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

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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
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.

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.

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) |

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. 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, 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. Moreover, sobuzoxane combined with etoposide led to long-term responses in refractory or relapsed NHL. 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. 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.

### 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

### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

### REFERENCES

1. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d’Etudes des Lymphomes de l’Adulte. Blood. 2010; 116 : 2040-2045.
2. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2005; 106 : 3725-3732.
3. Coiffier B, Lepage E, Brière J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002; 346 : 235-242.
4. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet. 2011; 377 : 42-51.
5. Nastoupi LJ, Sinha R, Byttek M, et al. The use and effectiveness of rituximab maintenance in patients with follicular lymphoma diagnosed between 2004 and 2007 in the United States. Cancer. 2014; 120 : 1830-1837.
6. Jaeger U, Trneny M, Melzer H, et al; AGMT-NHL13 Investigators. Rituximab maintenance for patients with aggressive B-cell lymphoma in first remission: results of the randomized NHL13 trial. Haematologica. 2015; 100 : 955-963.
7. Bergman AM, Pinedo HM, Talianidis I, et al. Increased sensitivity to gemcitabine of P-glycoprotein and multidrug resistance-associated protein-overexpressing human cancer cell lines. Br J Cancer. 2003; 88 : 1963-1970.
8. Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of
gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. Leuk Lymphoma. 2010; 51: 1523-1529.

9 Ohnishi K. [Oral antitumor drugs for Hematological Malignancies]. Gan to Kagaku Ryoho. 1999; 26: 295-300.

10 Tsunoda S, Kobayashi H, Inoue K, et al. [MTX-HOPE (methotrexate, hydrocortisone, vincristine, sobuzoxane, and etoposide) as a low-dose salvage chemotherapy for recurrent or refractory non-Hodgkin’s lymphoma]. Gan To Kagaku Ryoho. 2007; 34: 885-889.

11 Kano Y, Ohnuma T, Okano T, Holland JF. Effects of vincristine in combination with methotrexate and other antitumor agents in human acute lymphoblastic leukemia cells in culture. Cancer Res. 1988; 48: 351-356.

12 Ohno R, Masaoka T, Shirakawa S, et al. Treatment of adult T-cell leukemia/lymphoma with MST-16, a new oral antitumor drug and a derivative of bis(2,6-dioxopiperazine). Cancer. 1993; 71: 2217-2221.

13 Okamoto T, Nishimura Y, Yamada S, et al. Long-term administration of oral low-dose topoisomerase II inhibitors, MST-16 and VP-16, for refractory or relapsed non-Hodgkin’s lymphoma. Acta Haematol. 2000; 104: 128-130.

14 Swift LP, Cutts SM, Nudelman A, et al. The cardio-protecting agent and topoisomerase II catalytic inhibitor sobuzoxane enhances doxorubicin-DNA adduct mediated cytotoxicity. Cancer Chemother Pharmacol. 2008; 61: 739-749.