

Fludarabine-based versus CHOP-like regimens with or without rituximab in patients with previously untreated indolent lymphoma: a retrospective analysis of safety and efficacy

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Abstract: Fludarabine-based regimens and CHOP (doxorubicin, cyclophosphamide, vincristine, prednisone)-like regimens with or without rituximab are the most common treatment modalities for indolent lymphoma. However, there is no clear evidence to date about which chemotherapy regimen should be the proper initial treatment of indolent lymphoma. More recently, the use of fludarabine has raised concerns due to its high number of toxicities, especially hematological toxicity and infectious complications. The present study aimed to retrospectively evaluate both the efficacy and the potential toxicities of the two main regimens (fludarabine-based and CHOP-like regimens) in patients with previously untreated indolent lymphoma. Among a total of 107 patients assessed, 54 patients received fludarabine-based regimens (FLU arm) and 53 received CHOP or CHOPE (doxorubicin, cyclophosphamide, vincristine, prednisone, or plus etoposide) regimens (CHOP arm). The results demonstrated that fludarabine-based regimens could induce significantly improved progression-free survival (PFS) compared with CHOP-like regimens. However, the FLU arm showed overall survival, complete response, and overall response rates similar to those of the CHOP arm. Grade 3–4 neutropenia occurred in 42.6% of the FLU arm and 7.5% of the CHOP arm ($P < 0.000$). Moreover, the FLU arm also had a higher occurrence of infection than the CHOP arm (27.8% vs 8.5%; $P = 0.034$). Multi-factor regression of infection revealed that only age (>60 years) and presentation of grade 3–4 myelosuppression were the independent factors to infection, and the FLU arm had significantly higher myelosuppression. In conclusion, the present study revealed that the use of fludarabine-based regimens could induce high rates of myelosuppression over CHOP-like regimens, in spite of significant increases in PFS.

Keywords: indolent lymphoma, toxicity, fludarabine, CHOP, infection

Introduction

Per World Health Organization (WHO), indolent lymphomas account for nearly one-third of non-Hodgkin lymphoma (NHL). These mainly include follicular lymphoma (FL), small lymphocytic lymphoma/chronic lymphocytic leukemia (SCL/CLL), and marginal zone B-cell lymphoma.¹ Their natural history is characterized by a high initial response rate to both chemotherapy and radiotherapy, often with transformation to a more aggressive histology, and followed invariably by disease recurrence. Finally, the patients usually die due to disease progression or treatment-induced toxicity.²

Addition of rituximab to chemotherapy is associated with higher response, progression-free survival (PFS), and overall survival (OS) rates,^{3–5} but there is no clear evidence about which chemotherapy regimen should be the proper initial treatment

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of indolent lymphoma. In the late 1980s, the approval of nucleoside analogs such as fludarabine for the treatment of low-grade lymphomas brought significantly increased outcomes,^{6–9} but the benefit with regards to PFS and OS is still under debate, as few trials compared the efficacy of a fludarabine-based regimen with the classical CHOP (doxorubicin, cyclophosphamide, vincristine, prednisone) regimen for NHL.^{10–13} More recently, the use of fludarabine has also raised concerns due to its high toxicities, especially hematological toxicity and infectious complications.^{14,15} The present study aimed to evaluate retrospectively both the efficacy and the potential toxicities of the two main regimens (fludarabine-based and CHOP-like regimens) in patients with previously untreated indolent lymphoma.

Methods

Patients and criteria for eligibility

Data from patients with previously untreated indolent lymphoma ($n = 107$) were retrospectively included in the study. All these patients received chemotherapy consecutively at the Tianjin Medical University Cancer Institute and Hospital and the First Affiliated Hospital of Chinese PLA General Hospital between January 2007 and August 2012. All patients underwent the following routine staging procedures: complete physical examination; laboratory tests, including serum lactate dehydrogenase (LDH) and serum beta-2 microglobulin; type-B ultrasonic check; computed tomography (CT) scan of the chest, abdomen, and pelvis (or positron emission tomography-CT); bone marrow aspiration; and biopsy. Their disease condition was diagnosed by biopsy and immunophenotypical analysis per the WHO

criteria for indolent lymphoma,¹⁶ and the Ann Arbor staging system was used to define the stage of lymphoma.¹⁷ No patients had severe damage to their heart, liver, kidney, or other important organs; and the mean neutrophil count at baseline was $>3.0 \times 10^9/L$.

Treatment schedule

Patients received four to eight cycles of chemotherapy, either with CHOP-like or fludarabine-based regimens with or without rituximab. The treatment protocol and schedule followed the recommendations laid down by the National Comprehensive Cancer Network, USA. Dosage information and drug administration schedule are listed in Table 1. Additionally, patients with stage I–II cancer received radiotherapy. Also, the granulocyte colony-stimulating factor was administered only to patients who had more advanced grades of neutropenia (grade 3–4). However, no patients received any antibiotic prophylaxis. Response to therapy was assessed at the end of every two cycles of chemotherapy.

Safety analysis

Patient- and physician-reported adverse events were recorded per the Common Toxicity Criteria (version 2.0) of National Cancer Institute, USA for all cycles of chemotherapy. Hematotoxicity was assessed for treatment-specific nadir windows per the WHO grades for hematotoxicity.

Statistical methods

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Survival curves were calculated

Table 1 Dosage information and time schedule of chemotherapy regimens

Arms	Regimen	Drug	Dose	Route	Days
CHOP arm (every 21 days)	CHOP*	Doxorubicin	50 mg/m ²	IV	I
		Cyclophosphamide	750 mg/m ²	IV	I
		Vincristine	1.4 mg/m ²	IV	I
		Prednisone	100 mg/d	PO	I–5
	CHOPE*	Doxorubicin	50 mg/m ²	IV	I
		Cyclophosphamide	750 mg/m ²	IV	I
		Vincristine	1.4 mg/m ²	IV	I
		Prednisone	100 mg/d	PO	I–5
FLU arm (every 28 days)	FC*	Etoposide	100 mg/d	IV	3–5
		Fludarabine	25 mg/m ²	IV	I–3
	FND*	Cyclophosphamide	250 mg/m ²	IV	I–3
		Fludarabine	25 mg/m ²	IV	I–3
		Mitoxantrone	10 mg/m ²	IV	I
		Dexamethasone	20 mg/m ²	PO	I–5

Notes: *With or without rituximab 375 mg/m² as an IV infusion on day 0. The CHOP arm consisted of “CHOP” (doxorubicin, cyclophosphamide, vincristine, and prednisone), or “CHOPE” (CHOP plus etoposide). The FLU arm consisted of “FC” (fludarabine plus cyclophosphamide), or “FND” (fludarabine, mitoxantrone, and dexamethasone).

Abbreviations: IV, intravenous; PO, oral.

using Kaplan–Meier estimates, and statistical comparisons between curves were made using the log-rank test. The chi-square test and Fisher's exact test were used to compare variables. Two-sided *P*-values were used throughout.

Variables associated with myelosuppression and infection in cases and controls were compared using odds ratios and 95% confidence intervals (CIs) from univariate logistic regression models. Multivariable logistic regression was performed; the covariates identified in the univariate analysis were used to adjust the multivariate logistic regression model.

Results

Patient characteristics

Of the 107 patients, the condition of 37 patients was diagnosed as FL, 33 had SLL/CLL, and 37 had mucosa-associated lymphoid tissue lymphoma. The two treatment groups were comparable in terms of age, sex distribution, stage, extra-nodal site involvement, B symptoms (fever, weight loss, or night sweats), performance status, serum LDH levels, histological subtype, and combination of rituximab (Table 2). Patients with stage I and II disease accounted for nearly 50% of the study population, which was higher than previous reports. This distribution could mainly be attributed to the presence of B symptoms, presence of progressive bulky disease (especially superficial lymph nodes), and patients' desire to receive treatment.

Response and survival analysis

At the end of induction, the FLU arm had a similar complete response (CR) rate (68.5% vs 67.9%; *P* = 0.947) but a higher overall response rate (ORR) (96.3% vs 86.8%; *P* = 0.093) than the CHOP arm. After median follow-up of 26 months (range 2–66 months), overall 3-year PFS and 3-year OS were 68.0% and 78.8%, respectively (Figure 1). The FLU arm had a significantly better 3-year PFS (75.8% vs 61.0%; *P* = 0.011), but no differences were observed in the 3-year OS between the two arms (82.1% vs 74.8%; *P* = 0.209).

Safety evaluation

The most common adverse effects are hematologic toxicity and infection. Safety data were available for all 107 patients for a median follow-up of 25 months (range 7–66 months). No instance of grade 3–4 anemia or thrombocytopenia was evaluated, but significant difference in neutropenia was observed between the two treatment arms. Frequency of grade 3–4 neutropenia in the FLU arm was much larger than that in CHOP

Table 2 Patient demographic and clinical characteristics by treatment arm

Characteristics	No of assessable patients		Two-sided P-value	χ^2
	CHOP arm n = 53 [n (%)]	FLU arm n = 54 [n (%)]		
Sex			0.390	0.740
Male	28 (47.5)	30 (55.6)		
Female	31 (52.5)	24 (44.4)		
Age (years)			0.816	0.054
≤60	37 (62.7)	35 (64.8)		
>60	22 (37.3)	19 (35.2)		
Mean (range)	53 (18–80)	53 (20–79)		
Ann Arbor staging			0.209	1.577
I–II	31 (52.5)	22 (40.8)		
III–IV	28 (47.4)	32 (59.2)		
B-symptoms			0.610	0.260
No	43 (72.9)	37 (68.5)		
Yes	16 (27.1)	17 (31.5)		
Exnodal involvement			0.707	0.141
Present	37 (62.7)	32 (59.3)		
Absent	22 (37.3)	22 (40.7)		
Serum LDH level			0.089	2.887
Normal	36 (61.0)	41 (75.9)		
Abnormal	23 (39.0)	13 (24.1)		
ECOG performance status			0.871	0.026
≤1	53 (89.8)	48 (88.9)		
≥2	6 (10.29)	6 (11.1)		
Histological subtype			0.092	4.774
FL	20 (33.9)	18 (33.3)		
CLL/SLL	14 (23.7)	22 (40.7)		
MALT	25 (42.4)	14 (25.9)		
Treatment			0.209	1.577
With R	31 (52.5)	22 (40.7)		
Without R	28 (47.5)	32 (59.3)		

Notes: The CHOP arm consisted of "CHOP" (doxorubicin, cyclophosphamide, vincristine, and prednisone), or "CHOPE" (CHOP plus etoposide). The FLU arm consisted of "FC" (fludarabine plus cyclophosphamide), or "FND" (fludarabine, mitoxantrone, and dexamethasone).

Abbreviations: LDH, lactate dehydrogenase; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic lymphoma/small lymphocytic leukemia; MALT, mucosa-associated lymphoid tissue lymphoma; ECOG, Eastern Cooperative Oncology Group; R, rituximab.

arm (42.6% [23 in 54] vs 7.5% [4 in 53]; *P* < 0.001). Patients in the FLU arm had an increased rate of infections (15 in 54 patients [27.8%] vs 3 in 53 patients [5.7%]; *P* = 0.002).

In univariate regression analysis, the following variables were found to be significantly associated with infection: age over 60 years, III–IV Ann Arbor staging, presence of grade 3–4 myelosuppression, and combination of rituximab (Table 3). More myelosuppression occurred in patients receiving the fludarabine-based regimen and patients with B symptoms than in those who received the CHOP-like

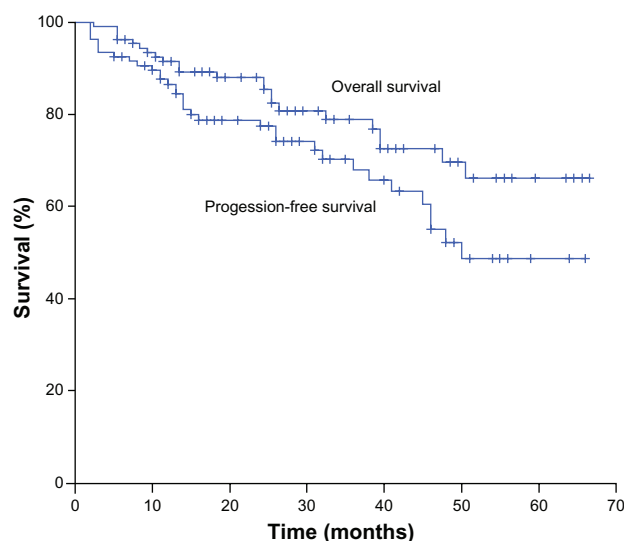


Figure 1 The overall survival and progression-free survival of 107 patients with indolent lymphoma.

chemotherapy (Table 4). Multi-factor regression was used to find the potential predictive factors of infection and myelosuppression. Factors identified in the multivariable logistic regression as being independently associated with infection included the following: age over 60 years and presence of grade 3–4 myelosuppression (Table 3). In the multivariable logistic regression analysis, patients who received a fludarabine-based regimen and patients with B symptoms had variables significantly related to myelosuppression (Table 4).

During the follow-up, two secondary malignancies were reported in the FLU arm: one myelodysplastic syndrome and one meningioma.

Discussion

The results of the present study demonstrated that the fludarabine-based regimen could induce significantly improved PFS compared with the CHOP-like regimen in patients with previously untreated indolent lymphoma. However, the FLU arm showed similar rates of OS, CR, and ORR rates as the CHOP arm. In spite of the improved PFS, the FLU arm was associated with a higher incidence of hematological toxicity, infections, and late events than the CHOP arm.

Potential risk of toxicities is one of the major concerns with the concurrent use of purine analogs, even though they possess superior response or survival rates. It was found that the myelosuppression was mainly presented as neutropenia. No instance of grade 3–4 anemia or thrombocytopenia was recorded among the two treatment arms. In terms of neutropenia, the findings were comparable to those of the randomized

FOLL05 trial comparing rituximab, cyclophosphamide, vincristine, and prednisolone (R-CVP), rituximab plus CHOP (R-CHOP), and rituximab plus fludarabine, and mitoxantrone for the initial treatment of advanced-stage FL.¹³ However, Zinzani et al¹⁰ and Leporrier et al¹² reported no difference in hematologic toxicity between the various treatment groups.^{10,12} These differences could partly result from the different treatment regimens, histological subtypes, and patient characteristics. Karmali et al¹⁸ hinted that the bone marrow involvement at presentation could also influence the pathogenesis of prolonged cytopenia in follicular or marginal zone lymphoma with rituximab, fludarabine, mitoxantrone, dexamethasone (R-FND) followed by radioimmunotherapy consolidation, but the researchers did not give any detailed evidence. In the present study, the multi-factor regression showed no correlation between bone marrow involvement and myelosuppression, although the bone marrow involvement was higher in the FLU arm than the CHOP arm (19/54 [35.2%] vs 6/53 [11.9%]; $P = 0.004$).

Another variable associated with myelosuppression was the presence of B symptoms, which was in accordance with the outcomes by Sharma et al.¹⁹ B symptoms were regarded as the independent predictors of myelosuppression from chemotherapy in patients with NHL. The correlation between disease stage and myelosuppression in univariate analysis has been reported previously, although the staging was not identified as an independent factor to myelosuppression in the multivariate regression.^{19,20} Such association was not identified in the present study. Potential reasons for these differences could be related to the supportive care practices or heterogeneity in chemotherapy. In addition, a small sample size could have some influence on the results.

The occurrence of infection was significantly higher in the FLU arm than in the CHOP arm. The predictors of infection during fludarabine-based chemotherapy included the following: >60 years of age, low serum immunoglobulin G, previous fludarabine exposure, >3 years from diagnosis to treatment, performance score of ≥ 2 , and baseline neutrophil count of $<2.0 \times 10^9/L$.^{21,22} In the present study, logistic regression showed that both the presentation of myelosuppression and age (>60 years) were independent factors to infection. This indicated that the proper control of myelosuppression could benefit patients by avoiding unwanted adverse events.

The addition of rituximab to standard chemotherapy in patients with cluster of differentiation (CD)-20 positive malignant lymphomas could increase the frequency of

Table 3 Association between potential predictive factors and infection

	Observation	Infection	Univariate logistic analysis		Forward stepwise logistic analysis	
	n	n (%)	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)			0.176 (0.037–0.847)	0.030	0.205 (0.059–0.719)	0.013
≤60	35	7 (9.7)				
>60	72	11 (31.4)				
Sex			1.041 (0.223–4.866)	0.959		
Male	57	10 (17.5)				
Female	50	8 (16)				
Ann Arbor–Cotswolds staging			13.762 (1.428–132.665)	0.023		
I–II	52	8 (15.4)				
III–IV	55	10 (18.2)				
Grade 3–4 myelosuppression			0.055 (0.009–0.339)	0.002	0.066 (0.019–0.233)	<0.001
Present	80	5 (6.3)				
Absent	27	13 (48.1)				
Bone marrow involvement			0.235 (0.018–3.086)	0.270		
Yes	82	7 (28.0)				
No	25	11 (13.4)				
B-symptoms			0.759 (0.143–4.013)	0.745		
No	80	10 (12.5)				
Yes	27	8 (29.6)				
Exnodal involvement			1.456 (0.197–10.776)	0.713		
Present	66	11 (16.7)				
Absent	41	7 (17.1)				
Serum LDH level			0.241 (0.38–1.518)	0.129		
Normal	77	10 (13.3)				
Abnormal	30	8 (25.0)				
Performance status (ECOG)			0.268 (0.37–1.943)	0.193		
≤1	96	14 (14.6)				
≥2	11	4 (36.4)				
Histological subtype			2.364 (0.215–26.004)	0.605		
FL	37	7 (18.9)	3.016 (0.353–25.785)			
CLL/SLL	33	6 (18.2)				
MALT	37	5 (13.5)				
Treatment			0.199 (0.043–0.932)	0.040		
With R	50	11 (22.0)				
Without R	57	7 (12.3)				
Regimen*			0.195 (0.027–1.428)	0.108		
FLU arm	54	15 (27.8)				
CHOP arm	53	3 (5.7)				
Cycles of chemotherapy			1.228 (0.219–6.891)	0.816		
≤4	49	8 (16.3)				
>4	58	10 (17.2)				

Notes: *Combined with or without rituximab. The CHOP arm consisted of “CHOP” (doxorubicin, cyclophosphamide, vincristine, and prednisone), or “CHOPE” (CHOP plus etoposide). The FLU arm consisted of “FC” (fludarabine plus cyclophosphamide), or “FND” (fludarabine, mitoxantrone, and dexamethasone).

Abbreviations: CI, confidence interval; CLL/SLL, chronic lymphocytic lymphoma/small lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; LDH, lactate dehydrogenase; MALT, mucosa-associated lymphoid tissue lymphoma; OR, odds ratio; R, rituximab.

myelosuppression and infectious complications.^{5,23,24} A meta-analysis conducted on the risk of infection with lymphoma with or without rituximab concluded that the addition of rituximab to standard chemotherapy could increase the risk of severe leukopenia (relative risk [RR] = 1.24; 95% CI 1.12–1.37) and granulocytopenia (RR = 1.07; 95% CI 1.02–1.12), but no increase in the overall risk of severe infections (RR = 1.00; 95% CI 0.87–1.14) was reported.²⁵

No association between combination of rituximab and infection was observed in this study.

It is unknown whether or not prophylaxis is needed to avoid side effects. However, no difference in safety profile was reported between the patients who had received early prophylaxis (including antibiotics, immunoglobulin, and low-dose interleukin-2) and patients without these prophylactics.^{6,26,27} Nevertheless, the addition of granulocyte colony-stimulating

Table 4 Association between potential predictive factors and myelosuppression

	Observation	Grade 3–4 myelosuppression	Univariate logistic analysis		Forward stepwise logistic analysis	
	n	n (%)	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)			0.689 (0.206–2.303)	0.545		
≤60	72	16 (22.2)				
>60	35	11 (31.4)				
Sex			1.250 (0.391–3.996)	0.707		
Male	57	15 (26.3)				
Female	50	12 (24.0)				
Ann Arbor–Cotswolds staging			0.723 (0.175–2.983)	0.654		
I–II	52	8 (15.4)				
III–IV	55	19 (34.5)				
Bone marrow involvement			0.965 (0.147–6.316)	0.970		
Yes	82	16 (19.5)				
No	25	11 (44.0)				
B-symptoms			0.289 (0.081–1.037)	0.057	0.298 (0.102–0.870)	0.027
No	80	15 (18.8)				
Yes	27	12 (44.4)				
Exnodal involvement			0.619 (0.113–3.387)	0.619		
Present	41	10 (24.4)				
Absent	66	17 (25.8)				
Serum LDH level			1.207 (0.311–4.686)	1.207		
Normal	75	18 (24.0)				
Abnormal	32	9 (28.1)				
Performance status (ECOG)			1.606 (0.219–11.771)	0.641		
≤1	96	23 (24.0)				
≥2	11	4 (36.4)				
Histological subtype			1.770 (0.344–9.102)	0.178		
FL	37	12 (32.4)	0.397 (0.081–1.941)			
CLL/SLL	33	7 (21.2)				
MALT	37	8 (21.6)				
Treatment			0.522 (0.170–1.604)	0.257		
With R	57	13 (22.8)				
Without R	50	14 (28.0)				
Regimen*			0.073 (0.018–0.302)	<0.001	0.098 (0.029–0.334)	<0.001
FLU arm	53	4 (7.5)				
CHOP arm	54	23 (42.6)				
Cycles of chemotherapy			0.404 (0.118–1.380)	0.148	–	
≤4	49	9 (18.4)				
>4	58	18 (31.0)				

Notes: *Combined with or without rituximab. The CHOP arm consisted of “CHOP” (doxorubicin, cyclophosphamide, vincristine, and prednisone), or “CHOPE” (CHOP plus etoposide). The FLU arm consisted of “FC” (fludarabine plus cyclophosphamide), or “FND” (fludarabine, mitoxantrone, and dexamethasone).

Abbreviations: CI, confidence interval; CLL/SLL, chronic lymphocytic lymphoma/small lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; LDH, lactate dehydrogenase; MALT, mucosa-associated lymphoid tissue lymphoma; OR, odds ratio; R, rituximab.

factor during chemotherapy was reported to have beneficial effects on infection-related morbidity and mortality.^{28,29} Further multicenter prospective studies with large sample sizes are recommended to understand the safety profile of these regimens and to achieve desired efficacy outcomes.

Conclusion

Fludarabine-based regimens improve PFS in patients with previously untreated indolent lymphoma to a greater extent than that of a CHOP-like regimen. However, the use of

fludarabine induces myelosuppression and contributes to a higher degree of infection. Based on the safety analysis, it can be concluded that a CHOP-like regimen has a better therapeutic index with fewer adverse effects. Being a retrospective study with a very small sample size, the authors recommend further prospective studies to evaluate a proper front-line treatment for indolent lymphoma.

Disclosure

The authors report no conflicts of interest in this work.

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