrophil count (ANC) < 1,000/μL until the third consecutive day patients showed an ANC > 3,000/μL in each cycle. Of the 32 evaluable patients, 24 patients (75%) achieved a CR, and six patients experienced disease progression in the final response evaluation (Table 2).

3. Survival analysis

Seven patients experienced relapse after CR, with two patients experiencing CNS involvement and five showing extra-CNS sites (two patients with skin and subcutaneous nodules, two patients with bone marrow involvement, and one patient with right inguinal lymph node involvement). After a median follow-up period of 20.0 months, the 2-year DFS, EFS, and OS rates of patients were 78.6%, 70.9%, and 81.4%, respectively (Fig. 1). According to univariate analysis, bone marrow involvement, an absolute lymphocyte count (ALC) < 1,200/μL, and being a member of the standard IPI-defined high-risk group were all associated with poorer EFS. Among IPI factors, age > 60 years and a poor Eastern Cooperative Oncology Group performance status (ECOG PS) contributed to lower EFS, whereas more than one extranodal

Table 2. Results of interim and final response evaluations according to the revised criteria

	Interim	Final
Complete response	26	24
Partial response	7	1
Stable disease	2	1
Progressive disease	1	6
Not evaluable (NE)	7	11
Causes of NE	Six early deaths One discontinuation of therapy due to intolerant toxicity and impaired performance status (PS)	Seven patients NE in the interim response evaluation Three discontinuations of therapy due to intolerant toxicity and impaired PS One could not complete the treatment schedule due to delayed marrow recovery

Table 3. Univariate and multivariate analyses of event-free survival in the 43 patients

Parameter	For event-free survival			For disease-free survival		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Univariate analysis						
High risk by standard IPI	5.7	2.0-16.4	0.001	2.9	0.8-10.6	0.1
Age > 60 yr	3.1	1.1-8.5	0.034	1.7	0.4-6.6	0.452
> 1 extranodal site	2	0.7-5.9	0.208	1.5	0.4-5.4	0.525
Elevated serum lactate dehydrogenase	1.5	0.4-5.2	0.553	0.9	0.2-3.5	0.872
Ann Arbor stage III/IV	2.2	0.5-9.6	0.31	1.4	0.3-6.4	0.706
ECOG PS ≥ 2	6.3	2.2-18.1	0.001	3.2	0.9-11.7	0.073
Age > 40 yr	3.5	0.8-15.6	0.101	2.3	0.5-11.0	0.294
Bulky lesion	0.8	0.2-3.0	0.786	0.8	0.2-4.0	0.836
B Symptoms	1.6	0.6-4.4	0.652	1.8	0.5-6.1	0.374
Bone marrow involvement	3.4	1.2-9.6	0.021	2.3	0.6-9.0	0.228
Absolute lymphocyte count < 1,200/μL	3.5	1.2-10.2	0.021	2.6	0.7-9.5	0.141
Multivariate analysis						
With individual IPI factors						
Age > 60 yr	3.9	1.3-12.1	0.018	For disease-free survival, multivariate analysis could not be performed since most parameters had a p-value of ≥ 0.1		
ECOG PS ≥ 2	7.4	2.4-23.3	0.001			
Absolute lymphocyte count < 1,200/μL	3.7	1.2-11.4	0.022			
High risk standard IPI as a single parameter	-	-	-			
High risk by standard IPI	5.8	2.0-16.6	0.001			
Absolute lymphocyte count < 1,200/μL	3.5	1.2-10.3	0.022			

CI, confidence interval; IPI, International Prognostic Index; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 4. Dose intensities of doxorubicin, vincristine, methotrexate, and cytarabine in the analyzed patients

	Doxorubicin (n=43)	Vincristine (n=43)	Methotrexate (n=38)	Cytarabine (n=38)
Median RDI (%)	64.3	65	66.1	58.9
Range	35.6-100	38.3-100	36.0-100	28.4-100
100% dose	4 (9.3)	4 (9.3)	1 (2.6)	1 (2.6)
> 90% dose	4 (9.3)	5 (11.6)	1 (2.6)	1 (2.6)
> 80% dose	8 (18.6)	10 (23.3)	4 (10.5)	4 (10.5)
> 70% dose	16 (37.2)	16 (37.2)	14 (36.8)	13 (34.2)
> 60% dose	25 (58.1)	27 (62.8)	24 (36.8)	19 (50.0)
> 50% dose	32 (74.4)	36 (83.7)	29 (76.3)	25 (65.8)
p-value (impact on RDI)				
Age (> 40 yr vs. ≤ 40 yr)	0.306	0.429	0.314	0.259
Age (> 60 yr vs. ≤ 60 yr)	0.384	0.512	0.813	0.566
ECOG PS (≥ 2 vs. < 2)	0.035	0.165	0.019	0.299

Values are presented as number (%) unless otherwise indicated. RDI, relative dose intensity; ECOG PS, Eastern Cooperative Oncology Group performance status.

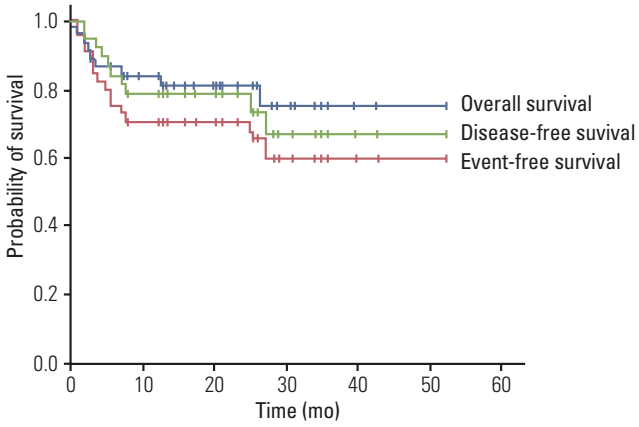

Fig. 1. Kaplan-Meier curves of time to progression, event-free survival, and overall survival of the analyzed patients.

site, stage III or IV, and elevated serum lactate dehydrogenase levels did not. According to multivariate analysis, ALC < 1,200/μL and being a member of the high-risk group were independent risk factors (Table 3). In contrast to the Cox regression test for EFS, most parameters did not have an impact on DFS (Table 3).

4. Toxicities

Early deaths were reported in cycles 1A (n=2; age, 51 and 64 years, respectively), 1B (n=1; age, 66 years), 2A (n=2; age, 67 and 72 years, respectively), and 2B (n=1; age, 47 years). Five of them (except for one 47-year-old patient) had an ECOG PS ≥ 2. Causes of treatment-related mortality (TRM) were bacterial septicemia (n=5) and tumor lysis syndrome (n=1; age, 51 years). In cycle 1A, four patients (9.3%) experienced tumor lysis syndrome. Two patients recovered from tumor lysis syndrome with the support of hemodialysis, one patient recovered with only hydration and oral allopurinol use, and the other patient died of rapidly progressing tumor lysis syndrome during preparation for continuous renal replacement therapy. Cerebellar ataxia also occurred in four patients during cycle 1B. All of these patients recovered, but re-introduction of cytarabine was limited thereafter, and one patient could not complete R-hyper-CVAD. Most patients had grade 3 or 4 hematologic toxicity. Of these patients, 34 patients (79.1%) experienced anemia, 42 patients (97.7%) had neutropenia, and 28 patients (86.0%) had thrombocytopenia. Eight patients experienced grade 3 or 4 non-hematologic toxicity, such as alanine transaminase elevation (n=4), nausea (n=2), diarrhea (n=1), and rituximab-induced pneumonitis (n=1). Thirty-nine patients (90.7%) had febrile neutropenia, and bacterial growth was reported in the blood cultures of 16 patients (41.0%).

5. Dose intensities

The median RDIs of adriamycin, vincristine, methotrexate, and cytarabine were 64.3%, 65.0%, 66.1%, and 58.9%, respectively. Only 10.5% to 23.3% of patients received greater than 80% of the planned doses of chemotherapeutic agents. When we analyzed patients according to age (> 40 years vs. ≤ 40 years, or > 60 years vs. ≤ 60 years), there were no differences in RDIs. However, PS was related to differences in RDIs of doxorubicin and methotrexate (Table 4). The

Table 5. Treatment outcomes of Burkitt or Burkitt-like lymphoma in adults from previous studies

Source	Study type	Regimen	No.	Median age (yr)	Complete remission rate (%)	ED rate	Event-free survival (%)	Overall survival (%)
Without rituximab								
Soussain et al. (1995) [14]	Retrospective	LMB pediatric protocol	65	26	89	3/65	64 (3 yr)	74 (3 yr)
Thomas et al. (1999) [6]	Prospective	Hyper-CVAD regimen	26	48	81	5/26	No report	49 (3 yr)
Lee et al. (2001) [15]	Prospective	CALGB 9251	54	44	80	7/54	No report	Median 3.6 yr
Mead et al. (2008) [16]	Prospective	mCODOX-M/IVAC	53	37	No report	No report	64 (2 yr)	67 (2 yr)
Choi et al. (2009) [17]	Retrospective	LMB pediatric protocol	38	47	74	4/38	75 (5 yr)	68 (5 yr)
With rituximab								
Thomas et al. (2006) [11]	Prospective	Hyper-CVAD regimen	31	46	86	0/31	80 (3 yr)	89 (3 yr)
Barnes et al. (2011) [18]	Retrospective	mCODOX-M/IVAC	40	46	90	4/40	74 (3 yr)	77 (3 yr)
Corazzelli et al. (2012) [10]	Prospective	mCODOX-M/IVAC	15	No report	100	0/15	92 (4 yr)	No report
Intermesoli et al. (2013) [19]	Prospective	GMALL protocol	105	47	79	12/105	67 (3 yr)	75 (3 yr)
Present study (2014)	Retrospective	Hyper-CVAD regimen	43	51	75	6/43	70.9 (2 yr)	81.4 (2 yr)

ED, early death.

median number of days required for a complete cycle of immunochemotherapy for each patient was 31.0 days (range, 21 to 54.8 days). There was no difference in the number of days required for a cycle of R-hyper-CVAD among patients ≤ 60 years versus > 60 years old (p=1.000). Patients with an ECOG PS of ≥ 2 tended to have longer cycles compared to those with a PS of 0 or 1. However, these results were not statistically significant (p=0.065).

Discussion

In the current study, R-hyper-CVAD showed overall treatment outcomes comparable to those of previous retrospective and prospective studies of dose-intense regimens (Table 5).

However, the result was not as excellent as a clinical trial reported by Thomas et al. [11]: in the current study, a substantial number of patients could not complete immunochemotherapy due to toxicities or impaired PS, including six episodes of TRM (14.0%). It is contrast to the patient characteristics of study by Thomas et al. [11], in which the patients were relatively younger (median age, 46 years), including three patients (9.7%) with a resected disease, and in particular, there were no patients with an ECOG PS of 3 or 4. These results imply that the treatment outcome of R-hyper-CVAD can be affected by patient suitability for dose-intense chemotherapy. Similar findings were also reported in a recent population-based analysis of 3,691 patients [7]. In that study, which was outside the context of clinical trials, the Surveillance Epidemiology and End Results (SEER) data analysis estimated time trends for outcomes of BL in the United States. According to the results, more effective therapies are needed for older patients with BL despite improvements in survival from the 1973-2001 era to 2002-2008 era [7].

To escape early death, excellent supportive care is essential. Considering an incidence of febrile neutropenia of over 90% with five episodes of death due to bacterial septic shock in the current study, as well as frequent infectious complications in other studies [5,10,11,18,20], prophylactic antibiotics and G-CSF should be utilized [21]. In addition, prophylaxis with rasburicase can reduce fatal consequences of tumor lysis syndrome [22]. A gap between DFS and EFS in the current study strongly suggests that survival could be substantially improved by reducing early death. Therefore, supportive care should be strictly and routinely performed.

Despite the fact that higher IPI scores and lower ALCs were shown to be poor prognostic factors of EFS, their significance was lost in terms of DFS. Therefore, they might be risk factors for fatal complications of dose-intense treatment, rather than risk factors for treatment failure. However, as the prognostic factors in this study are only exploratory, these findings should be interpreted cautiously. Poorer PS had a significant impact on the unsatisfactory RDIs of doxorubicin and methotrexate. Concerns regarding development of peripheral neuropathy and cerebellar ataxia might mitigate the effect of poor PS on the reduced RDIs of vincristine and cytarabine. Overall, poor PS seems to keep patients from maintaining an adequate RDI of several drugs.

Since treatment of acute lymphoblastic leukemia is determined according to a patient's age (adults vs. young and adolescents) due to tolerability of the protocols [23], a similar question may be raised in the case of BL. It is reasonable to question whether or not a particular treatment protocol is as suitable for patients in their 20s as those applied to patients older than 60. Considering that age was one of the independent prognostic factors in the current study, R-hyper-CVAD might not be an optimal treatment for elderly patients. However, in our study, there were no significant differences in RDI or number of days required for a complete cycle of R-hyper-CVAD according to age. These results suggest that some elderly patients can tolerate R-hyper-CVAD well. A review article in 2009 on treatment of adult patients with BL [24] concluded that a part of patients over 40 years of age could have highly favorable outcomes to modern dose-intense, multi-agent chemotherapy. Their conclusion is also in line with a previous study on R-hyper-CVAD in BL by Thomas et al. [11], in which nine of 31 patients (29%) were ≥ 60 years, and all were in continuous CR except for only one episode of later death due to infection. Therefore, selection of patients according to chronological age seems not to be an ideal strategy. Instead, other tools such as comprehensive geriatric assessment can be performed in patients with BL or Burkitt-like lymphoma in the future.

For those who are clearly intolerant to dose-intense regimens, alternative therapeutic strategies should be sought. A recent uncontrolled prospective study conducted by Dunleavy et al. [25] reported that lower-dose, short-course chemotherapy consisting of infused etoposide, doxorubicin, and cyclophosphamide along with vincristine, prednisone, plus a double dose of rituximab (SC-EPOCH-RR) showed promising outcomes among 11 patients with HIV-associated BL. In that study, 100% progression-free survival and 90% OS were achieved after a median follow-up time of 73 months, and toxicities were manageable. Although patients receiving SC-EPOCH-RR were older (median age, 44 years vs. 25 years; p=0.03) than the 19 patients treated with standard dose-adjusted EPOCH-R, and patients receiving SC-EPOCH-RR also showed poorer PS (55% vs. 16% of patients with ECOG PS ≥ 2, p=0.04), the

outcomes were comparable [25]. Therefore, focusing on exposure-concentration time of drugs rather than peak concentration can be a reasonable strategy, and future studies are warranted, especially in a subgroup of patients who are not suitable for dose-intense chemotherapy.

Although the activity of rituximab has been demonstrated in most B-cell malignancies, data on the role of rituximab in BL or BL-U are limited. Two phase II studies [10,11] and several retrospective studies [18,20] have demonstrated that rituximab contributes to the improvement of OS in patients with BL or Burkitt-like lymphoma. A retrospective population-based study compared OS between patients on rituximab (n=111) to those without rituximab therapy (n=52), and according to their univariate analysis, addition of rituximab confirmed an association with improved OS, mainly in the cohort of patients aged 40-65. However, when adjusted for age and chemotherapy regimen, this association failed to maintain significance [8]. Compared to the MD Anderson study, a lower dose of rituximab was administered in the current study due to limitations in national insurance coverage, which might have an impact on outcomes. However, upon assessing the results of previous studies with or without rituximab, the role of rituximab does seems to be, at least, not absolute. Rather, more refined patient selection, maximization of supportive care, and efforts to improve dose intensity are more important considerations and future efforts should focus on how to solve these problems.

Since we did not conduct a central pathologic review and did not analyze outcomes according to fluorescence *in situ* hybridization due to the scarcity of tested patients, other high-grade mature B-cell lymphomas such as DLBCL may be included in this patient population, and the poor prognosis of double-hit B-cell lymphoma may not be reflected, which is an obvious weakness of this study. Notwithstanding, we believe that our assertion on the limitation of R-hyper-CVAD in terms of toxicity and its resultant insufficient dose intensity in certain frail patients is still appropriate.

Conclusion

R-hyper-CVAD is an effective treatment regimen for highly aggressive B-cell lymphomas such as BL. However, due to its significant toxicity and unsatisfactory RDI among more frail Korean patients, a more tolerable regimen with preserved efficacy is required for frail patients with BL or Burkitt-like lymphomas, even in the rituximab era.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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