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Original Article

MTX-HOPE is a low-dose salvage chemotherapy for aged patients with relapsed or refractory non-Hodgkin lymphoma

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As the aging society advances, the number of non-Hodgkin lymphoma (NHL) patients is increasing. Aged relapsed or refractory (r/r) NHL patients have limited treatment options. Therefore, a safe and effective regimen is urgently needed for these patients. Thus, we originally developed the MTX-HOPE (methotrexate, hydrocortisone, vincristine, sobuzoxane, and etoposide) regimen for r/r NHL and validated the safety and efficacy of this regimen in a clinical setting. We analyzed the data of 42 r/r NHL patients who received MTX-HOPE in this single-center retrospective cohort study. The median age of the patients was 81 years. The overall response rate was 45.3%. The median overall survival (OS) was 7 months, the one-year OS was 43.7%, and the two-year OS was 40.8%. Grade ≥3 neutropenia and renal dysfunction were observed in 47.6% and 11.9% of patients, respectively, and treatment-related death were not observed. Appropriate supportive care enabled these patients to continue the MTX-HOPE regimen. The proportion of patients who needed hospitalization during MTX-HOPE therapy was only 21.4%. Multivariable analyses with the Cox proportional hazards model revealed that both OS and progression-free survival (PFS) were significantly influenced by high Ki-67 expression in pathology, with response to the MTX-HOPE regimen after three to five cycles as a time-dependent covariate. Our results suggest that MTX-HOPE therapy can be an option for non-aggressive r/r NHL patients. To validate MTX-HOPE therapy, further prospective investigation is needed.

Keywords: MTX-HOPE, QOL, Ki-67, non-Hodgkin lymphoma, salvage chemotherapy

INTRODUCTION

The aged population is increasing, particularly in advanced countries. As this population advances, the incidence of cancers, including malignant lymphoma, is rising.[1-3] Because cancer can be considered an age-related disease, it is an urgent task to take measures for elderly patients with cancer in advanced countries.[4] Because most vulnerable older adult patients cannot be enrolled in clinical trials, there are few data regarding the management of aged cancer patients, including those with lymphoma. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)/CHOP (CHOP) therapy is the gold standard regimen for elderly non-Hodgkin lymphoma (NHL) patients.[5-8] However, even if complete response (CR) is reached with initial treatment, 20-50% of patients with diffuse large B cell lymphoma (DLBCL) experience relapse,[9] and there are few therapeutic options, especially for aged patients with relapsed NHL.

Thus, it is unclear whether aged relapsed or refractory (r/r) NHL patients are suitable for certain therapeutic strategies. Aged patients with some comorbidities cannot receive sufficient intensity salvage chemotherapies in the clinic. We thus developed a combination salvage therapy for r/r NHL based on isobologram analysis data for these vulnerable patients.[10-16] We selected methotrexate (MTX), hydrocortisone (HC), vincristine (VCR), sobuzoxane (MST-16), and etoposide (ETP) and named this regimen MTX-HOPE (Table 1).[17] This regimen has the advantage of being performed on an outpatient basis. We previously reported the safety and efficacy of the MTX-HOPE regimen in a small number of NHL patients. In a previous study, the median age of the patients was 70 years,

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Table 1. The protocol of MTX-HOPE

Agent	Dose/day	Route	Days
Methotrexate (MTX)	20 mg	po	1
Hydrocortisone (HC)	100 mg	div (15min)	2
Vincristine (VCR)	1 mg	div (15min)	2
Sobuzoxane (MST-16)	400 mg	po	3, 4
Etoposide (ETP)	25 mg	po	3, 4

Abbreviations: MTX-HOPE, methotrexate, hydrocortisone, vincristine, sobuzoxane, and etoposide; po, per os; div, intravenous drip

and the median overall survival (OS) was 11.1 months. In addition, another group recently reported the efficacy of the MTX-HOPE regimen, and the median OS and progression-free survival (PFS) were 10 months and 7 months, respectively.[18] However, the characteristics of NHL patients who are more likely to respond to MTX-HOPE therapy are still unknown. We need to identify patients suitable for this regimen from the perspective of safety and effectiveness. Thus, we performed a single-center retrospective cohort study to validate the MTX-HOPE regimen.

MATERIALS AND METHODS

Study design and patients

This study was conducted as a single-center retrospective cohort study. A total of 42 patients who received MTX-HOPE therapy agreed to participate in this study, which was approved by the local Ethics Committee of Aizu Medical Center of Fukushima Medical University (FMU) and carried out in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all subjects prior to enrollment. We obtained patient characteristics and laboratory data from the clinical records of all patients diagnosed with NHL, including DLBCL, mantle cell lymphoma (MCL), peripheral T cell lymphoma (PTCL), and others, from 2009 to 2020.

Treatment protocol

The MTX-HOPE regimen was repeated every 2-3 weeks and involved the administration of MTX (20 mg) orally on day 1, HC (100 mg) and VCR (1 mg) infusion on day 2, and MST-16 (400 mg) and ETP (25 mg) orally on days 3 and 4 (Table 1). Granulocyte colony-stimulating factor (G-CSF) was administered to patients who experienced neutropenia as supportive therapy.

Treatment response and toxicity criteria

Efficacy assessments were performed according to the international consensus on the revised response criteria for malignant lymphoma. According to these criteria, we defined therapy responses as follows: complete response (CR), unconfirmed CR (uCR), partial response (PR), stable disease (SD), and progressive disease (PD). Physical examination and laboratory tests were used to evaluate adverse reactions and toxicities. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, Version 4.0.

Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.[19] The Kolmogorov-Smirnov test was used to analyze the normality of the distribution of parameters.[20,21] All variables with a normal distribution are expressed as the mean ± standard deviation, and those with a log-normal distribution are expressed as the median with the interquartile range (IQR). OS was defined as the time from the start of MTX-HOPE therapy to death or the date of the last follow-up.[22] PFS was defined as the time from the start of MTX-HOPE therapy to relapse, death, or the date of the last follow-up. The OS and PFS rates were estimated according to the Kaplan-Meier method and compared by the log-rank test.[19,22] The hazard ratios (HRs) and their associated 95% confidence intervals (CIs) for potential prognostic factors were calculated using the Cox proportional hazards regression model. Variables with $p < 0.10$ in the univariate analysis were used as independent variables in the multivariate analysis.[23] All statistical tests were two-sided, and a significance level of 0.05 was used.

RESULTS

Patient characteristics

The median age of the 42 patients who received MTX-HOPE therapy for r/r NHL in this study was 81 years (range, 57 to 90 years), and 35.7% were women (Table 2). In our study, seven patients (16.7%) who received the MTX-HOPE regimen were less than 70 years old. Six patients had a history of multiple pretreatment regimens, and the other patient had severe pulmonary disease and poor performance status (PS). These patients had no indication for intensive chemotherapy and agreed to receive the MTX-HOPE regimen. The proportion of patients who needed hospitalization during MTX-HOPE therapy was only 21.4%. Twenty-five patients were refractory to previous treatment, and 17 had relapsed disease. The proportion of patients with worse Eastern Cooperative Oncology Group (ECOG) PS scores (more than 2) was 59.5%, the proportion of patients with anemia (hemoglobin less than 10 g/dL) was 42.9%, and the proportion of patients with lactate dehydrogenase (LDH) levels greater than the upper limit of normal was 54.8%. At the time of diagnosis, the proportion of patients with intermediate- and high-risk International Prognostic Index (IPI) scores was 92.9%, and the proportion of patients with advanced stage (stage III and IV) disease was 85.6%. The lymphoma histology

Table 2. Patient characteristics

Characteristics patients	MTX-HOPE
Patients, n	42
Hospitalization during MTX-HOPE administration	9 (21)
At the start of treatment	
Age, median [min, max]	81 [57, 90]
Women, n (%)	15 (36)
Performance status, n (%)	
0-1	17 (41)
2-4	25 (60)
Status before MTX-HOPE treatment, n (%)	
Relapsed	17 (41)
Refractory	25 (60)
Number of pretreatment regimens, n (%)	
1	31(74)
2	3 (7.1)
≥3	8 (19)
Pretreatment regimen, n (%)	
CHOP +/-R	28 (67)
DeVIC +/-R	5 (12)
GDP +/-R	3 (7.1)
Other	6 (14)
Previous treatment history of rituximab, n (%)	29 (69)
Histology, n (%)	
B cell lymphoma	30 (71)
DLBCL	28 (67)
FL	1 (2.4)
MCL	1 (2.4)
T cell lymphoma	11 (26)
Extranodal NK/T cell lymphoma	1 (2.4)
Anemia (Hb <10), n (%)	18 (43)
CKD, n (%)	16 (38)
LDH high (≥upper normal limit; 240)	23 (55)
BMI (<20 kg/m^2), n (%)	15 (36)
At diagnosis	
IPI, n(%)	
Low risk	3(7.1)
Intermediate risk	16 (38)
High risk	23 (55)
Stage, n(%)	
I	4 (9.5)
II	2 (4.8)
III	9 (21)
IV	27 (64)
Bone marrow involvement, n (%)	12 (29)
Extranodal lesion, n (%)	33 (79)
B symptoms present, n (%)	12 (29)
Ki-67 high (≥50%), n(%)	15 (36)
DLBCL	12 (29)
MCL	1 (2.4)
T cell lymphoma	2 (4.8)
Response after 3 to 5 cycles, n (%)	
Complete response (CR)/unconfirmed CR	8 (19)
Partial response (PR)	11 (26)
Stable disease (SD)	13 (31)
Progressive disease (PD)	10 (24)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; CKD, chronic kidney disease

of the patients included 28 DLBCL, one follicular lymphoma (FL), one MCL, 11 T cell lymphoma, and one extranodal NK/T cell lymphoma. In addition, the proportion of patients with Ki-67 positivity greater than 50% by immunohistochemistry (IHC) was 36%. Furthermore, the MTX-HOPE regimen was given to patients as salvage therapy. We assessed the response to MTX-HOPE after three to five cycles by computed tomography (CT). The percentage of patients who achieved CR or unconfirmed CR was 19%, PR was 26.2%, SD was 31%, and PD was 23.8% at that time.

Safety of MTX-HOPE

The hematological and nonhematological toxicities of MTX-HOPE are shown in Table 3. Grade 3 and 4 neutropenia were observed in 47.6% of the patients, and febrile neutropenia was observed in 9.5%. Grade 3 and 4 anemia and thrombocytopenia were observed in 35.7% and 14.3% of the patients, respectively. Severe nonhematological toxicities, such as liver damage, renal dysfunction, nausea, vomiting, and infection, were infrequent in patients treated with MTX-HOPE therapy. Seventeen patients temporarily discontinued VCR due to grade 1 neuropathy in our study. However, most patients could continue VCR while administered vitamin B12 and pregabalin. The other drugs did not need to be reduced. Furthermore, there were no treatment-related deaths. However, there were six treatment discontinuation events: four pneumonia, one sepsis and one acute kidney injury (Table 3).

Survival analysis

The median follow-up duration of the survivors was 213 days (range, 12-2763). The median OS was 7 months

Table 3. Adverse effects of MTX-HOPE therapy

Hematological toxicity	All Grades	Grade ≥3
Neutropenia n, (%)	33 (79)	20 (48)
Febrile neutropenia n, (%)	-	4 (9.5)
Anemia n, (%)	39 (93)	15 (36)
Thrombocytopenia n, (%)	30 (71)	6 (14)
Nonhematological toxicity		
Liver damage	10 (24)	2 (4.8)
Renal dysfunction	24 (57)	5 (12)
Nausea	8 (19)	0 (0)
Vomiting	1 (2.4)	0 (0)
Infection	10 (24)	3 (7.1)
Neuropathy	17 (40)	0 (0)
Hematological supportive care		
Red blood cell transfusion	13 (30.9)	
Platelet transfusion	4 (9.5)	
G-CSF	24 (57.1)	
Treatment-related deaths	0 (0)	
Treatment discontinuation events	6 (14)	
Pneumonia	4 (9.5)	
Sepsis	1 (2.4)	
Acute kidney injury	1 (2.4)	

(range, 0-91) (Figure 1a), and the median PFS was 3.5 months (range, 0-91) (Figure 1b). Next, we performed univariate analysis to identify the independent factors for OS and PFS by univariate analyses (Table 4). OS was significantly influenced by Ki-67 positivity in pathology (≥50%) (P = 0.020) and PR to the MTX-HOPE regimen after three to five cycles (P = 0.002) (Figure 1c). PFS was also significantly influenced by Ki-67 positivity in pathology (≥50%) (P = 0.039) and PR to the MTX-HOPE regimen after three to five cycles (P < 0.001) (Figure 1d). IPI, lymphoma status (r/r), lymphoma histology (B cell lymphoma or T cell lymphoma), and other factors did not influence OS or PFS.

Furthermore, we performed multivariable analyses of OS and PFS with the Cox proportional hazards model to control confounding factors. Response to MTX-HOPE better than PR after three to five cycles was treated as a time-dependent covariate.[23] Each analysis was evaluated by adding age (≥75), IPI (≥3), and lymphoma histology (B cell lymphoma or T cell lymphoma) to the independent factors (Table 5). The final models for OS and PFS included Ki-67 positivity (≥ 50%) (HR 2.42, 95% CI 1.15-5.09, P = 0.020 and HR 2.10, 95% CI 1.04-4.25, P = 0.039).

DISCUSSION

In the present study, we analyzed the safety and efficacy of MTX-HOPE for aged r/r NHL patients who are vulnerable and were not eligible for autologous stem cell transplantation (ASCT) and conventional high-dose salvage chemotherapy. Our results showed that the MTX-HOPE regimen is effective and tolerable for these r/r NHL patients. High Ki-67 positivity was extracted as an independent factor of OS and PFS by multivariable analyses using response to MTX-HOPE treatment as a time-dependent covariate. In addition, most patients who receive MTX-HOPE can be treated without hospitalization.

Ki-67 is one of the cell cycle related protein and strongly associated with the lymphoma cell proliferation, leading to

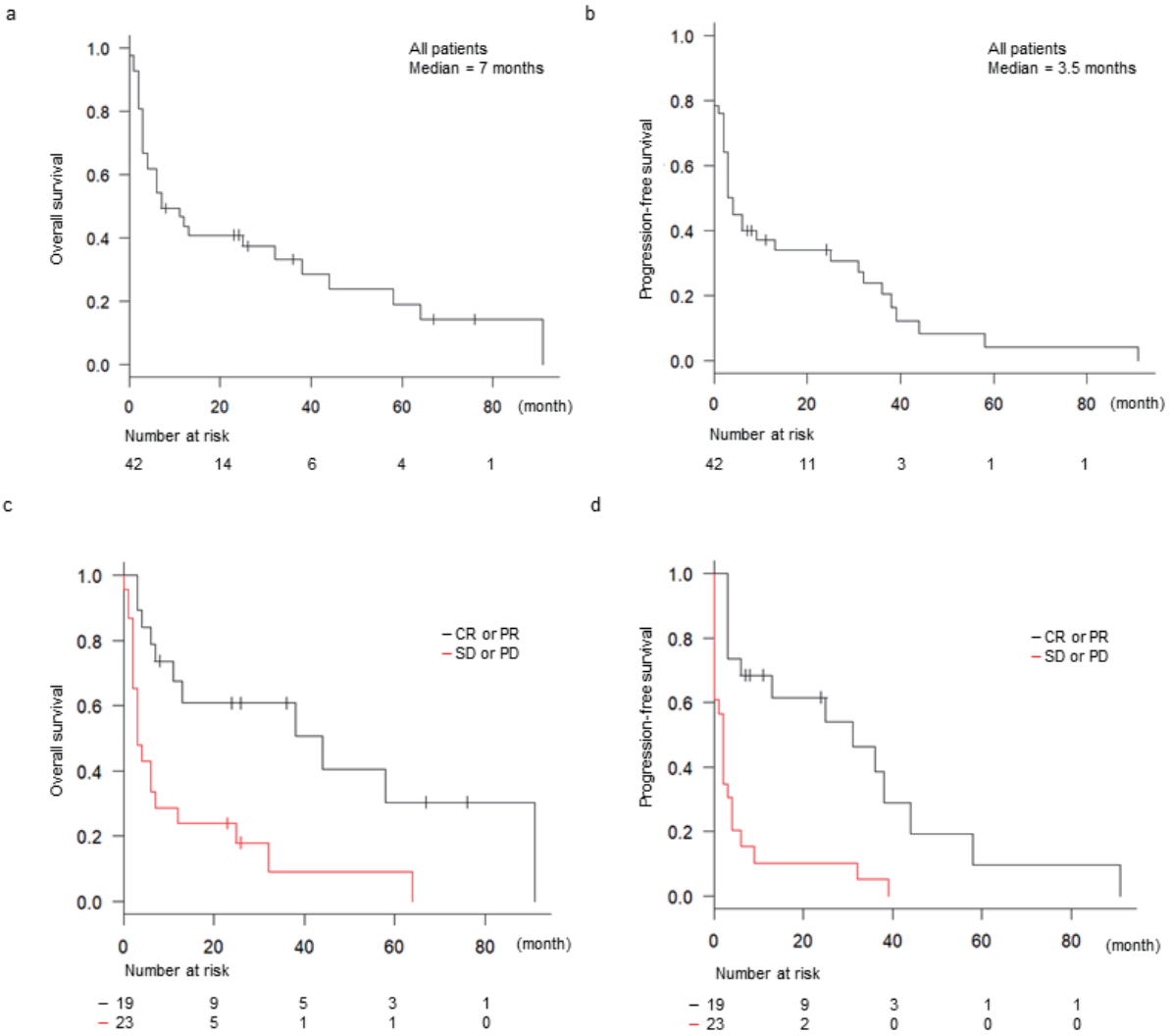

Fig. 1. Kaplan-Meier estimates. (***a***) Overall survival (OS) and (***b***) progression-free survival (PFS) of all patients who received MTX-HOPE therapy. (***c***) OS and (***d***) PFS stratified by the response to MTX-HOPE therapy after three to five cycles.

Table 4. Univariate analysis of overall survival and progression-free survival

Variable	Overall survival		Progression-free survival	
	Hazard ratio (95%CI)	p-value	Hazard ratio (95%CI)	p-value
Age ≥ 75	1.11 (0.51-2.41)	0.79	1.23 (0.59-2.53)	0.58
Sex (female)	0.89 (0.42-1.92)	0.77	0.82 (0.40-1.65)	0.58
BMI ≥ 20 kg/m^2	0.64 (0.29-1.43)	0.28	0.73 (0.35-1.54)	0.41
Hb > 10	0.61 (0.29-1.31)	0.20	0.97 (0.48-1.98)	0.94
eGFR > 60	0.75 (0.36-1.58)	0.45	0.75 (0.37-1.51)	0.42
Number of pretreatment regimens ≥ 2	1.37 (0.63-3.00)	0.43	1.44 (0.70-2.97)	0.32
IPI ≥ 3	0.69 (0.29-1.63)	0.39	1.02 (0.44-2.36)	0.96
Stage ≥ III	0.63 (0.26-1.56)	0.32	0.97 (0.40-2.35)	0.94
PS ≥ 2	1.22 (0.58-2.55)	0.61	1.22 (0.62-2.40)	0.57
Extra nodal lesion	1.30 (0.52-3.25)	0.57	1.54 (0.63-3.80)	0.34
LDH (>UNL)	1.65 (0.79-3.45)	0.18	1.36 (0.69-2.66)	0.38
Bone marrow involvement	0.74 (0.32-1.70)	0.48	0.90 (0.44-1.85)	0.78
B symptoms	0.89 (0.39-2.00)	0.77	0.89 (0.43-1.87)	0.77
Relapsed status	0.50 (0.23-1.09)	0.082	0.78 (0.38-1.58)	0.48
T-cell lymphoma histology	0.58 (0.25-1.37)	0.22	0.63 (0.29-1.35)	0.24
Ki-67 ≥50%	2.42 (1.15-5.09)	0.020*	2.10 (1.04-4.25)	0.039*
Response of PR after 3-5 cycles	0.30 (0.13-0.65)	0.002**	0.25 (0.12-0.53)	< 0.001***

Abbreviations: UNL; upper normal limit, PR; partial response
*P < 0.05, **P < 0.01, ***P < 0.001

Table 5. Multivariate analysis of overall survival (OS) and progression-free survival (PFS) with the Cox proportional hazards model. Response to the MTX-HOPE regimen better than partial response after three to five cycles was treated as a time-dependent covariate.

Variable	Hazard ratio (95% CI)	p-value
Overall survival		
Ki-67 (≥50%)	2.42 (1.15-5.09)	0.020*
Progression-free survival		
Ki-67 (≥50%)	2.10 (1.04-4.25)	0.039*

Age (≥75), B cell lymphoma or T cell lymphoma, and International Prognostic Index (≥3) were also added to the OS and PFS analyses. The final models with significant differences are shown in the table.

lymphoma progression. High Ki-67 positivity is also related to poor prognosis within the same lymphoma subtypes, such as DLBCL and FL.[24-26] Our results suggest that MTX-HOPE is less effective for the highly Ki-67 positive lymphoma patients. Because there were a few patients other than DLBCL in our study, further study is needed to confirm these results.

In this study, the patients who received MTX-HOPE therapy were elderly individuals and had worse PS scores. Because these patients had some comorbidities, such as renal dysfunction and anemia, they could not receive other intensive salvage treatments. The overall response rate (ORR) of MTX-HOPE was 45.2%. The rate of treatment responsiveness above SD was 76.2%, and treatment response was observed in many cases. The median OS was 7 months, the 1-year OS was 43.7%, and the 2-year OS was 40.8%. Some patients achieved long-term survival. Moreover, MTX-HOPE therapy resulted in no treatment-related deaths and the acceptable rate of treatment discontinuation events. According to the SCHOLAR-1 study of relapsed DLBCL (the largest, patient-level pooled analysis), the median OS was 6.3 months, and the 2-year OS was 20%.[27] Given our target frail population, these results indicate that MTX-HOPE therapy is tolerable and effective. Although there were several side effects of MTX-HOPE therapy worse than grade 3, these were temporary and recoverable. Appropriate supportive care, including blood transfusion and G-CSF, is generally important for elderly patients to continue chemotherapy.

Furthermore, most patients treated with MTX-HOPE were able to continue without hospitalization, leading to a great advantage in medical costs. Previous reports have shown that the medical costs of aggressive NHL are estimated at $5,871 per patient per month (PPPM) for the first two years of treatment,[28] and those for elderly patients with r/r DLBCL are more than $97,000 per year.[29] In addition, the costs of patients for febrile neutropenia (FN) are more expensive.[30] In our study, the average medical cost of MTX-HOPE calculated by the medical claims data was ¥94,297/month. These data revealed that MTX-HOPE is a cost-effective regimen. Multivariable analysis with the Cox proportional hazards model revealed Ki-67 positivity in pathology and PR to the MTX-HOPE regimen as independent factors for OS and PFS. These results are useful for the indication of MTX-HOPE therapy.

There are some limitations in this study. First, although the response to MTX-HOPE was evaluated based on the International Workshop Response Criteria (IWRC), the evaluations were not conducted at fixed cycles. Therefore, there were differences in the response evaluation periods among

MTX-HOPE patients. Last, this was a single-center, single-arm study. A prospective controlled trial with other salvage regimens may be needed to confirm the safety and effectiveness of MTX-HOPE therapy.

In conclusion, the MTX-HOPE regimen is safe and effective for r/r NHL patients. Pathologically high Ki-67 positivity was identified as an independent factor for MTX-HOPE treatment. The advantage of the MTX-HOPE regimen is that it contributes to maintaining quality of life (QOL) without hospitalization. Our results may help in considering the indications for MTX-HOPE. We concluded that MTX-HOPE is an attractive salvage regimen for aged patients or those with non-aggressive r/r NHL. To validate this regimen, further prospective studies are needed.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest (COIs).

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