Original Works

Feasibility of Modified MECP Regimen as Second-line Chemotherapy for Refractory or Relapsed Aggressive Non-Hodgkin Lymphoma

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Abstract: Standard salvage chemotherapy for refractory or relapsed aggressive non-Hodgkin lymphoma (NHL) is not yet established. We retrospectively evaluated the efficacy of modified MECP (m-MECP), a combination therapy of mitoxantrone, etoposide, carboplatin, and prednisolone. Thirty-six patients with CHOP-resistant aggressive NHL consisting of 24 with diffuse large B-cell lymphoma (DLBL) and 12 with peripheral T-cell lymphoma-unspecified (PTCL-U) have been treated. Age ranged from 22 to 88 with median of 60.5 years old. After 1 to 8 cycles of m-MECP with median of 3, total response rate was 63.9%. Complete response (CR) was acquired more frequently in DLBL than PTCL-U. Overall and event free survival (OS, EFS) rates at 5 years of total patients were 12.1% and 11.9%, respectively. Multivariate analysis revealed significant association between survival benefit and achievement of CR. Autologous hematopoietic stem cell transplantation was carried out in 8 patients who showed a response to m-MECP. Either of 5-year OS and EFS rate of them was 37.5%. Although hematological adverse events were still relatively frequent, m-MECP was effective for a part of CHOP-resistant NHL, especially DLBL.

Key Words: Modified MECP, Non-Hodgkin lymphoma, Refractory, Relapse.

Introduction

A chemotherapy regimen CHOP that consists of cyclophosphamide (CPM), doxorubicin, vincristine, and prednisolone (PDN) is considered as standard first-line therapy for advanced non-Hodgkin lymphoma (NHL)[1]. Addition of rituximab (R), a monoclonal antibody against CD20, is

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recognized to have improved response rate and survival of B-cell NHL[2]. However, a considerable part of patients show refractoriness or relapse. Many regimens have been reported as second line chemotherapy, but apparently superior one has not yet been defined.

Combination of mitoxantrone (MIT), etoposide (ETOP), carboplatin (CBDCA), and PDN, so called MECP, was reported to be effective for refractory or relapsed NHL of various subtypes[3]. Although histological diagnosis was made by the former Japanese classification in the study, a greater part of patients responded to MECP[3]. The facts that MIT, ETOP, or CBDCA has no cross tolerance between CHOP and that they synergize anti-tumor activity each other are associated with its salvage effect. However, frequent febrile neutropenia and transfusion of red blood cells or platelets documented in the study of MECP[3] implicate severe hematological toxicity. Hematopoiesis tends to be exhausted by preceding chemotherapy in patients who have refractory or relapsed disease. On the other hand, less toxic agents are recently available for indolent NHL[4,5]. Thus, we introduced a modification to reduce excessive toxicity and applied this modified-MECP (m-MECP) for patients with CHOP-resistant aggressive NHL. We also performed autologous peripheral blood stem cell transplantation (ASCT) in selected salvage-sensitive patients with the aim at prolonged disease control. The objective of this study is to retrospectively evaluate the salvage effect of m-MECP.

Patients and Methods

Patients

Between April 1997 and March 2010, 36 consecutive patients with aggressive NHL who had initially been treated with CHOP or R-combined CHOP (R-CHOP) and showed refractoriness or relapse have received m-MECP at Aiseikai-Yamashina Hospital. Their clinical records were retrospectively reviewed for following analyses of this study.

Included in this study were 24 patients with diffuse large B-cell lymphoma (DLBL) and 12 peripheral T-cell lymphoma-unspecified (PTCL-U) according to the Revised European and American Lymphoma (REAL)[6] or World Health Organization (WHO) classification[7] (Table 1). Referring to the Response Evaluation Criteria in Solid Tumors (RECIST) established by Therasse et al[8], response to preceding (R-)CHOP was retrospectively assessed. Refractoriness to (R-)CHOP was defined as stable or progressive disease during the first two courses and relapse as regrowth of remitted lesion or development of new lesion after complete or partial response (CR, PR). Risk groups at the time of refractoriness or relapse were also re-evaluated by using recent prognostic index[9,10]. Age ranged from 22 to 88 years old with median of 60.5. Patients with any of poor performance status by Eastern Cooperative Oncology Group (3 or 4), cardiac dysfunction (ejection fraction less than 50%), severe liver dysfunction (elevation of transaminases with four folds or more of upper normal limits), or renal failure (serum creatinine exceeds 3 mg/dl) were excluded.

Chemotherapy regimen

To reduce hematological toxicity of original MECP, dose modification of ETOP and CBDCA was introduced. Administrations of ETOP were decreased from 5 to 3 days. Since absorption of orally given ETOP is unstable[11], intravenous delivery was chosen. Although CBDCA is usually infused at single dose calculated by the area under curve, division into 5 days as described by Sica et al.[12,13] was employed. Then, m-MECP consisted of intravenous administration of MIT 8 mg/m^2 on day 1, ETOP 80 mg/m^2/day on days 1, 3, and 5, and CBDCA 60 mg/m^2/day and PDN 40 mg/m^2/day on days 1 through

Table 1. Characteristics of 36 patients.

Age (range 22-88: median 60.5)	
<60 y. o.	15
>=60 y. o.	21
Sex	
Male	20
Female	16
Histology	
DLBL	24
PTCL-U	12
Stage at diagnosis	
$I_{A/B}$	1 / 0
$II_{A/B}$	3 / 1
$III_{A/B}$	6 / 6
$IV_{A/B}$	5 /14
Refractory / Relapse	14 / 22
Lower / Higher risk*	5 / 31

DLBL indicates diffuse large B cell lymphoma and PTCL-U peripheral T-cell lymphoma unspecified.
*Lower risk includes low and low-intermediate groups by International Prognostic Index for DLBL and groups 1 and 2 by Prognostic Index for PTCL-U. Higher risk includes others.

5. The chemotherapy regimen had been certified by the review board of Aiseikai Yamashina Hospital. In accordance with the Helsinki declaration, patients were informed about presumable benefit and risk of m-MECP and a right to receive other regimen.

The therapy was carried out every 3 or 4 weeks with maximal cycles of 8 and was discontinued when intolerable side effects or refractoriness appeared. Doses of drugs but PDN were not multiplied by body surface area in patients over 70 years old. When neutrophil count is less than 1000/μl or platelet 7×10^4/μl, the therapy was delayed until the recovery. Granulocyte-colony stimulating factor (G-CSF) was appropriately used during neutropenic periods. R was given in combination with m-MECP in 8 of 24 B-NHL patients. At the time of this analysis, response to m-MECP was reassessed according to RECIST and Common Terminology Criteria for Adverse Events version 4.0-JCOG was used to retrospectively describe side effects.

Procedure of ASCT

Patients who achieved CR or PR after one or two courses of m-MECP were recognized to be chemosensitive. ASCT was scheduled in patients who belonged to higher risk groups and were under 70 years old. Stem cells were mobilized with high-dose ETOP (500 mg/m^2 on day 1 through 3) and G-CSF. Conditioning regimen was as follows: carmustine 200 mg/m^2 on days -8 and -3, CBDCA 300 mg/m^2 on day -7 through -4, ETOP 500 mg/m^2 on day -6 through -4, and CPM 2000 mg/m^2 on days -3 and -2. Stem cells were infused on day 0 and stimulated by G-CSF.

Statistical analysis

Response rate was compared between two groups using Fisher's exact test. Overall survival was assessed from the initiation of m-MECP to death or the last contact. Event was defined as death from any cause, relapse, refractoriness, or progressive disease. Survival curve was estimated by Kaplan-Meier method and compared by log-rank test. Cox-regression test was used to estimate multivariate analysis. These were analyzed by using SPSS ver. 19.0

Results

Response

Each patient has received 1 to 8 cycles of m-MECP with median of 3. Response was observed totally in 23 patients (63.9%), including 7 CR (19.4%) and 16 PR (44.4%). CR was more frequently seen in DLBL (6/24, 25.0%) than PTCL-U (1/12, 8.3%) although the difference was not significant (p=0.46) (Table 2). Age (60 or older or younger), disease status (refractory or relapse), and risk group did not affect the response rate (Table 2). The use of R for DLBL was not associated with response rate (5 of 8, 62.5% with R and 10 of 16, 62.5% without R; p=0.65). Discontinuation after the first course was observed in 4 patients (2 DLBL and 2 PTCL) because of rapid progression of the disease.

Outcome of ASCT

8 patients who had responded to m-MECP, containing 5 CR and 3 PR, underwent ASCT. They consisted of 7 DLBL and 1 PTCL. They had received 2 to 6 courses (median 2.5) of m-MECP before ASCT. 1.1-16.7 (median 3.8)$\times 10^6$/kg of CD34-positive cells, corresponding to 3.4-21.2 (median 5.9)$\times 10^5$/kg of colony-forming units granulocyte-macrophage, were infused after conditioning chemotherapy in each patient, resulting in immediate hematopoietic recovery. A patient with refractory PTCL-U who had achieved PR by m-MECP was additionally led into continuous CR. There was no transplant-related death.

Survival

With a median observation period of 10 months (ranged from 1 to 158), median overall and event free survival (OS, EFS) of all patients were 10 and 5 months, respectively. OS and EFS rates at 5 years of total of 36 patients were 12.1% and 11.9% (Fig. 1). Median OS and EFS of patients who obtained CR were 88 and 64 months with 5-year rate of 51.4% for both. These were significantly better than those who did not (median 9 and 4 months, 5-year rate 3.6 and 3.5%, respectively; p=0.008 and 0.004 by log-rank test, respectively) (Fig. 2). These results were also confirmed by multivariate analysis (Table 3). Both 5-year OS and EFS rates were 37.5% with median survival of 16 and 15 months among 8 patients who had received ASCT. EFS was significantly better than that of those who had responded with median of 3 courses but not received ASCT (p=0.018 by log-rank test).

Table 2. Response to m-MECP

	CR	p	PR	p	Total	p
Age						
<60	3 / 15 (20.0%)		6 / 15 (40.0%)		9 / 15 (60.0%)	
		0.72		0.91		0.95
>=60	4 / 21 (19.1%)		10 / 21 (47.6%)		14 / 21 (66.7%)	
Histology						
DLBL	6 / 24 (25.0%)		9 / 24 (37.5%)		15 / 24 (62.5%)	
		0.46		0.41		0.90
PTCL-U	1/12 (8.3%)		7/12 (58.3%)		8/12 (66.7%)	
Disease status						
Refractory	4 / 14 (28.6%)		4 / 14 (28.6%)		8 / 14 (57.1%)	
		0.50		0.24		0.75
Relapse	3 / 22 (13.6%)		12 / 22 (54.5%)		15 / 22 (68.2%)	
Risk group						
Low	0 / 5 (0%)		3 / 5 (60.0%)		3 / 5 (60.0%)	
		0.57		0.77		0.76
High	7 / 31 (22.6%)		13 / 31 (41.9%)		20 / 31 (64.5%)	

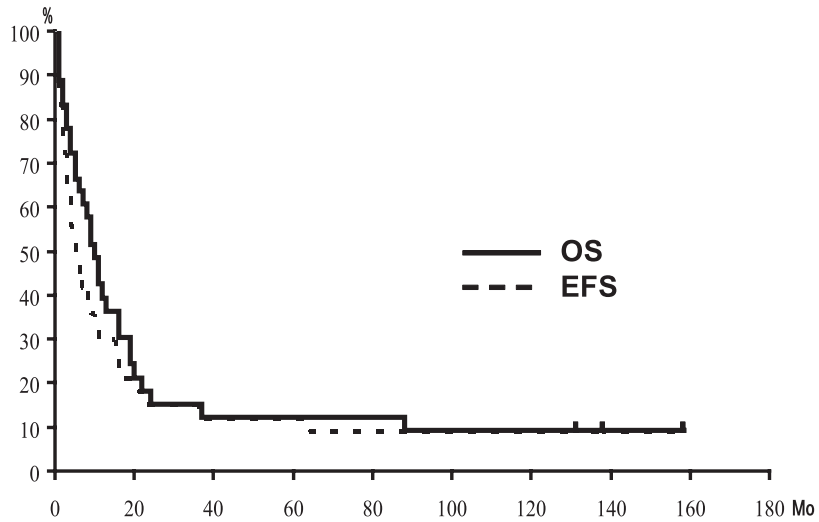

Fig. 1. Survival analysis of 36 patients. Rates of overall and event free survival (OS and EFS) at 5 years are 12.1% and 11.9%, respectively.

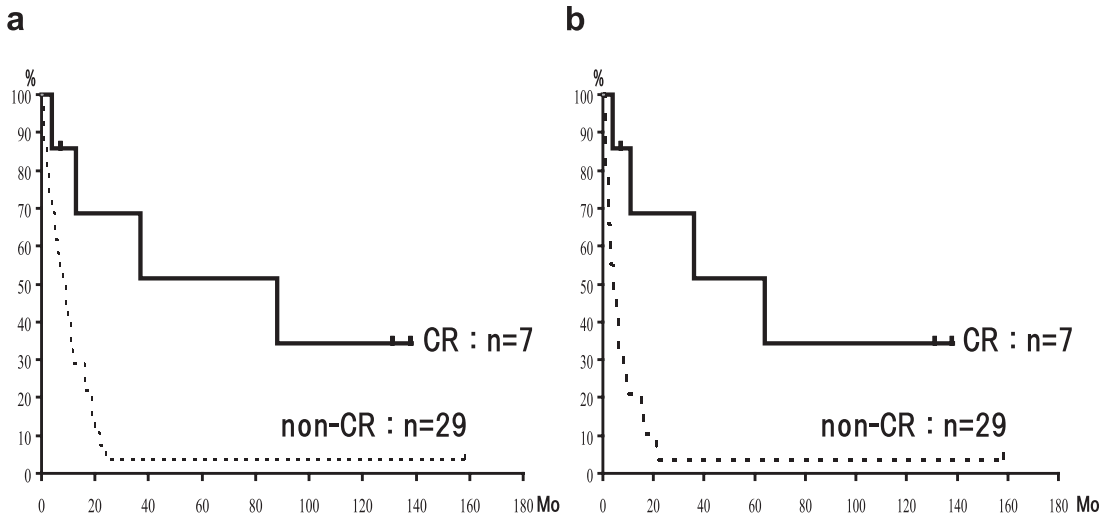

Fig. 2. Survival results according to response to m-MECP. Overall (a) and event free (b) survival (OS and EFS) of CR group are significantly better than non-CR group (p=0.008 and 0.004 by log-rank test).

Table 3. Multivariate analysis for survival of all patients.

	OS			EFS		
Factors	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Age <60 vs >=60	0.540	0.213-1.371	0.195	0.518	0.209-1.281	0.154
DLBL vs PTCL-U	0.762	0.297-1.956	0.573	0.594	0.208-1.695	0.331
Refractory vs Relapse	1.457	0.403-5.264	0.566	1.640	0.426-6.314	0.472
CR vs non-CR	0.157	0.033-0.753	<u>0.021</u>	0.140	0.029-0.669	<u>0.014</u>
Low risk vs High risk	0.505	0.108-2.365	0.505	0.420	0.088-2.009	0.277

Statistically significant p value is underlined.

Side effects

Either of neutropenia or thrombocytopenia with grade 3 or 4 was observed in 20 patients (55.6%) and therapeutic delay due to hematological toxicity was experienced in 6 patients (16.7%). However, transfusion of red cell or platelet was not required. At least one episode of febrile neutropenia occurred in 13 patients (27.8%). Among those, one patient with PTCL-U in relapse (2.8%) complicated bacterial pneumonia during a neutropenic period after the first course. Reversible congestive heart failure (grade 3) was caused by the first course in a patient with relapsed DLBL (2.8%), resulting in discontinuation of this therapy. Severe (grade 3 or more) mucositis, vomiting, liver function disorder, or renal toxicity was not recorded. At the time of this analysis, secondary hematological disorder was not observed.

Discussion

In the past, intensification of induction chemotherapy regimens against NHL has not been proven superior to CHOP[1]. In addition, whether up-front ASCT improves survival in aggressive NHL, even in high-risk groups, is still debatable[14][15]. Therefore, to improve the prognosis of aggressive NHL, appropriate salvage therapy should be established. In this case series, m-MECP re-induction of more than 60% of CHOP-resistant patients into remission is discussed. It should be noted that despite dose modification, the rates of CR (7/36, 19.4%), PR (16/36, 44.4%), and total response (23/36, 63.9%) were not significantly different from those observed with original MECP (7/22, 31.8%. $p=0.45$; 4/22, 18.2%. $p=0.08$; 11/22, 50%. $p=0.44$, respectively by Fisher's exact test), although patients' backgrounds were not matched. These results suggest that our dose modification is acceptable. However, cautious dose application and appropriate supportive therapy are needed because severe toxicity was observed.

Response to m-MECP also affected the survival. When multivariate analysis was applied using CR as one factor, a significant increase was seen in both OS and EFS. However, we encountered some difficulties to induce CR. First, CR rate between tumor phenotypes was different. While 6 of 24 (25.0%) patients with B-cell lymphoma achieved CR, only 1 of 12 (8.3%) with T-cell lymphoma did so. Murohashi et al. demonstrated efficacy of similar combination chemotherapy for DLBL[11]. In addition, we applied m-MECP for T-cell NHL. However, the result was unsatisfactory. This is consistent with previous report of Gisselbrecht et al. in which T-cell phenotype was recognized as independent adverse prognostic factor[16]. Second, a combination of R with m-MECP did not affect response rate in DLBL patients. Among 24 patients with DLBL in our case series, 9 patients had received R-CHOP as preceding therapy. Although use of R with first-line therapy was reported to be associated with poor prognosis of relapsed patients[17], difference in OS or EFS was not found between two groups of 9 patients who had received R-CHOP and 15 who had received CHOP ($p=0.85$ and 0.60 by log-rank test, respectively). Reduced CD20 expression found by Terui et al.[18] may be seen in refractory or relapsed lymphoma cells. This resistance to R remains to be overcome.

Among patients who responded to m-MECP, ASCT was performed on 8 patients. Stem cells were sufficiently harvested from each patient after 2 or 3 courses of m-MECP. The 5-year OS and EFS rates of these 8 patients were 37.5%, indicating significantly prolonged survival. ASCT in this study resulted in longer survival in the CR group. ASCT has been recommended for chemosensitive relapses of aggressive lymphomas including DLBL and PTCL[19]. Kewalramini et al. reported[20] that prognostic

disadvantage of T-cell phenotype may be overcome by ASCT. Our patient with refractory PTCL-U has been uneventful after ASCT for 158 months.

In general, the prognosis of CHOP-resistant aggressive NHL is extremely poor. Most patients included in this retrospective study have died within a few years, resulting in very low survival rate after a long term observation. However, m-MECP appears to be feasible for patients with CHOP-resistant aggressive NHL, especially DLBL. To benefit more patients, alternative salvage therapy that is active against T-cell subtype is required. Post-remission therapy should also be investigated for whom ASCT is not indicated.

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〈和文抄録〉

治療抵抗性または再発 aggressive 非ホジキンリンパ腫に対する modified MECP の有用性

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治療抵抗性または再発 aggressive 非ホジキンリンパ腫（NHL）に対する救援化学療法に確立されたレジメンはない．我々は mitoxantrone，etoposide （ETOP），carboplatin （CBDCA），prednisolone からなる MECP 療法の血液毒性を軽減する目的で ETOP および CBDCA を減量した modified MECP（m-MECP）の有用性を検討した．標準治療である CHOP 療法無効の 36 例（びまん性大細胞 B リンパ腫（DLBL）24 例および末梢性 T 細胞リンパ腫（PTCL-U）12 例）を対象とした．1〜8 コースの治療により全奏効率は 63.9%であった．全体の 5 年全生存率（OS）および無イベント生存率（EFS）は各々 12.1%，11.9%であった．完全寛解（CR）は DLBL により多くみられ，CR 例の生存率は非 CR 例よりも有意に良好であった．寛解例のうち自己末梢血幹細胞移植を施行した 8 例の 5 年 OS･EFS は 37.5%であった．本療法は治療抵抗性または再発 aggressive NHL，特に DLBL に対して有用な救援化学療法となると考えられた．

キーワード：modified MECP，非ホジキンリンパ腫，治療抵抗性，再発．