

Original Article

# Efficacy of salvage therapy with MTX-HOPE for elderly patients with heavily pretreated non-Hodgkin's lymphoma

Akiko Fukunaga, Yoshio Okamoto, Sho Shibata, Shojiro Inano, Yoko Takiuchi,  
Kazuyo Yamamoto, Sumie Tabata, Toshiyuki Kitano

Methotrexate, hydrocortisone, vincristine, sobuzoxane, and etoposide (MTX-HOPE) chemotherapy was originally reported in 2007 as a salvage regimen for relapsed or refractory non-Hodgkin's lymphoma. To clarify the safety and efficacy of this regimen, we retrospectively analyzed patients at our institute. We analyzed 18 patients, including 16 with diffuse large B-cell lymphoma (DLBCL), one with follicular lymphoma (FL), and one with T-cell lymphoma. The median age at MTX-HOPE therapy was 79 (range: 68-87). Ten patients received more than 3 previous chemotherapy regimens. The median period from the initial treatment to the first MTX-HOPE administration was 53 months. No patient had severe renal dysfunction. The overall response rate was 78%, with 39% achieving CR and 39% achieving PR. The median OS and PFS after the initiation of MTX-HOPE were 10 months (range: 0.5-86 months) and 7 months (range: 0.2-86 months), respectively. The one-year OS rate was 44% and the two-year OS rate was 22%. The median number of treatment cycles was 7 (range: 1-46), and 6 patients received more than 10 cycles. Among eight patients who were over 80 years of age, 7 responded to the therapy, and the median OS and PFS of this subgroup were 19 months and 11 months, respectively. All patients tolerated the treatment well, mostly on an outpatient basis, except for one who died from infection and one who developed intracranial hemorrhage. MTX-HOPE may be a promising treatment option for elderly patients with refractory or relapsed malignant lymphoma.

**Keywords:** Malignant lymphoma, MTX-HOPE, sobuzoxane, salvage, MST-16

## INTRODUCTION

Treatment outcomes of patients with both aggressive and indolent CD20+ non-Hodgkin's lymphoma (NHL) have recently been markedly improved by combining molecular targeted therapies (rituximab) with standard chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).<sup>1,2</sup> Although there have been long-term disease-free survival improvements, approximately 50% of patients eventually relapse or have recurrent disease.<sup>3</sup> Furthermore, rituximab maintenance therapy during the first remission improves progression-free survival (PFS) in follicular lymphoma, but it does not prolong event-free, progression-free, or overall survival in patients with aggressive B-cell NHL.<sup>4-6</sup>

Although treatment regimens differ depending on the disease profile and individual background, including age and comorbidities, there is no standard salvage treatment for these patients once lymphoma relapses or becomes refractory to treatment. In heavily pretreated lymphoma, gemcitabine

(GEM)-based regimens are frequently preferred, as this agent is able to overcome multidrug resistance secondary to increased P-glycoprotein overexpression.<sup>7</sup> GEM combined with carboplatin, dexamethasone, and rituximab (R-GCD) has been demonstrated as effective in refractory or relapsed lymphoma patients<sup>8</sup> who have been safely treated in an outpatient setting.

The oral topoisomerase II inhibitor sobuzoxane (MST-16) is a derivative of bis(2,6-dioxo-piperazine), a ICRF-154 active prodrug. As sobuzoxane has no cross-resistance with vincristine, doxorubicin, cyclophosphamide, 5-fluorouracil, etoposide, or mitomycin C, cytoidal effects can be expected in patients with refractory disease.<sup>9</sup> The sobuzoxane-containing chemotherapy regimen MTX-HOPE (methotrexate / hydrocortisone/ vincristine/sobuzoxane /etoposide) was originally investigated by Tsunoda S *et al.*<sup>10</sup> who conducted a clinical study on 14 relapsed or refractory NHL patients, among whom 5 achieved complete response (CR) and 5 achieved partial response (PR) using MTX-HOPE, with an estimated overall survival (OS) of 11.1 months. In the original paper,

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Department of Hematology, Kitano Hospital The Tazuke Kofukai Medical Research Institute, Osaka, Japan

**Corresponding author:** Akiko Fukunaga, 2-4-20 Ohgimachi, Kita-ku, Osaka 530-8480, Japan. E-mail: a-fukunaga@kitano-hp.or.jp

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among the 14 patients treated, grade 4 neutropenia and thrombocytopenia were observed in 4 and 2 patients, and grade 3 transaminase increase and stomatitis were observed in 4 and 2 patients, respectively. In the present study, we retrospectively analyzed 18 NHL patients treated using the MTX-HOPE regimen at our institute.

## PATIENTS AND METHODS

This study included a total of 18 patients with malignant lymphoma, including 16 with diffuse large B-cell lymphoma, one with follicular lymphoma, and one with T-cell lymphoma who received MTX-HOPE (Table 1). The MTX-HOPE regimen consisted of 20 mg of oral methotrexate on day 1, 100 mg of hydrocortisone and 1 mg of vincristine intravenous (iv) on day 2, and oral sobuzoxane at 400 mg and etoposide at 25 mg on days 3 and 4. All patients were treated in 21-day cycles according to the original paper.

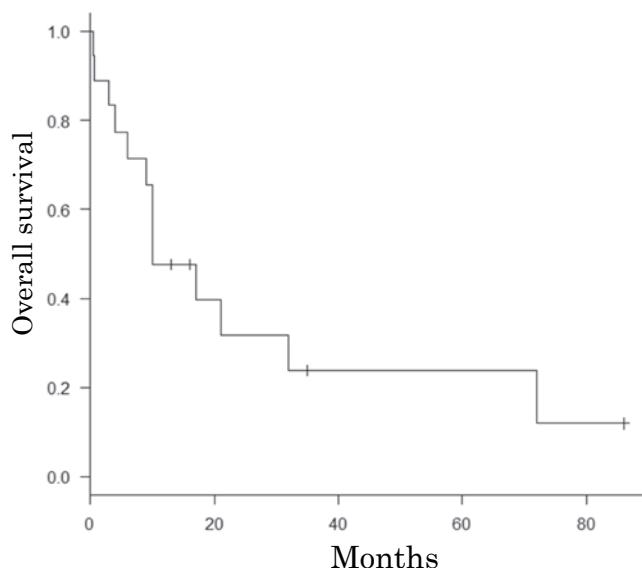
Most patients had previously received more than 3 treatment regimens (Table 1). The median time from the first treatment to the first MTX-HOPE administration was 53 months. Nine of 18 patients had a performance status higher than 2. The study was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice.

**Table 1.** Patient characteristics

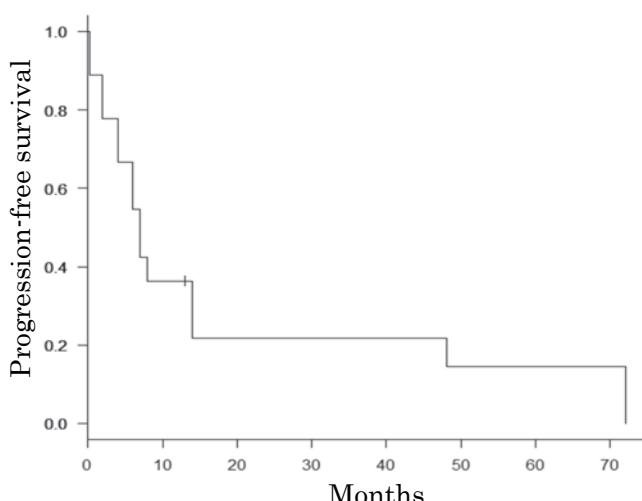
Clinical characteristics	N=18
Age, median (range), years	79 (68-87)
Age distribution	
>80 years	6 (33)
70-80 years	11 (61)
<70 years	1 (6)
Sex, n (%)	
Male	8 (44)
Female	10 (56)
Performance status	
0-1	9 (50)
2-4	9 (50)
Histology	
DLBCL	16 (88)
FL	1 (6)
T-cell lymphoma	1 (6)
Clinical stage at diagnosis	
I	2 (17)
II	1 (9)
III	6 (33)
IV	8 (44)
Months from diagnosis, median (range)	53 (5-120)
Months from pre-therapy, median (range)	3 (0.5-84)
Disease status	
Relapsed	7 (39)
Refractory	11 (61)
Previous chemotherapy	
None or one regimen	8 (44)
Two or more regimens	10 (56)

## RESULTS

The overall response rate of patients treated using MTX-HOPE was 78%, with 39% achieving CR and 39% achieving PR (Fig 1,2). The median OS and PFS after starting MTX-HOPE were 10 months (range, 0.5–86 months) and 7 months (range, 0.2–86 months), respectively. One- and two-year OS rates were 44% and 22%, respectively. Among MTX-HOPE-treated patients, the median number of treatment cycles was 7 (range, 1–46); 6 patients received more than 10 cycles, 2 of whom received more than 40 cycles. Among the 8 patients over the age of 80, 7 responded to therapy; the median OS and PFS in this subgroup were 19 and 11 months, respectively. Patients were mostly treated on an outpatient setting.



**Fig. 1.** Overall survival of patients treated using MTX-HOPE. The median overall survival with MTX-HOPE was 10 months.



**Fig. 2.** The progression-free survival of patients treated using MTX-HOPE . The median progression-free survival with MTX-HOPE was 7 months.

The toxicity profiles are shown in Table 2. Grade 3 and 4 neutropenia were observed in 38 and 22% of patients, and grade 3 and 4 thrombocytopenia were observed in 5 and 11% of patients, respectively. There were few non-hematological toxicities; one patient developed grade 3 febrile neutropenia and one patient died from severe infection 15 days after the initiation of MTX-HOPE treatment. This patient had preceding bone marrow suppression due to lymphoma progression and heavy treatment history. Another patient developed intracranial hemorrhage of unknown cause, thus chemotherapy was withdrawn. For 10 of the 18 patients previously treated by more than 3 chemotherapy regimens, the time from the previous chemotherapy regimen was short, with 14 patients having received the previous therapy up to 3 months prior. Before MTX-HOPE treatment, 7 patients exhibited disease relapse and 11 patients had progressive disease.

## DISCUSSION

Once lymphoma relapses or becomes refractory to treatment, no standard salvage treatment is currently available. The present study investigated patients in this setting who were treated using the MTX-HOPE regimen. MTX-HOPE treatment outcomes were first reported by Tsunoda *et al.* in 14 recurrent or refractory NHL patients who were not eligible for high-intensity chemotherapy. This combined regimen was developed based on evidence from acute lymphoblastic leukemia cell lines demonstrating that although MTX and VCR simultaneous administration had antagonistic effects, when MTX preceded VCR administration by 8 to 24 hours, strong synergistic anti-tumor effects were observed.<sup>11</sup> The same authors found that the simultaneous administration of sobuzoxane and etoposide had strong synergistic effects, and that the combination of these drugs may improve anthracycline-resistant lymphoma treatment outcomes without increasing toxicity.

In this study, patients who received the MTX-HOPE regimen at our institute were retrospectively investigated. In the original paper, the MTX-HOPE regimen was administered every 2 to 3 weeks, but at our institute, we treated the patients every 3 weeks in consideration of bone marrow recovery. Although most patients were heavily pretreated and a significant proportion was over 80 years of age,

**Table 2.** Toxicity profile

Toxicity	Grade, n (%)			
	1	2	3	4
Neutropenia	0(0)	0(0)	7(38)	4(22)
Thrombocytopenia	0(0)	1(5)	1(5)	1(5)
Anemia	0(0)	5(28)	1(5)	0(0)
Intracranial hemorrhage	0(0)	0(0)	1(5)	0(0)
Fever	1(5)	0(0)	0(0)	0(0)
Febrile neutropenia	0(0)	0(0)	1(5)	0(0)
Infection	0(0)	0(0)	0(0)	1(5) *

\*death

treatment outcomes of MTX-HOPE were favorable. Of note, MTX-HOPE yielded better treatment outcomes than GEM-based chemotherapy. Sobuzoxane was reported to be effective as a single agent in adult T-cell leukemia/lymphoma.<sup>12</sup> Moreover, sobuzoxane combined with etoposide led to long-term responses in refractory or relapsed NHL.<sup>13</sup> Sobuzoxane was also reported to inhibit topoisomerase II, but in the presence of doxorubicin, it increases the production of doxorubicin-DNA adducts, resulting in a higher cytotoxic response.<sup>14</sup> Most patients included in this study were elderly, heavily pretreated, and had a short interval time since the previous treatment and progressive disease. In this frail population, MTX-HOPE demonstrated satisfactory efficacy. Moreover, most patients tolerated treatment in an outpatient setting without notable adverse events. Overall, MTX-HOPE may be a promising treatment option for elderly patients with refractory or relapsed malignant lymphoma.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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