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Clinical Trial Results

A Phase II Study of Ifosfamide, Methotrexate, Etoposide, and Prednisolone for Previously Untreated Stage I/II Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type: A Multicenter Trial of the Korean Cancer Study Group

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Author Summary

Abstract

Background. Combination chemotherapy consisting of ifosfamide, methotrexate, etoposide, and prednisolone (IMEP) was active as first-line and second-line treatment for extranodal natural killer/T-cell lymphoma (NTCL).

Methods. Forty-four patients with chemo-naïve stage I/II NTCL were enrolled in a prospective, multicenter, phase II study and received six cycles of IMEP (ifosfamide 1.5 g/m^2 on days 1–3; methotrexate 30 mg/m^2 on days 3 and 10; etoposide 100 mg/m^2 on days 1–3; and prednisolone 60 mg/m^2 per day on days 1–5) followed by involved field radiotherapy (IFRT).

Results. Overall response rates were 73% (complete remission [CR] in 11 of 41 evaluable patients [27%]) after IMEP chemotherapy and 78% (CR 18 of 27 evaluable patients [67%]) after IMEP followed by IFRT. Neutropenia and thrombocytopenia were documented in 33 patients (75%) and 7 patients (16%), respectively. Only 8 patients (18%) experienced febrile neutropenia. Three-year progression-free survival (PFS) and overall survival (OS) were 66% and 56%, respectively. High Ki-67 (≥70%) and Ann Arbor stage II independently reduced PFS ($p = .004$) and OS ($p = .001$), respectively.

Conclusion. Due to the high rate of progression during IMEP chemotherapy, IFRT needs to be introduced earlier. Moreover, active chemotherapy including an L-asparaginase-based regimen should be use to reduce systemic treatment failure in stage I/II NTCL. ***The Oncologist*** 2014;19:1129–1130

Discussion

Our trial was based on the scheme of chemotherapy followed by radiotherapy (sequential). However, other trials used concurrent chemoradiation followed by ifosfamide plus etoposide-based combination chemotherapy [4, 5]. Although the designs of two concurrent chemoradiation trials [4, 5] were very similar, large differences were observed regarding survival data. We chose the JCOG0211 study [4] for comparison with our data because the other study provided limited information on patterns of failure due to short-term follow-up [5]. Our study showed a relatively higher locoregional failure rate (18% vs. 4%) but lower rates of systemic failure than in the JCOG0211 study (14% vs. 33%). These data suggest that upfront chemoradiation is favorable for locoregional control, but it is unfavorable for systemic failure in stage I/II natural killer/T-cell lymphoma (NTCL). Extended chemotherapy of up to six cycles in our study might be a factor for the high incidence of locoregional failure. Better coordination of the sequence between chemotherapy and radiotherapy might reduce both locoregional and systemic failures. A reduced number of cycles of chemotherapy, for example, followed by involved field radiotherapy (IFRT), concurrent chemoradiation, or sandwich radiotherapy during chemotherapy may be more efficacious for untreated stage I/II NTCL. Considering that the planned doses were reduced for

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Table 1. Treatment outcomes after completion of each treatment

Response	2nd cycle ($n = 41$)	4th cycle ($n = 36$)	6th cycle ($n = 34$)	IFRT ($n = 27$)
CR	7 (17)	9 (25)	9 (26)	18 (67)
PR	18 (44)	15 (42)	16 (47)	3 (11)
SD	14 (34)	9 (25)	6 (18)	2 (7)
PD	2 (5)	3 (8)	3 (9)	4 (15)
ORR, %	61	67	73	78

Data are shown as *n* (%) unless specified otherwise.
Abbreviations: CR, complete response; IFRT, involved field radiotherapy; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

11 patients (25%) in 35 of 229 cycles (15%) in our study, the ifosfamide, methotrexate, etoposide, and prednisolone (IMEP) regimen was safe and relatively well tolerated.

Recently, regimens based on L-asparaginase (L-asp) have shown promising efficacy in patients with refractory/relapsed or newly diagnosed advanced NTCL (overall response rate of 78%–81% and complete response [CR] of 45%–66%) [6–8] and with untreated stage I/II NTCL (CR of 90%, 2-year overall survival [OS] of 88%, and 2-year progress-free survival [PFS] of 90%) [10]. Furthermore, gemcitabine, which is active against NTCL [11], plus oxaliplatin and L-asp followed by IFRT resulted in a CR rate of 74% and 2-year PFS of 86% in stage I/II upper aerodigestive tract NTCL [12]. Furthermore, sandwich L-asp, vincristine, and prednisolone chemotherapy with IFRT showed a promising outcome (2-year OS of 88.5% and 2-year PFS of 80.6%) [13]. Consequently, more active L-asp-based regimens should be introduced in patients with stage I/II NTCL.

The IMEP regimen is effective and safe in patients with stage I/II NTCL before the introduction of L-asp, and IMEP followed by IFRT resulted in improved treatment outcomes in localized NTCL (Table 1). However, a short-course of the L-asp-based regimen followed by IFRT or concurrent or sandwich radiation with an L-asp-based regimen should be introduced in patients with untreated stage I/II NTCL.

Author disclosures and references available online.

For Further Reading:
Xi Li, Xiaobo Tian, Bo Zhang et al. Polymorphisms in MicroRNA-Related Genes Are Associated With Survival of Patients With T-Cell Lymphoma. ***The Oncologist*** 2014;19:243–249.

Implications for Practice:
Besides the characteristics of a tumor itself, genetic polymorphisms in relevant genes are considered to be important in influencing the clinical outcomes of patients. Previous studies have suggested that microRNAs are associated with survival of patients with T-cell lymphoma (TCL); therefore, we performed association analyses of 13 carefully selected polymorphisms in microRNA-related genes. The results suggested that four polymorphisms in microRNA-related genes are associated with survival of patients with TCL. These polymorphisms may be used to predict the survival of patients with TCL individually or collectively. Although the results are exploratory, they provide clues to warrant further investigation.

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