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Etoposide, dexamethasone, and pegaspargase with sandwiched radiotherapy in early-stage natural killer/T-cell lymphoma: A randomized phase III study

Huijuan Zhong,[1,35] Shu Cheng,[1,35] Xi Zhang,[2,35] Bing Xu,[3,35] Jiayi Chen,[4] Xufeng Jiang,[5] Jie Xiong,[1] Yu Hu,[6] Guohui Cui,[6] Juying Wei,[7] Wenbin Qian,[8] Xiaobing Huang,[9] Ming Hou,[10] Feng Yan,[11] Xin Wang,[12] Yongping Song,[13] Jianda Hu,[14] Yuanhua Liu,[15] Xuejun Ma,[16] Fei Li,[17] Chongyang Wu,[18] Junmin Chen,[19] Li Yu,[20] Ou Bai,[21] Jingyan Xu,[22] Zunmin Zhu,[23] Li Liu,[24] Xin Zhou,[25] Li Huang,[26] Yin Tong,[27] Ting Niu,[28] Depei Wu,[29] Hao Zhang,[30] Chaofu Wang,[31] Binshen Ouyang,[31] Hongmei Yi,[31] Qi Song,[32] Gang Cai,[4] Biao Li,[5] Jia Liu,[2] Zhifeng Li,[3] Rong Xiao,[9] Luqun Wang,[10] Yujie Jiang,[12] Yanyan Liu,[13] Xiaoyun Zheng,[14] Pengpeng Xu,[1] Hengye Huang,[33] Li Wang,[1] Saijuan Chen,[1,34] and Weili Zhao[1,34,*]

*Correspondence: zhao.weili@yahoo.com

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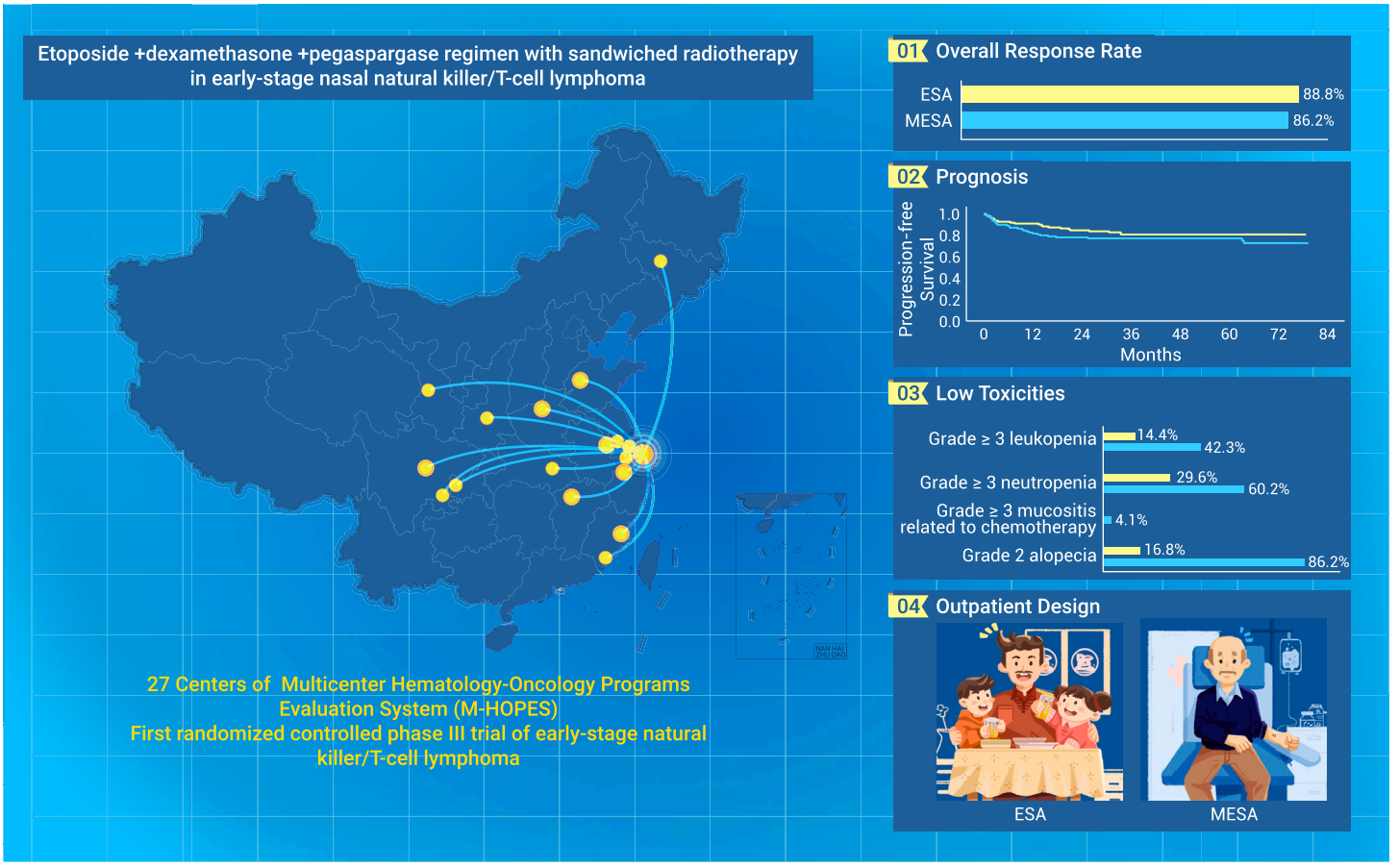
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- It is the first and largest phase III study comparing the effect of ESA with MESA in early-stage NKTCL.
- ESA has similar ORR, PFS, and OS as MESA, with sandwiched radiotherapy.
- ESA regimen is well tolerated, with low toxicities and outpatient design.
- ESA regimen can be a promising first-line chemotherapy option for early-stage NKTCL.

ARTICLE

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[1]Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[2]Department of Hematology, Xinqiao Hospital, Chongqing 400037, China

[3]Department of Hematology, First Affiliated Hospital of Xiamen University, Xiamen, Fujian 361009, China

[4]Department of Radiation Oncology, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[5]Department of Nuclear Medicine, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[6]Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, China

[7]Department of Hematology, First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang 310003, China

[8]Department of Hematology, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China

[9]Institute of Hematology, Department of Hematology, Sichuan Provincial People's Hospital, Chengdu, Sichuan 610072, China

[10]Department of Hematology, Shandong Provincial Key Laboratory of Immunohematology, Qilu Hospital, Shandong University, Jinan, Shandong 250012, China

[11]Department of Hematology, Third Affiliated Hospital of Suzhou University, First People's Hospital of Changzhou, Changzhou, Jiangsu 213004, China

[12]Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong 250021, China

[13]Department of Hematology, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, Henan 450003, China

[14]Fujian Institute of Hematology, Fujian Medical University Union Hospital, Fuzhou, Fujian 350401, China

[15]Department of Medical Oncology, Jiangsu Cancer Hospital, Nanjing, Jiangsu 210009, China

[16]Department of Medical Oncology, Shanghai Cancer Center, Fudan University, Shanghai 200032, China

[17]Department of Hematology, First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China

[18]Department of Hematology, Second Hospital of Lanzhou University, Lanzhou, Gansu 730030, China

[19]Department of Hematology and Rheumatology, First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian 350004, China

[20]Department of Hematology, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330008, China

[21]Department of Hematology, First Hospital of Jilin University, Changchun, Jilin 130061, China

[22]Department of Hematology, Nanjing Drum Tower Hospital, Nanjing, Jiangsu 210008, China

[23]Department of Hematology, Henan Province People's Hospital, Zhengzhou, Henan 450003, China

[24]Department of Hematology, Tangdu Hospital, Fourth Military Medical University, Xi'an, Shanxi 710032, China

[25]Department of Hematology, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu 214023, China

[26]Department of Oncology and Hematology, Hospital Affiliated to Southwest Medical University, Luzhou, Sichuan 646000, China

[27]Department of Hematology, Shanghai General Hospital Affiliated to Shanghai Jiao Tong University, Shanghai 200080, China

[28]Department of Hematology, Hematology Research Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China

[29]First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, China

[30]Department of Otolaryngology, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[31]Department of Pathology, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[32]Department of Radiology, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[33]School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[34]Pôle de Recherches Sino-Français en Science du Vivant et Génomique, Laboratory of Molecular Pathology, Shanghai 200025, China

[35]These authors contributed equally

*Correspondence: zhao.weili@yahoo.com

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Methotrexate, etoposide, dexamethasone, and pegaspargase (MESA) with sandwiched radiotherapy is known to be effective for early-stage extranodal natural killer/T-cell lymphoma, nasal type (NKTCL). We explored the efficacy and safety of reduced-intensity, non-intravenous etoposide, dexamethasone, and pegaspargase (ESA) with sandwiched radiotherapy. This multicenter, randomized, phase III trial enrolled patients aged between 14 and 70 years with newly diagnosed early-stage nasal NKTCL from 27 centers in China. Patients were randomly assigned (1:1) to receive ESA (pegaspargase 2,500 IU/m^2 intramuscularly on day 1, etoposide 200 mg orally, and dexamethasone 40 mg orally on days 2–4) or MESA (methotrexate 1 g/m^2 intravenously on day 1, etoposide 200 mg orally, and dexamethasone 40 mg orally on days 2–4, and pegaspargase 2,500 IU/m^2 intramuscularly on day 5) regimen (four cycles), combined with sandwiched radiotherapy. The primary endpoint was overall response rate (ORR). The non-inferiority margin was −10.0%. From March 16, 2016, to July 17, 2020, 256 patients underwent randomization, and 248 (ESA [n = 125] or MESA [n = 123]) made up the modified intention-to-treat population. The ORR was 88.8% (95% confidence interval [CI], 81.9–93.7) for ESA with sandwiched radiotherapy and 86.2% (95% CI, 78.8–91.7) for MESA with sandwiched radiotherapy, with an absolute rate difference of 2.6% (95% CI, −5.6–10.9), meeting the non-inferiority criteria. Per-protocol and sensitivity analysis supported this result. Adverse events of grade 3 or higher occurred in 42 (33.6%) patients in the ESA arm and 81 (65.9%) in the MESA arm. ESA with sandwiched radiotherapy is an effective, low toxicity, non-intravenous regimen with an outpatient design, and can be considered as a first-line treatment option in newly diagnosed early-stage nasal NKTCL.

INTRODUCTION

Natural killer/T-cell lymphoma (NKTCL) is highly prevalent in Asia and South American countries with aggressive clinical behavior and strong association with Epstein-Barr virus (EBV) infection. Primarily resistant to anthracycline, the prognosis of NKTCL patients has been significantly improved by intensive asparaginase-based chemotherapy regimens,[1] namely methotrexate-containing SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide),[2–4] modified SMILE (mSMILE, dexamethasone, methotrexate, ifosfamide, pegaspargase, etoposide),[5] and MESA (methotrexate, etoposide, dexamethasone, pegaspargase).[6–8] The SMILE regimen induces an overall response rate (ORR) of 82% in early-stage NKTCL.[2] The mSMILE regimen has an ORR of 89%, progression-free survival (PFS) rate of 92%, and overall survival (OS) rate of 100% at a median follow-up of 31 months.[5] The MESA regimen was derived from the SMILE regimen and is widely used in China.[6–8] However, considerable hematological and non-hematological toxicity may limit the application of intensive chemotherapy in early-stage nasal NKTCL, thus providing a clinical rationale for reducing the intensity of chemotherapy. Modified approaches are subsequently developed and can achieve comparable responses and outcomes.[9,10] The DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin)[11] and VIPD (etoposide, ifosfamide, cisplatin, dexamethasone)[12] regimens replace asparaginase with platinum. P-Gemox and GELOX regimens use gemcitabine, pegaspargase/L-asparaginase, and oxaliplatin.[13–15] In addition to chemotherapy, early-stage NKTCL generally involves the nasal cavity and its adjacent sites, and radiotherapy is given as routine clinical practice.[16,17] Long-term survival for most early-stage patients treated with radiotherapy alone was unsatisfactory, with 5-year PFS and OS rates of 56% and 61%, respectively.[18,19] For nomogram-revised risk index (NRI) low-risk patients (who account for 20% of early-stage patients), radiotherapy alone was effective; however, for NRI intermediate-/high-risk patients (who account for 80%), combined chemoradiotherapy modality was the most effective strategy in the modern treatment era.[18,20] Concurrent and sequential chemoradiotherapy lead to similar outcomes in early-stage NKTCL.[19] Sandwiched radiotherapy showed significantly higher PFS rates and a trend toward improved loco-regional control when compared with sequential chemotherapy and radiotherapy.[21] Therefore, to maximize disease control while minimizing toxic effects, further exploration of optimal low-intensity regimens with sandwiched radiotherapy in early-stage NKTCL based on randomized, phase III clinical trials remains of great interest.

Considering that asparaginase-associated metabolites are significantly related to clinical responses in early-stage NKTCL[6] and that methotrexate may not alter natural killer leukemia/lymphoma cell growth *in vitro*,[22] we removed methotrexate from the MESA regimen and subsequently developed a low-intensity, non-intravenous ESA regimen for an outpatient design, consisting of only intramuscular pegaspargase, oral etoposide, and dexamethasone. The Multicenter Hematology-Oncology Programs Evaluation System (M-HOPES) network from China coordinated this first and largest prospective, multicenter, randomized study (NHL-004) to compare the efficacy and safety of ESA and MESA in combination with sandwiched radiotherapy as a first-line treatment for newly diagnosed early-stage NKTCL.

In the past decades, important clinical prognostic models have been established for the risk stratification of NKTCL patients, including the International Prognostic Index (IPI),[23] the prognostic index of natural killer lymphoma in combination with peripheral blood EBV DNA (PINK-E),[24] the Chinese Southwest Oncology Group and Asia Lymphoma Study Group ENKTL (CA) system,[25] and NRI.[26] As for molecular biomarkers, proliferation-associated Ki-67 protein predicts poor prognosis in NKTCL patients.[16,27] More recently, we defined molecular subtypes of genomic and transcriptomic alterations, including the TSIM (based on mutations in the JAK-STAT pathway and TP53, as well as amp9p24.1/JAK2 locus, amp17q21.2/STAT3/5B/5A locus, amp9p24.1/PD-L1/2 locus, and del6q21), MB (based on MGA mutation and 1p22.1/BRDT LOH), and HEA (based on HDAC9, EP300, and ARID1A mutation) subtypes.[28] Here, we also investigate the role of these prognostic markers in the era of asparaginase-based treatment.

RESULTS

Patients

From March 16, 2016, to July 17, 2020, a total of 256 patients were randomly assigned to receive ESA with sandwiched radiotherapy (n = 128) or MESA with sandwiched radiotherapy (n = 128). Four patients withdrew their informed consent before the start of treatment, two patients did not receive assigned treatment, and two had an advanced stage. The remaining 248 patients received at least one cycle of assigned treatment (ESA [n = 125] or MESA [n = 123]) and made up the modified intention-to-treat (mITT) population. The per-protocol (PP) population included 225 patients (ESA [n = 114] or MESA [n = 111]) (Figure 1). The median follow-up time was 47 months (95% confidence interval [CI]: 41.4–52.5). The mean number of chemotherapy cycles received was 3.6 (standard deviation, 0.9) in the ESA arm and 3.5 (standard deviation, 0.9) in the MESA arm. Discontinuation of treatment was related to adverse events (8 [6.4%] patients with ESA, 11 [8.9%] patients with MESA), disease progression (6 [4.8%], 8 [6.5%]), patient's decision (6 [4.8%], 7 [5.7%]), and physician's decision (1 [0.8%], 1 [0.8%]). The demographic characteristics of the patients and the disease characteristics at baseline were well balanced between the two groups (Table 1).

Efficacy

In the mITT population, overall response occurred in 111 (88.8%; 95% CI, 81.9–93.7) patients in the ESA arm with sandwiched radiotherapy compared with 106 (86.2%; 95% CI, 78.8–91.7) patients in the MESA arm with sandwiched radiotherapy, with an absolute rate difference of 2.6% (95% CI, −5.6–10.9). The lower limit of 95% CI for the absolute rate difference was greater than the designated non-inferiority margin of −10%, thus meeting the non-inferiority criteria. One hundred (80.0%), 11 (8.8%), 3 (2.4%), and 7 (5.6%) patients in the ESA arm achieved complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), while the rates were 97 (78.9%), 9 (7.3%), 2 (1.6%), and 11 (8.9%) patients in the MESA arm, respectively. There were four patients in the ESA arm and four patients in the MESA arm who could not be evaluated because of treatment discontinuation due to adverse events. Median duration of response was not reached in either arm (Table 2).

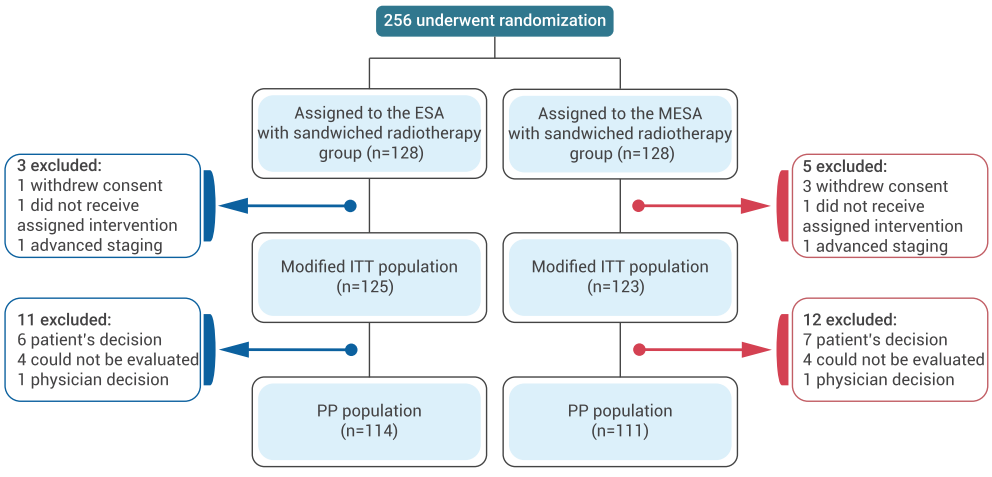


Figure 1. Patient flow diagram ESA, etoposide, dexamethasone and pegaspargase; MESA, methotrexate, etoposide, dexamethasone, and pegaspargase.

Table 1. Baseline characteristics of the modified intention-to-treat population

	ESA (n = 125)	MESA (n = 123)	p value
Sex, n (%)			0.122
Female	41 (32.8)	29 (23.6)	
Male	84 (67.2)	94 (76.4)	
Age, years			0.087
Median (range)	50 (14–70)	46 (15–70)	
>60, n (%)	26 (20.8)	15 (12.2)	
ECOG performance status score, n (%)			>0.999
<2	119 (95.2)	118 (95.9)	
2	6 (4.8)	5 (4.1)	
B symptoms, n (%)	52 (41.6)	43 (35.0)	0.298
Primary site, n (%)			>0.999
Nasal	125 (100)	123 (100)	
Ann Arbor stage, n (%)			0.794
I	77 (61.6)	78 (63.4)	
II	48 (38.4)	45 (36.6)	
Local tumor invasion, n (%)	50 (40.0)	49 (39.8)	>0.999
Elevated lactic dehydrogenase, n (%)	47 (37.6)	48 (39.0)	0.896
Positive Epstein-Barr virus DNA, n (%)	57 (45.6)	58 (47.2)	0.899
Ki-67 > 50%, n (%)	92 (73.6)	98 (79.7)	0.295
International Prognostic Index, n (%)			0.413
Low	112 (89.6)	115 (93.5)	
Intermediate-low	12 (9.6)	6 (4.9)	
Intermediate-high	1 (0.8)	2 (1.6)	
PINK-E, n (%)			0.824
Low	113 (90.4)	113 (91.9)	
Intermediate	12 (9.6)	10 (8.1)	
High	0	0	
CA, n (%)			0.935
I	44 (35.2)	43 (35.0)	
II	33 (26.4)	35 (28.4)	
III	48 (38.4)	45 (36.6)	
Nomogram-revised risk index, n (%)			0.345
Low	19 (15.2)	29 (23.6)	
Intermediate-low	54 (43.2)	43 (34.9)	
Intermediate-high	37 (29.6)	37 (30.1)	
High	15 (12.0)	14 (11.4)	

ECOG, Eastern Cooperative Oncology Group; ESA, etoposide, dexamethasone, and pegaspargase; MESA, methotrexate, etoposide, dexamethasone, and pegaspargase; PINK-E, prognostic index of natural killer lymphoma-Epstein-Barr virus; CA, Chinese Southwest Oncology Group and Asia Lymphoma Study Group ENKTL system.

Table 2. Efficacy outcomes

	ESA	MESA	Rate difference (95% CI)
Modified intention-to-treat population			
No. of patients	125	123	
Overall response, n (%; 95% CI)	111 (88.8; 81.9–93.7)	106 (86.2; 78.8–91.7)	2.6 (−5.6–10.9)
Complete response, n (%)	100 (80.0)	97 (78.9)	
Partial response, n (%)	11 (8.8)	9 (7.3)	
Stable disease, n (%)	3 (2.4)	2 (1.6)	
Progressive disease, n (%)	7 (5.6)	11 (8.9)	
Not evaluated, n (%)	4 (3.2)	4 (3.3)	
Duration of response (median [range])	NR (3.8–75.2)	NR (1.0–75.8)	
Relapse after complete response, n/N (%)	7/100 (7.0)	8/97 (8.2)	
Relapse after partial response, n/N (%)	2/11 (18.2)	0	
Per-protocol population			
No. of patients	114	111	
Overall response, n (%; 95% CI)	106 (93.0; 86.6–96.9)	98 (88.3; 80.8–93.6)	4.7 (−2.9–12.3)
Complete response, n (%)	96 (84.2)	92 (82.9)	
Partial response, n (%)	10 (8.8)	6 (5.4)	
Stable disease, n (%)	1 (0.9)	2 (1.8)	
Progressive disease, n (%)	7 (6.1)	11 (9.9)	
Duration of response (median [range])	NR (4.7–75.2)	NR (1.0–75.8)	
Relapse after complete response, n/N (%)	6/96 (6.3)	8/92 (8.7)	
Relapse after partial response, n/N (%)	2/10 (20.0)	0	
Sensitivity analysis			
No. of patients	125	123	
Overall response, n (%; 95% CI)	111 (88.8; 81.9–93.7)	110 (89.4; 82.6–94.3)	−0.6 (−8.4–7.1)

ESA, etoposide, dexamethasone and pegaspargase; MESA, methotrexate, etoposide, dexamethasone, and pegaspargase; NR, not reached.

The 2-year PFS rates were 85.5% (95% CI, 79.6–92.0) in the ESA arm and 79.7% (95% CI, 72.9–87.1) in the MESA arm (hazard ratio [HR] = 0.73; 95% CI, 0.41–1.30; p = 0.283), with an absolute rate difference of 5.8% (95% CI, −3.6–15.3; p value of non-inferiority: <0.001) (Figure 2A). The 2-year OS rates were 92.0% (95% CI, 87.3–96.9) in the ESA arm and 84.6% (95% CI, 78.4–91.2) in the MESA arm (HR = 0.66; 95% CI, 0.35–1.24; p = 0.192), with an absolute rate difference of 7.4% (95% CI, −0.5–15.4) (Figure 2B). Two (1.6%) patients in the ESA arm and three (2.4%) patients in the MESA arm had central nervous system progression during the treatment. Seventeen patients relapsed, the relapse rates for patients with CR were similar in both arms (Table 2). Fifteen out of 17 patients had systemic relapses and 2 had in-field relapses.

Results of the PP analysis and sensitivity analysis were consistent with the mITT analysis. The absolute rate differences of ORR (ESA vs. MESA) were 4.7% (95% CI, −2.9–12.3) in the PP analysis and −0.6% (95% CI, −8.4–7.1) in the sensitivity analysis (Table 2), thus meeting non-inferiority criteria. In the PP analysis, the 2-year PFS rates were 87.7% (95% CI, 81.9–94.0) in the ESA arm and 79.3% (95% CI, 72.1–87.2) in the MESA arm (HR = 0.62; 95% CI, 0.33–1.14; p = 0.122), with an absolute rate difference of 8.4% (95% CI, −1.2–18.1; p value of non-inferiority: <0.001) (Figure 2C). The 2-year OS rates were 94.7% (95% CI, 90.7–98.9) in the ESA arm and 84.7% (95% CI, 78.2–91.7) in the MESA arm (HR = 0.52; 95% CI, 0.26–1.06; p = 0.066), with an absolute rate difference of 10.0% (95% CI, 2.2–17.9) (Figure 2D).

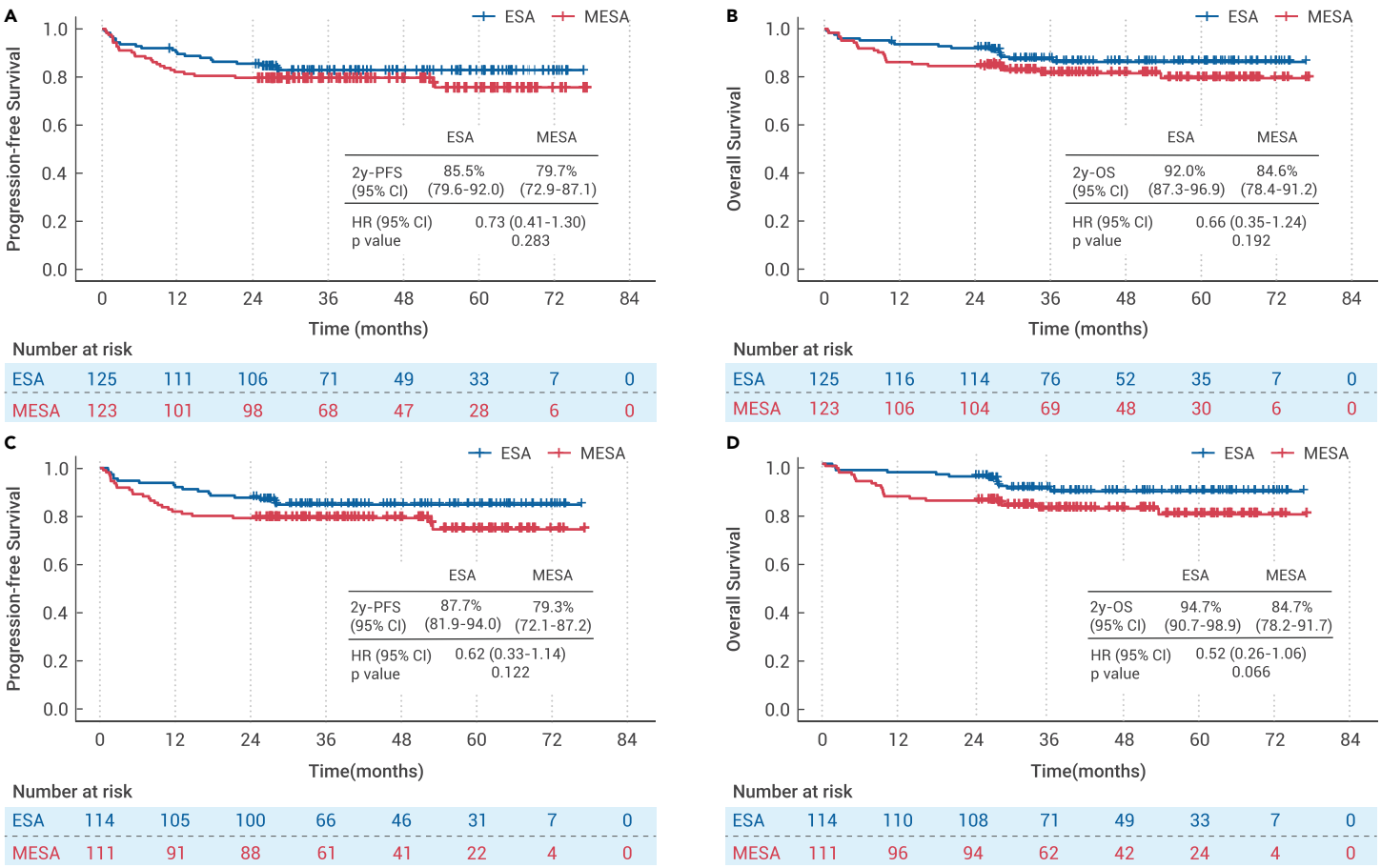


Figure 2. Kaplan-Meier of progression-free survival and overall survival (A) Progression-free survival in the modified intention-to-treat population. (B) Overall survival in the modified intention-to-treat population. (C) Progression-free survival in the per-protocol population. (D) Overall survival in the per-protocol population. HR, hazard ratio; ESA, etoposide, dexamethasone and pegaspargase; MESA, methotrexate, etoposide, dexamethasone, and pegaspargase.

In the sensitivity analysis for the patients enrolled after protocol amendment (n = 242) (supplemental data), both the ORR (final primary endpoint, absolute rate difference: 1.0% [95% CI, −7.4–9.4]) and 2-year PFS rate (original primary endpoint, absolute rate difference: 5.4% [95% CI, −4.5–15.2; p value of non-inferiority: 0.002]) met the non-inferiority criteria. The 2-year OS rate was also similar between the ESA arm and the MESA arm. Results of sensitivity analysis were consistent with the primary analysis.

Safety

Almost all patients had an adverse event of some grade (92.8% for ESA with sandwiched radiotherapy and 100% for MESA with sandwiched radiotherapy) (Table 3). The incidence of grade 3 or higher adverse events occurred in 42 (33.6%) patients in the ESA arm and 81 (65.9%) in the MESA arm. Adverse events of grade 3 or higher that occurred less frequently in the ESA arm when compared with the MESA arm included leukopenia (14.4% vs. 42.3%), neutropenia (29.6% vs. 60.2%), and mucositis related to chemotherapy (0% vs. 4.1%). Severe infection occurred in three patients (2.4%) in the ESA arm and seven patients (5.7%) in the MESA arm, which correlated with more frequent incidence of neutropenia in the MESA arm. Two patients discontinued treatment because of severe mucositis related to MESA. Grade 3 or higher adverse events that occurred at a similar rate between the two arms included anemia, thrombocytopenia, alanine aminotransferase/aspartate aminotransferase elevation, hyperbilirubinemia, nausea, and acute pancreatitis. Severe acute pancreatitis was observed in two patients in each treatment group. Three patients in the ESA arm died due to adverse events (one from acute pancreatitis, one from pneumonia, and one from sepsis). Five patients in the MESA arm died due to adverse events, including one from acute pancreatitis, two from pneumonia, and two from sepsis. Only 21 (16.8%) patients in the ESA arm had grade 2 alopecia, which was observed in 106 (86.2%) patients in the MESA arm.

Post hoc analysis

In post hoc analysis, the ORR was similar between the two arms in subgroups of both mITT and PP populations (Figure 3). In patients in the mITT population, when univariate analysis for PFS and OS was performed, no significant differences were observed by subgroups of sex, age, Eastern Cooperative Oncology Group (ECOG), Ann Arbor stage, local tumor invasion, lactic dehydrogenase, Ki-67, IPI, PINK-E, CA, NRI, molecular typing, or treatment arms. B symptoms and EBV DNA positivity predicted inferior OS (Figure S1). EBV DNA positivity was also an adverse factor for non-response (SD/PD at the final assessment) and PFS at 2 years (PFS24) (Figure S2). The estimated 5-year PFS and OS rates were 79.7% and 84.3% for NRI low-risk patients, 79.1% and 82.5% for NRI intermediate-/high-risk patients, respectively (PFS, p = 0.584; OS, p = 0.487).

DISCUSSION

Evidence from this first and largest prospective, multicenter, randomized controlled, phase III study showed that early-stage nasal NKTCL can be treated effectively with ESA combined with sandwiched radiotherapy. Similar ORR, 2-year PFS, and OS rates were found between ESA with sandwiched radiotherapy and MESA with sandwiched radiotherapy; however, ESA with sandwiched radiotherapy had notably lower toxicity rates and a non-intravenous design.

Compared with outcomes of other treatments for early-stage NKTCL, the ORR, 2-year PFS, and OS rates of the ESA arm with sandwiched radiotherapy were 88.8%, 85.5%, and 92.0%, respectively, which is comparable with methotrexate-containing SMILE, mSMILE, and MESA regimens,[2,5,6] platinum-containing DeVIC, VIPD, and VIDL (etoposide, ifosfamide, dexamethasone, L-asparaginase, cisplatin) regimens,[11,12,29] and gemcitabine-containing P-Gemox and GELOX regimens[13,15] (Table S1). The percentage of elderly patients, B symptoms, and risk distribution in this study were similar to other studies.[5,11,15] Of note, hematological toxicities of the ESA regimen were considerably less frequent than those of the MESA regimen, as reported in the gemcitabine-containing P-Gemox regimen.[15] Compared with other methotrexate-containing SMILE and mSMILE,

Table 3. Adverse events

	ESA (n = 125)	MESA (n = 123)	p value
Any grade, n (%)	116 (92.8)	123 (100)	0.003
Hematological, n (%)			
Leukopenia	87 (69.6)	93 (75.6)	0.321
Neutropenia	79 (63.2)	93 (75.6)	0.039
Anemia	52 (41.6)	53 (43.1)	0.898
Thrombocytopenia	23 (18.4)	36 (29.3)	0.053
Non-hematological, n (%)			
ALT/AST elevation	46 (36.8)	48 (39.0)	0.794
Hyperbilirubinemia	36 (28.8)	36 (29.3)	>0.999
Nausea	42 (33.6)	50 (40.7)	0.293
Mucositis related to chemotherapy	5 (4.0)	22 (17.9)	<0.001
Infection	25 (20.0)	29 (23.6)	0.540
Acute pancreatitis	4 (3.2)	2 (1.6)	0.684
Alopecia	110 (88.0)	123 (100)	<0.001
Alopecia (grade 2)	21 (16.8)	106 (86.2)	<0.001
Grade $\geq$ 3, n (%)	42 (33.6)	81 (65.9)	<0.001
Hematological, n (%)			
Leukopenia	18 (14.4)	52 (42.3)	<0.001
Neutropenia	37 (29.6)	74 (60.2)	<0.001
Anemia	1 (0.8)	3 (2.4)	0.368
Thrombocytopenia	3 (2.4)	7 (5.7)	0.214
Non-hematological, n (%)			
ALT/AST elevation	4 (3.2)	4 (3.3)	>0.999
Hyperbilirubinemia	0	0	>0.999
Nausea	1 (0.8)	6 (4.9)	0.065
Mucositis related to chemotherapy	0	5 (4.1)	0.029
Infection	3 (2.4)	7 (5.7)	0.214
Acute pancreatitis	2 (1.6)	2 (1.6)	>0.999

ESA, etoposide, dexamethasone and pegaspargase; MESA, methotrexate, etoposide, dexamethasone, and pegaspargase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

or platinum-containing DeVIC, VIPD, VIDL, and DDGP (dexamethasone, cisplatin, gemcitabine, and pegaspargase) regimens, the incidence of grade 3 or higher toxicities such as neutropenia (29.6% vs. 60%–93%), thrombocytopenia (2.4% vs. 11%–45%), and anemia (0.8% vs. 10%–35%) was lower in the ESA regimen.[2,5,11,12,29,30] Meanwhile, mucositis related to chemotherapy was less common and less severe in the ESA arm than in the MESA arm. Fewer patients suffered from greater than 50% hair loss in the ESA arm. Together, low-intensity ESA can maintain high rates of disease control in patients with early-stage nasal NKTCL with multiple benefits: (1) the use of only intramuscular and oral agents, designed for day-care unit and significantly shorter hospital days, (2) lower hematological and non-hematological toxicities for outpatient management, and (3) no leucovorin rescue, prophylactic hydration, and methotrexate concentration monitoring, making clinical practice more convenient and safer. Therefore, along with a recent phase II study suggesting that pegaspargase combined with concurrent radiotherapy was effective for newly diagnosed early-stage NKTCL,[31] the low-intensity asparaginase-based regimen can achieve high efficacy, which may be the backbone in a combination with sandwiched radiotherapy. Without methotrexate, incidence of central nervous system progression was similar in both the ESA and MESA arms, which is quite low and consistent with the data of early-stage NKTCL.[32,33]

Another key objective of this phase III trial is to maintain durable tumor control in poor-risk subgroups of early-stage NKTCL. Asparaginase, which selectively hydrolyzes the extra-cellular amino acid L-asparagine into L-aspartate, is the most commonly used anti-metabolic agent in treating NKTCL. NK/T lymphoma cells lack asparagine synthetase, are unable to carry out primary asparagine synthesis, and are thereby highly sensitive to asparaginase-induced cell death. No significant difference in efficacy and survival outcome was observed in the two arms divided by Ki-67 expression, an antigen of proliferating cells and an adverse prognostic factor in gemcitabine-treated patients.[34] Moreover, the MB subtype had similar outcomes with HEA and TSIM subtype, consistent with results from the previous study,[28] confirming the efficacy of anti-metabolic regimes with sandwiched radiotherapy in poor-risk subgroups of early-stage NKTCL. Etoposide, as a major cytotoxic agent, is widely applied in NKTCL, exerting cell-cycle-specific cytotoxicity and enhancing cell apoptotic death *in vitro* and *in vivo*.[35] Of note, a recent study provided new evidence that L-asparaginase may enhance the antitumor effect of etoposide by inhibiting c-Myc expression and the PI3K/Akt/mTOR signaling pathway in EBV-positive lymphoma cells.[36]

EBV is an important pathogenic mechanism,[37] and is strongly associated with disease progression in both early-stage and advanced-stage NKTCL.[24,38,39] The post hoc analysis confirmed that EBV DNA positivity was closely related to poor outcomes. Although etoposide in combination with dexamethasone may treat chronic active EBV infection[40] and EBV-associated hemophagocytic lymphohistiocytosis,[41,42] new therapeutic approaches are still needed. PD-L1 upregulation and epigenetic alterations are induced in EBV-associated cancers.[43,44] Immune checkpoint blockade and epigenetic modification agents have been proven effective for refractory/relapse NKTCL.[45–47] Meanwhile, a combination of anti-PD-1 antibody and P-Gemox also serves as a potential immunochemotherapy for advanced NKTCL.[48]

The strength of this trial lies in the fact that it is the first and largest randomized controlled, phase III clinical trial performed in early-stage nasal NKTCL, with the active participation of 27 Chinese Hospitals of M-HOPES in China. The limitation of this study pertains to the change of the primary endpoint from 2-year PFS rate to ORR, since we believed that accurate ORR of MESA with sandwiched radiotherapy obtained from external evidence of a phase II study on newly diagnosed early-stage NKTCL (NCT02825147)[6] provided solid evidence for sample size consideration. It is worth pointing out that, even as the key secondary endpoint, the 2-year PFS rate was met, which was similar between the ESA arm and the MESA arm (85.5% vs. 79.7%), with an absolute rate difference of 5.8% (95% CI, −3.6–15.3; p value of non-inferiority <0.001). Indeed, if the primary endpoint remained 2-year PFS rate, the power would be 90% based on the final sample size of 256 to detect a non-inferiority margin difference of −10%, which is greater than the power of 80% based on the initial sample size of 190. Moreover, results of the sensitivity analysis that excluded the 14 patients enrolled before the protocol amendment were consistent with those of the primary analysis.

In conclusion, ESA with sandwiched radiotherapy was an effective, low-intensity, non-intravenous regimen, and can be administered in a day-care unit or outpatient clinic as a promising first-line treatment in early-stage NKTCL.

MATERIALS AND METHODS

Study design and patients

This was a multicenter, randomized, phase III, non-inferiority[49] trial (NCT02631239) conducted at 27 centers (Table S2) in China within the M-HOPES network. Eligible patients were aged between 14 and 70 years; had newly diagnosed, histologically confirmed NKTCL by the World Health Organization classification 2008; an ECOG performance status of 0–2; Ann Arbor stage of IE-IIE, and a life expectancy of at least 6 months. The exclusion criteria are provided in supplemental methods.

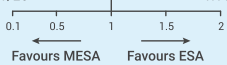
A steering committee and an independent data monitoring committee oversaw the trial. The study was approved by the institutional review boards of all centers. Informed consent forms were obtained from all patients in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Randomization and masking

After obtaining informed consent from all patients, the investigators accessed all patient data online at the M-HOPES data center (Shanghai Rui Jin Hospital, which collected all the

A

Subgroup	No. of events/No. of patients ESA	MESA	Relative risk for ORR (95%CI)	P interaction
All patients	111/121	106/119	1.03(0.95–1.13)	
Age				
≤60y	87/97	93/105	1.01(0.91–1.12)	1.00
>60y	24/24	13/14	1.08(0.91–1.08)	
Gender				
Male	75/80	80/90	1.06(0.96–1.17)	0.40
Female	36/41	26/29	0.98(0.81–1.21)	
ECOG				
<2	107/116	102/115	1.04(0.95–1.14)	1.00
2	4/5	4/4	0.80(0.38–1.65)	
B symptom				
Yes	43/50	35/40	0.98(0.83–1.19)	0.26
No	68/71	71/79	1.07(0.97–1.19)	
Ann Arbor stage				
I	66/75	68/76	0.98(0.87–1.11)	0.12
II	45/46	38/43	1.11(0.99–1.30)	
Local tumor invasion				
Yes	44/49	41/47	1.03(0.88–1.22)	0.90
No	67/72	65/72	1.03(0.93–1.16)	
Elevated lactic dehydrogenase				
Yes	43/46	39/45	1.08(0.93–1.28)	0.40
No	68/75	67/74	1.00(0.89–1.12)	
EBVDNA				
Positive	48/54	47/56	1.06(0.90–1.25)	0.97
Negative	63/67	59/63	1.00(0.91–1.12)	
Ki–67				
≤50%	28/32	23/25	0.95(0.77–1.19)	0.30
>50%	83/89	83/94	1.06(0.96–1.17)	
IPI				
Low	99/109	100/112	1.02(0.93–1.12)	1.00
Intermediate–low	11/11	5/6	1.20(0.86–1.30)	
Intermediate–high	1/1	1/1	1	
PINKE				
Low	101/111	98/110	1.02(0.93–1.12)	1.00
Intermediate	10/10	8/9	1.13(0.80–1.54)	
CA				
I	38/42	40/43	0.97(0.83–1.13)	0.16
II	28/33	28/33	1.00(0.79–1.26)	
III	45/46	38/43	1.11(0.99–1.30)	
NRI				
Low	17/18	28/29	0.98(0.77–1.15)	0.16
Intermediate–low	45/53	35/42	1.02(0.85–1.25)	
Intermediate–high	35/36	31/35	1.10(0.95–1.32)	
High	14/14	12/13	1.08(0.84–1.21)	
Molecular type				
MB	6/9	8/10	0.83(0.42–1.50)	0.33
HEA	12/12	12/14	1.17(0.87–1.31)	
TSIM	25/28	21/26	1.11(0.87–1.46)	



B

Subgroup	No. of events/No. of patients ESA	MESA	Relative risk for ORR (95%CI)	P interaction
All patients	106/114	98/111	1.05(0.97–1.16)	
Age				
≤60y	83/91	87/99	1.04(0.94–1.15)	1.00
>60y	23/23	11/12	1.09(0.93–1.09)	
Gender				
Male	71/75	75/85	1.07(0.97–1.18)	0.47
Female	35/39	23/26	1.01(0.84–1.28)	
ECOG				
<2	102/110	95/108	1.05(0.96–1.16)	1.00
2	4/4	3/3	1	
B symptom				
Yes	41/46	34/39	1.02(0.86–1.24)	0.41
No	65/68	64/72	1.08(0.97–1.21)	
Ann Arbor stage				
I	65/72	63/71	1.02(0.90–1.15)	0.20
II	41/42	35/40	1.12(0.98–1.33)	
Local tumor invasion				
Yes	40/44	37/43	1.06(0.90–1.27)	0.87
No	66/70	61/68	1.05(0.95–1.18)	
Elevated lactic dehydrogenase				
Yes	41/44	38/44	1.08(0.93–1.28)	0.71
No	65/70	60/67	1.04(0.93–1.17)	
EBVDNA				
Positive	46/51	45/54	1.08(0.92–1.28)	0.84
Negative	60/63	53/57	1.02(0.92–1.15)	
Ki–67				
≤50%	25/28	22/24	0.97(0.78–1.22)	0.31
>50%	81/86	76/87	1.08(0.98–1.21)	
IPI				
Low	94/102	93/105	1.04(0.95–1.15)	1.00
Intermediate–low	11/11	4/5	1.25(0.89–1.26)	
Intermediate–high	1/1	1/1	1	
PINKE				
Low	96/104	90/102	1.05(0.95–1.16)	1.00
Intermediate	10/10	8/9	1.13(0.80–1.54)	
CA				
I	38/41	36/39	1.00(0.86–1.18)	0.27
II	27/31	27/32	1.03(0.82–1.30)	
III	41/42	35/40	1.12(0.98–1.33)	
NRI				
Low	17/18	25/26	0.98(0.77–1.18)	0.22
Intermediate–low	45/51	34/41	1.06(0.89–1.30)	
Intermediate–high	31/32	28/32	1.11(0.95–1.35)	
High	13/13	11/12	1.09(0.83–1.28)	
Molecular type				
MB	6/9	8/10	0.83(0.42–1.50)	0.36
HEA	12/12	11/13	1.18(0.88–1.42)	
TSIM	22/25	20/25	1.10(0.84–1.48)	

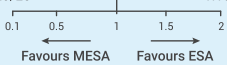


Figure 3. Subgroup analysis for overall response rate (A) Subgroup analysis for overall response rate (ORR) in the modified intention-to-treat population (excluded eight patients without assessments). (B) Subgroup analysis for ORR in the per-protocol population. ECOG, Eastern Cooperative Oncology Group; ESA, etoposide, dexamethasone, and pegaspargase; MESA, methotrexate, etoposide, dexamethasone, and pegaspargase; IPI, International Prognostic Index; PINK-E, prognostic index of natural killer lymphoma-Epstein-Barr virus; CA, Chinese Southwest Oncology Group and Asia Lymphoma Study Group ENKTL system; NRI, nomogram-revised risk index.

data) for patient registration and central randomization. We used computer-assisted permuted-block randomization with a block size of four and allocation ratio of 1:1, which was blinded to investigators and patients. The principal investigators at each center enrolled the patients and assigned them in terms of the randomization results. A statistician (H.H.) at the M-HOPES data center supervised the randomization procedure. Investigators and patients were not masked to treatment assignment because of the significant difference in the administration methods of the two regimens.

Treatments

Eligible patients were randomly assigned to receive either ESA with sandwiched radiotherapy or MESA with sandwiched radiotherapy. Patients treated with ESA received pegaspargase 2,500 IU/m^2 intramuscularly on day 1, etoposide 200 mg orally on days 2–4, and dexamethasone 40 mg orally on days 2–4. Patients treated with MESA received methotrexate 1 g/m^2 intravenously over 24 h on day 1, etoposide 200 mg orally on days 2–4, dexamethasone 40 mg orally on days 2–4, and pegaspargase 2,500 IU/m^2 intramuscularly on day 5. Leucovorin was given at a dose of 50 mg 12 h after the end of methotrexate every 6 h as rescue therapy. The concentration of methotrexate was monitored every day from day 2 until the concentration level was lower than 100 nmol/L.

ESA or MESA was repeated every 21 days with a total of 4 cycles. Interim assessment was performed 21 days after 2 cycles. Patients with CR, PR, and SD then received radiotherapy, while those with PD discontinued study treatment. Radiotherapy was sandwiched 21–35 days after 2 cycles for the involved local focus at a dose of 50 Gy. ESA or MESA was restarted 21–35 days after radiotherapy. The final assessment was conducted 21 days after the end of 4 cycles. Granulocyte-colony stimulating factor prophylaxis was not planned in the study until absolute neutrophil count was less than 1.0 × 10^9 cells/L. Radiotherapy was performed following the guidelines of the International Lymphoma Radiation Oncology Group.[50] Details regarding radiotherapy and discontinuation of study treatment are provided in supplemental methods.

Pretreatment staging procedures included physical examination, bone marrow aspirate, and core biopsy, ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT), or contrast-enhanced CT of head, neck, thorax, abdomen, and pelvis, and enhanced magnetic resonance imaging (MRI) of the head and neck. Patients were staged according to the Ann Arbor staging system. PET-CT or CT was repeated for interim and final assessment. Treatment response was assessed according to revised response criteria for malignant lymphoma.[51] To prevent possible biases caused by unmasking, a central review of the PET-CT, CT, and MRI was conducted. Ninety-eight percent of patients were staged with PET-CT and 2% with CT, 80% of patients were assessed with PET-CT and 20% with CT. No significant difference in stage and response was observed between patients analyzed with PET-CT vs. CT. Nasal MRI was performed for local tumor invasion evaluation before treatment and for involved field confirmation[50,52] before radiotherapy. Local tumor invasion was defined as bony invasion or perforation or invasion of the skin or paranasal extension, as reported previously.[53] Disease recurrence was assessed through physical examination and enhanced CT of head, neck, thorax, abdomen, and pelvis, which were repeated every 3 months thereafter until the end of 2 years.

Endpoints

The primary endpoint was ORR, calculated as the proportion of patients with a response at the end of treatment (CR and PR). The secondary endpoints were 2-year PFS rate (defined as the proportion of patients with the time longer than 2 years from randomization to first disease progression, relapse, or death from any cause), 2-year OS rate (defined as the proportion of patients with the time longer than 2 years from randomization to death from any cause), and toxicity, assessed according to the National Cancer Institute Common Terminology Criteria of Adverse Events, v.4.0. We use PFS at 2 years (PFS24) as an efficacy endpoint, which has been proven to significantly stratify subsequent outcomes in patients with NKTCL.[54]

Subgroups

IPI,[23] PINK-E,[24] CA,[25] and NRI[26] were calculated. The EBV DNA load was measured at the time of diagnosis. Real-time fluorescent polymerase chain reaction (PCR) was used to detect circulating EBV DNA in the plasma using the Detection Kit for Epstein-Barr virus Nucleic Acid (PCR-Fluorescence Probing) (DaAnGene, Guangzhou, China) at all institutions. Any detectable load of EBV DNA was defined as positive. Pathological data were reviewed by the pathology panel of M-HOPES. Immunohistochemical slides for Ki-67 were reviewed by three designated pathologists (Chaofu Wang, B.O., and H.Y.). The expression of Ki-67 was graded from 10% to 90% in increments of 10%, according to the proportion of positive cells. The pathologists who performed cell counts were blinded to the clinical characteristics and survival status. A total of 100 patients had molecular subtypes, of whom 67 had been reported in our previous study,[28] the other 33 were analyzed by targeted sequencing. Targeted sequencing was performed with a mutation detection panel (TP53, MGA, JAK-STAT pathway, EP300, ARID1A, etc.) for lymphoma obtained from YuanQi Biomed (Shanghai, China) on the MiniSeq platform (Illumina).

Statistical analysis

The sample size was adjusted from 190 to 256 in the early phase of the trial, in which 14 (5.5%) patients were enrolled at the time. The reason was that an external phase II study on MESA (NCT02825147)[6] indicated that the ORR of MESA with sandwiched radiotherapy for newly diagnosed early-stage NKTCL was 92%, thus providing solid evidence of ORR for sample size calculation. The primary endpoint was changed from 2-year PFS rate to ORR following a discussion involving all principal investigators in this investigator-initiated trial. The original primary endpoint, 2-year PFS rate, was kept as the key secondary endpoint. Assuming that estimated ORR of the ESA arm was the same as the MESA arm (with a 10% drop-out and loss-to-follow-up rate and 80% power to detect a 10% non-inferiority margin at a one-sided alpha level of 2.5%), the sample size was increased to 256 patients needed for randomization. The amendment (Table S3) was approved by the Ethics Committee and received continuous funding from Multicenter Clinical Research Project by Shanghai Jiao Tong University School of Medicine (DLY201601).

Non-inferiority could be claimed if the lower limit of the 95% CI for absolute rate difference of ORR (final primary endpoint) in the ESA arm vs. the MESA arm (calculated using approximate normal distribution method) was greater than −10%. The 2-year PFS rates (original primary endpoint) were compared by the naive method in Klein et al.[55] Efficacy analyses were based on the mITT population and PP population, the former included all patients who underwent randomization and had received at least one cycle of trial treatment, and the latter included all the patients who followed the protocol with available primary outcome data. Safety analyses were performed on the mITT population. Regarding the sensitivity analysis, missing primary outcome data were replaced by "treatment failure" in the ESA arm and "success" in the MESA arm. The subgroup (stratification by prognostic models and biomarkers in the mITT population) analysis was presented as post hoc analysis. Moreover, sensitivity analysis for the patients enrolled after protocol amendment (n = 242) is presented in supplemental data.

Descriptive statistics were used to summarize the characteristics of the patients. Fisher's exact test was applied to compare categorical variables, including adverse events between groups. Survival estimates were calculated using Kaplan-Meier method and survival curves were compared using the log rank test. HR and associated 95% CI were estimated using univariate Cox proportional hazards models. Subgroup analysis on efficacy was estimated with relative risk and associated 95% CI using Koopman asymptotic score method. A two-sided p value of <0.05 was considered significant. Data analyses and figure generation were performed using R 3.5.1, SPSS v.23.0 or GraphPad Prism 9.

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AUTHOR CONTRIBUTIONS

Conceptualization, W.Z., Saijuan Chen, and P.X.; formal analysis, Huijuan Zhong, Shu Cheng, Xi Zhang, B.X., Jiayi Chen, X.J., Jie Xiong, W.Z., Saijuan Chen, and P.X.; investigation, Huijuan Zhong, Shu Cheng, Xi Zhang, B.X., Jiayi Chen, X.J., Jie Xiong, Y.H., Guohui Cui, J.W., W.Q., X.H., M.H., F.Y., X.W., Y.S., J.H., Yuanhua Liu, X.M., F.L., Chongyang Wu, Junmin Chen, L.Y., O.B., Jingyan Xu, Z.Z., L.L., Xin Zhou, L.H., Y.T., T.N., D.W., Hao Zhang, Chaofu Wang, B.O., H.Y., Q.S., Gang Cai, B.L., J.L., Z.L., R.X., Luqun Wang, Y.J., Yanyan Liu, Xiaoyun Zheng, Li Wang, W.Z., Saijuan Chen, and P.X.; writing – original draft, Huijuan Zhong, Shu Cheng, W.Z., Saijuan Chen, and P.X.; writing – review & editing, Huijuan Zhong, Shu Cheng, Xi Zhang, B.X., Jiayi Chen, X.J., Jie Xiong, Y.H., Guohui Cui, J.W., W.Q., X.H., M.H., F.Y., X.W., Y.S., J.H., Yuanhua Liu, X.M., F.L., Chongyang Wu, Junmin Chen, L.Y., O.B., Jingyan Xu, Z.Z., L.L., Xin Zhou, L.H., Y.T., T.N., D.W., Hao Zhang, Chaofu Wang, B.O., H.Y., Q.S., Gang Cai, B.L., J.L., Z.L., R.X., Luqun Wang, Y.J., Yanyan Liu, Xiaoyun Zheng, Li Wang, H.H., W.Z., Saijuan Chen, and P.X.; methodology, H.H., W.Z., Saijuan Chen, and P.X.; supervision, H.H., W.Z., Saijuan Chen, and P.X.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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SUPPLEMENTAL INFORMATION

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