

RESEARCH ARTICLE

Ki-67 Can Predict the Response to the Gemcitabine, Oxaliplatin And L-asparaginase Regimen (GELOX) and Prognosis in Patients with Nasal Natural Killer/T-cell Lymphoma

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Abstract

GELOX (gemcitabine, oxaliplatin and L-asparaginase) regimen showed an impressive result in our previous study, but the effect of this new regimen is still dissatisfying for some patients, so it is necessary to identify which patients will benefit from this regimen. A total of fifty-one cases with nasal natural killer/T-cell lymphoma receiving initial GELOX chemotherapy were enrolled in this study. The ki-67 expression detected by immunohistochemistry (IHC) in the specimens ranged from 10% to 90%, with a median value of 70%, so cases higher than the median value ($\geq 70\%$) were defined as high ki-67 expression, and the others were designated as low ki-67 expression. The response rate had no statistical difference between low ki-67 expression group and high ki-67 expression group ($P=0.291$) though the value in the former group was relatively high. After a median follow-up of 18.03 months, the 3-year progression-free survival (PFS) for patients with low ki-67 expression was significantly higher than those with high ki-67 expression (83.8% vs. 47.9%, $P=0.038$). In the stage I/II subgroup, 3-year PFS and overall survival (OS) were statistically higher in the patients with low ki-67 expression than those with high ki-67 expression. Multivariate analysis revealed high ki-67 expression was an independent prognostic factor for PFS. These results suggest that low ki-67 expression can predict a good response of GELOX in these patients, and the combination of ki-67 expression and early stage is helpful to identify an excellent prognosis subgroup from patients receiving GELOX in this disease.

Keywords: Ki-67 - gemcitabine - oxaliplatin - l-asparaginase - natural killer/T-cell lymphoma

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Introduction

Extranodal natural killer (NK)/T-cell lymphoma (ENKTL) is a relatively common disease in China (Liu et al., 2011). It tends to be resistant to conventional chemotherapy, such as CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone). L-asparaginase (L-asp), showing an excellent activity in acute lymphoblastic leukemia, was firstly reported to have the antitumor role in relapsed or refractory ENKTL (Yong et al., 2000). Then, L-asp induced durable remission in a 60-year-old Japanese woman with relapsed nasal ENKTL after autologous peripheral blood stem cell transplantation (Nagafuji et al., 2001). Thereafter, more studies confirmed the role of L-asp in the salvage chemotherapy of ENKTL (Jaccard et al., 2009; Jaccard et al., 2011; Wen et al., 2014). Based on the low toxicity and good effect of gemcitabine and oxaliplatin in B-cell and T-cell lymphoma (Oki et al., 2005; El Gnaoui et al., 2007; Zinzani et al., 2010), we evaluated the effect of GELOX in the first-

line chemotherapy of stage I/II ENKTL in a prospective study (Wang et al., 2013). This new regimen produced an impressive result that the complete response (CR) rate was as high as 55.6% after 2-cycle chemotherapy. But the effect of GELOX is still dissatisfying in some patients. So it is necessary to identify which patients will benefit from the GELOX regimen.

Ki-67 is a nuclear protein synthesized as a cell begins proliferation, and it is expressed in the proliferation-associated phase of the cell cycle (Schluter et al., 1993). The ki-67 proliferation index was taken as a quantitative indicator of unfavorable outcome in B-cell lymphoma, such as diffuse large B cell lymphoma (DLBCL) (Grogan et al., 1988; Li et al., 2012; He et al., 2014), mantle cell lymphoma (MCL) (Argatoff et al., 1997; Raty et al., 2002; Katzenberger et al., 2006). Furthermore, similar prognostic significances of the ki-67 index in T-cell lymphoma and ENKTL were also observed in some studies (Went et al., 2006; Kim et al., 2007; Yasuda et al., 2009). However, the predictive value of ki-67 has never

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been studied in patients with ENKTL receiving GELOX regimen. Therefore, we performed this study to explore whether ki-67 index can predict the treatment response of GELOX regimen and prognosis in ENKTL.

Materials and Methods

Eligibility criteria

This study used a retrospective cohort study design. Patients with nasal ENKTL who experienced the initial GELOX regimen in Sun Yat-Sen University Cancer Center between June 2008 and August 2013 were systematically reviewed. All eligible cases were selected consecutively. The inclusion criteria in this study were as follows: (1) pathologically confirmed diagnosis of ENKTL based on the World Health Organization classification; (2) no previous anti-tumor treatment; (3) available ki-67 index detected by IHC at diagnosis; (4) complete follow-up results; (5) without prior or concomitant malignant tumors; (6) without co-existing serious medical problems. This study was approved by the Institutional Review Board of Sun Yat-Sen University Cancer Center, and an informed consent for the collection of medical information was provided in the first visit of all patients. Additionally, this study was conducted in accordance with the Helsinki Declaration. All enrolled patients were staged according to the Ann Arbor staging system based on history, physical examination, whole body positron emission tomography/computed tomography (PET/CT) scans, CT scans or magnetic resonance imaging of the involved organs of the head and neck and CT scans of the chest, abdomen and pelvis.

Treatment

Patients received at least one cycle and a maximum of six cycles of primary GELOX chemotherapy (Wang et al., 2013). After the first-line chemotherapy, patients with early stage were referred to radiation therapy. Involved-field radiotherapy of 50-60 Gy was delivered in daily fractions of 1.8-2.0 Gy with five fractions each week. Whether radiotherapy was given to patients with advanced disease was at the oncologists' discretion. Tumor response was assessed after every 1-2 cycles of chemotherapy or before and after radiotherapy according to the standardized response criteria for non-Hodgkin lymphomas (NHL) (Cheson et al., 1999). After the completion of treatment, patients were followed by their ambulatory oncologists on a regular interval.

IHC for ki-67

IHC staining for ki-67 was performed through the anti-ki-67 mouse monoclonal antibody (Invitrogen, Carlsbad, CA, USA) as described previously (Jiang et al., 2014). The tissues were deparaffinized with xylene, rehydrated with a ranked series of alcohols, quenched the endogenous peroxidase with 3% hydrogen peroxide, soaked in 10mM citrate buffer (pH 6.0) in a steam pressure cooker for antigen retrieval, blocked with 10% goat serum for 30 min, and then incubated with primary antibody at a 1:100 dilution at 4°C overnight. The slides were removed and washed with phosphate buffer saline (PBS) and distilled

water. Then the secondary antibody was applied for 30 min. Slides were again washed with PBS and color was developed by 5-min incubation in diaminobezidine solution. Slides were counterstained with hematoxylin.

The highest ki-67 protein expression area on a thorough high-power scanning of the tissue section was taken for analysis, and at least five hundreds tumor cells were counted. The ki-67 expression level was determined by the number of positive cells expressing nuclear ki-67 among the total number of tumor cells in the high-power field ($\times 400$). Slides were reviewed by pathologists (Zhang and Liu) in a single laboratory, and all interpretations of IHC were performed without knowledge of clinical outcome. An average of both values was used for further analysis.

Statistical analysis

Simple descriptive statistics were used to report general clinical information. The correlation of ki-67 expression with clinical variables was evaluated using the chi-squared test or Fisher's exact test. PFS was measured from the time of diagnosis until disease progression, relapse, or death from any cause or until the last follow-up. OS was measured from the time of diagnosis until death from any cause. PFS and OS were estimated using the Kaplan-Meier method, and compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard model. All statistical analyses were performed using PASW Statistics 18.0 software (Apache Software Foundation, Forest Hill, Md). A two-sided $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of fifty-one cases formed the population of the study. The clinical characteristics of the enrolled patients were presented in Table 1. The median age was forty-two years old with a male-female ratio 2.4:1. Most patients had good performance status (Eastern Cooperative Oncology Group 0-1). B symptoms were presented in 43.1% of the patients, and lactate dehydrogenase (LDH) was elevated in 39.2% of the patients. Nine patients (17.6%) initially presented as stage III or IV. 15.7% of the patients had unfavorable prognosis according to the International Prognostic Index (IPI). However, 43.1% of the patients showed unfavorable prognosis based on Korean Prognostic Index (KPI).

Ki-67 expression

The ki-67 index in the specimens from the fifty-one patients ranged from 10% to 90%, with a median value of 70%, which was designated as a cut-off value. Thus cases higher than the median value ($\geq 70\%$) were defined as high ki-67 expression, and less than the median value ($< 70\%$) were designated as low ki-67 expression for the further analysis (Figure 1). The ki-67 expressions had no obvious differences in nearly all clinical factors except the lymphocyte counting (Table 1). Patients with a lower lymphocyte counting (less than normal range) had a higher ki-67 expression ($P=0.036$).

Response to treatment and survival analysis

The average cycle number of GELOX chemotherapy in this cohort was 3.63 (range 1-6), and the median cycle number was 3. There were 20 (39.2%) patients in CR, 20 (39.2%) patients in partial remission (PR), 8 (15.7%) patients in stable disease (SD), and 3 (5.9%) patients in progressive disease (PD), respectively. The ki-67 index was no less than 80% in those who experienced PD after initial GELOX chemotherapy. The response rate had no statistical difference between low ki-67 expression group and high ki-67 expression group ($P=0.291$) though the value in the former group was relatively high.

After a median follow-up of 18.03 months (1.2-57.6 months), the 3-year PFS for all patients was 68.1% (95% CI 68.0-75.5%), and the 3-year OS was 76.9% (95% CI 69.0-84.8%) (Figure 2). The 3-year PFS for patients with low ki-67 expression was 83.8% (95% CI 76.4-91.2%), which was significantly higher than 47.9% (35.2-60.6%) for those with high ki-67 expression ($P=0.038$). There was no statistical difference on the 3-year OS (low ki-67 expression vs. high ki-67 expression subgroup: 85.4% vs. 70.4%, $P=0.282$) (Figure 3). Staging also played an important role on the survival without surprise. The median PFS was significantly longer in the patients with early stage than those with advanced stage (25.5 months

vs. 16.0 months, $P<0.001$). With respect to the median OS, it also had a statistical difference between early stage and advanced stage subgroup (26.3 months vs. 22.37 months, $P=0.002$).

In the stage I/II subgroup, no progression occurred in patients with low ki-67 expression, however, seven patients experienced PD in patients with high ki-67 expression (3-year PFS: 100% vs. 57%, $P=0.003$). No patients in the early stage died in the low ki-67 expression group, but five patients with high ki-67 expression in the early stage died of ENKTL (3-year OS: 100% vs. 76.1%, $P=0.029$) (Figure 4). Univariate analysis involving other clinical factors revealed that no factor could be predictive of PFS or OS in this subgroup except the age (Table 2). Young age (≤ 60 years) could predict longer PFS ($P=0.021$), but not OS ($P=0.145$).

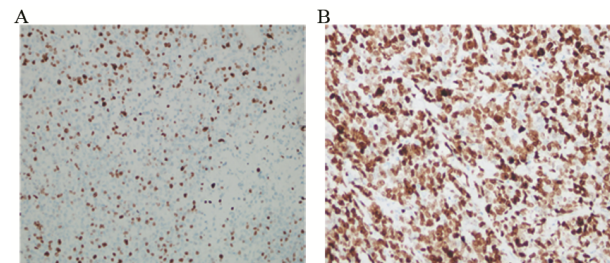
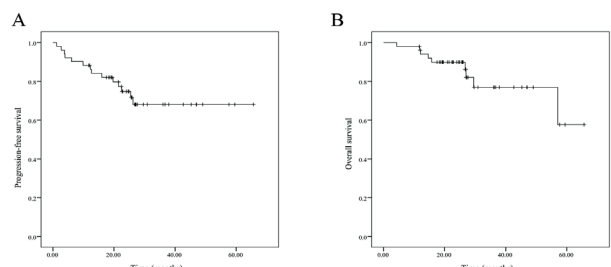
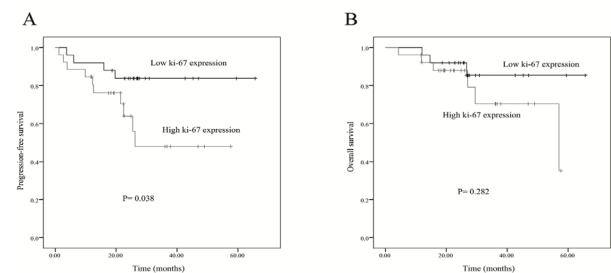
Multivariate analysis

The above clinical factors included in the univariate analysis were also involved in the multivariate analysis for all patients ($n=51$). Multivariate analysis revealed that

Table 1. Clinical Characteristics at Baseline According to Different ki-67 Expression

Characteristics	No.			P value
	Total	Ki-67<70%	Ki-67≥70%	
Gender				0.148
Male	36	20	16	
Female	15	5	10	
Age, y				0.643
Median (range)	42(16-72)			
≤60	44	21	23	
>60	7	4	3	
ECOG performance status				0.629
0	18	8	10	
1-2	33	17	16	
Ann Arbor stage				1.000
I	27	13	14	
II	15	7	8	
III-IV	9	5	4	
B symptoms				0.313
Present	22	9	13	
Absent	29	16	13	
Serum LDH				0.301
Normal	31	17	14	
>normal	20	8	12	
IPI				0.478
0-1	43	22	21	
2-5	8	3	5	
KPI				0.628
0	12	7	5	
1	17	9	8	
2	10	3	7	
3-4	12	6	6	
Lymphocyte counting				0.036
Normal	25	16	9	
<normal	26	9	17	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, international prognostic index; KPI, Korean prognostic index

**Figure 1. Representative of High and Low ki-67 expression (x400). A: The ki-67 index was 40%. B: The ki-67 index was 90%****Figure 2. The Survival Analysis for all Patients (n=51). A: The 3-year progression-free survival was 68.1% in this cohort. B: The 3-year overall survival was 76.9% in this cohort****Figure 3. The Survival Analysis for All Patients (n=51) According to Different ki-67 Expression. A: The 3-year progression-free survival for patients with low ki-67 expression was statistically higher than those with high ki-67 expression (83.8% vs. 47.9%). B: There was no statistical difference on the 3-year overall survival between these two groups (85.4% vs. 70.4%)**

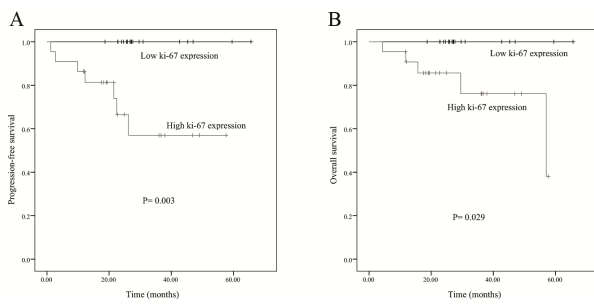


Figure 4. The Survival Analysis for Patients with Early Stage (n=42) According to Different ki-67 Expression. **A:** The 3-year progression-free survival in low ki-67 expression group and high ki-67 expression group were 100% and 57%, respectively. **B:** The 3-year overall survival in these two groups were 100% and 76.1%, respectively

Table 2. Clinical Factors in the Univariate Analysis for Patients with Early Stage ENKTL

Clinical factors	P value	
	PFS	OS
Age: ≤60 vs. >60	0.021	0.145
Performance status: 0 vs. 1-2	0.952	0.428
Ann Arbor stage: I vs. II	0.646	0.280
Serum LDH: normal vs. >normal	0.110	0.831
B symptom: absent vs. present	0.769	0.307
Lymphocyte counting : normal vs. <normal	0.276	0.382
IPI : 0 vs. 1-2	0.094	0.492
KPI: 0/1/2/3,4	0.693	0.612
Ki-67 expression: <70% vs. ≥70%	0.003	0.029

*Abbreviations: ENKTL, extranodal natural killer /T-cell lymphoma; LDH, lactate dehydrogenase; IPI, international prognostic index; KPI, Korean prognostic index; PFS, progression-free survival; OS, overall survival

the independent prognostic factors for PFS were high ki-67 expression ($P=0.026$; relative risk, 6.777; 95% CI 1.234-37.208) and KPI ($P=0.014$; relative risk, 4.463; 95% CI 1.355-14.698). Nonetheless, no factor could be independently predictive of OS.

Discussion

L-asparaginase has a different anticancer mechanism from common chemotherapy drugs, which can hydrolyze serum asparagines and deprives some cells of the required amino acid to yield anticancer effects in certain tumor cells, especially in lymphocytic leukemic cells or lymphoma cells that lack L-asparagine synthetase. So L-asparaginase can overcome the P-glycoprotein mediated multidrug resistance. Based on the remarkable effect of L-asparaginase in refractory or relapsed ENKTL (Jaccard et al., 2011; Yamaguchi et al., 2011), more clinical researchers explored its role in the first-line treatment in this disease. CHOP plus L-asparaginase regimen made a CR rate as high as 71.5% in ENKTL with stage I/II in a phase II study (Lin et al., 2013). Another study indicated that the effect was statistically superior in patients treated with IMEP (ifosfamide, etoposide, methotrexate and prednisolone) plus L-asparaginase, compared to those treated with IMEP without L-asparaginase (overall response rate, 90.0% vs. 34.8%, $P<0.001$; CR rate, 65.0% vs. 21.7%, $P=0.001$) in stage III/IV ENKTL (Kim et al., 2015). We also reported the favorable result of GELOX in the first-line treatment

of early stage ENKTL. All these studies established the first-line status of L-asparaginase in the primary chemotherapy of ENKTL. Although L-asparaginase has showed excellent activity in ENKTL, some patients indeed show primary or secondary resistance to L-asparaginase in our clinical observation. The specific resistant mechanism of L-asparaginase is still unknown in this aggressive lymphoma. In the present study, we explored to identify which subgroup patients with ENKTL would be likely to benefit from the GELOX regimen.

A detailed cell cycle analysis showed that the ki-67 was expressed in the G1, S, G2 and mitosis, but not in the Go phase (Gerdes et al., 1984), so it was easy to determine the proliferation index of a malignant tumor by the ki-67 antibody, which could reflect the aggressiveness or prognosis of the malignant disease. The ki-67 index has been served as one of the diagnostic criteria for Burkitt lymphoma and gray zone lymphomas, in which its value is nearly 100% (Rosenwald and Ott, 2008). A ki-67 cut-off value of 45% could help differentiate indolent from aggressive disease, and for diffuse large B-cell lymphoma, a cut-off value of 70% can distinguish patients with a good and bad prognosis when combined with IPI score and bulky disease (Broyde et al., 2009). High ki-67 ($\geq 65\%$) was associated with a worse OS ($P=0.021$) and disease-free survival ($P=0.044$) in a retrospective analysis of 50 patients with early stage ENKTL (Kim et al., 2007). In addition, a meta-analysis demonstrated a significant correlation between high ki-67 expression and a poor survival outcome in the NHL subtypes, including DLBCL, MCL, ENKTL, but not in Hodgkin lymphoma (He et al., 2014). All these studies confirmed the significant prognosis role of ki-67 in B-cell or T-cell lymphomas, though it failed to show prognostic role on lymphoma in some studies (Bahnassy et al., 2006; Ott et al., 2010).

In the present study, ki-67 expression had no significant differences on most clinical factors except lymphocyte counting. However, high ki-67 expression ($\geq 60\%$) was more common in patients with B symptoms, bulky disease and extraupper aerodigestive tract NK/T-cell lymphoma (Jiang et al., 2014). Different ki-67 threshold and enrollment criteria may be mainly responsible for these inconsistent results. Previous studies considered lymphocytopenia was correlated with inferior prognosis in lymphoma (Ayoub et al., 1999; Bari et al., 2010). The preexisting immune suppression may contribute to the poor outcome in patients with lymphoma. Another study also found low lymphocyte count ($<1.0 \times 10^9/l$) at diagnosis was related to more adverse clinical features in ENKTL (Huang et al., 2011). These results gave a potential explanation for the correlation between lymphocytopenia and ki-67 expression. With respect to response rate, GELOX did not produce a statistical difference between low and high ki-67 expression groups. However, it tended to be relatively high in the former group. The 3-year PFS and OS for all patients in the present study were inferior to historic series, for we enrolled nine patients (17.6%) with advanced stage. The 3-year PFS was statistically longer in the low ki-67 expression group than high ki-67 expression group for both the whole patients and stage I/II subgroup, and 3-year OS in different ki-67 expression group also had a significant difference for stage I/II subgroup ($P=0.029$);

especially, no progression and death were observed in patients with early stage and low ki-67 expression, which suggests that ki-67 expression is helpful to identify a subgroup with an excellent prognosis in the patients with early stage ENKTL receiving GELOX chemotherapy. The result of multivariate analysis further proved that low ki-67 expression can be independently predictive of longer PFS. Our results were also consistent with a study in which high expression of ki-67 was shown to be correlated with worse OS and PFS (Huang et al., 2014). Furthermore, in the univariate analysis, young patients showed a better prognosis, which might result from a well tolerance to treatment. Like many published series, in the multivariate analysis, we also found that IPI lost its predictive value, and KPI can be a better prognostic index than IPI in ENKTL. Due to fairly small subgroup and fatal outcome in advanced stage, survival and prognostic analysis were not made in the subgroup with stage III/IV. Since patients with different stages received various salvage treatment, it was unclear whether it would affect the predictive role of ki-67 in this disease.

In conclusion, the present study demonstrated that patients with ENKTL showing low ki-67 expression tended to have a relatively high response rate when receiving GELOX treatment. Additionally, the combination of ki-67 expression and early stage was helpful to identify an excellent prognosis subgroup from patients receiving GELOX in ENKTL. Large prospective studies are essential to further confirm our findings.

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