Clinical Cancer Research

DDGP versus SMILE in Newly Diagnosed Advanced Natural Killer/T-Cell Lymphoma: A Randomized Controlled, Multicenter, Open-label Study in China

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Abstract

Purpose: Optimal treatment strategies for advanced natural killer/T (NK/T)-cell lymphoma have not been fully defined. We compared the safety and efficacy of DDGP and SMILE regimens for advanced NK/T-cell lymphoma in a randomized controlled, multicenter, and open-label clinical trial.

Experimental Design: Patients were newly diagnosed in stages III–IV and had performance scores in 0 to 2. Six cycles of DDGP (dexamethasone, cisplatin, gemcitabline, and pegaspargase) or SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) chemotherapy were randomly assigned to them. The primary end point was progression-free survival (PFS). Secondary end points included response rate and overall survival (OS). The trial is ongoing and is registered with ClinicalTrials.gov (No. NCT01501149).

Results: Of 42 patients enrolled, 21 were treated with DDGP therapy, and 21 patients were treated with SMILE therapy. The 1-year PFS and 2-year OS rates were better in the DDGP group than that in the SMILE group (86% vs. 38% for 1-year PFS, $P = 0.006$; 74% vs. 45% for 2-year OS, $P = 0.027$). Complete remission (CR) rate and overall response rate (ORR) of the DDGP group were higher than that in the SMILE group (71% vs. 29%, $P = 0.005$ for CR rate; 95% vs. 67%, $P = 0.018$ for ORR). The SMILE group showed more serious leucopenia ($P = 0.030$) and severe allergic reaction ($P = 0.015$) than the DDGP group. In addition, two cases in the SMILE group underwent grade 4 mucosal reaction.

Conclusions: DDGP chemotherapy resulted in significant improvement in PFS, OS, and better tolerability compared with SMILE chemotherapy for newly diagnosed advanced NK/T-cell lymphoma patients. *Clin Cancer Res; 22(21); 5223–8. ©2016 AACR.*

Introduction

Extranodal natural killer/T-cell lymphoma (ENKL) is a rare, distinctive clinicopathologic disease entity with aggressive clinical feature and strong association with Epstein-Barr virus infection. It is much more frequent in Asian and Latin American countries than in Western countries (1). NK cells express high concentrations of the multidrug-resistant P-glycoprotein (P-gp), so that anthracycline-containing regimens, such as CHOP and CHOP-like regiments usually provide poor clinical outcomes (2–4). Recently, an L-asparaginase (L-Asp)–based regimen, including dexamethasone, methotrexate, ifosfamide, L-Asp and etoposide (SMILE), has been devised to tackle these problems. It brought higher response rate, prolonged overall survival (OS) and progression-free survival (PFS) than anthracycline-containing regimens. But at the same time, severe hematologic toxicity leaded serious chemotherapy-related infection or even death. Up to 92% of patients were at risk of undergoing a grade 4 neutropenia. Allergic reactions also happened in half of the patients (5, 6). In addition, the short plasma half-life of L-Asp causes frequent dosing that adds the patients' suffering. Physicians were looking for new chemotherapeutic regimens with high efficacy and low toxicity for ENKL. The Lymphoma Center of the First Affiliated Hospital of Zhengzhou University formulated a novel pegaspargase (PEG-Asp)–based chemotherapy regimen: dexamethasone, cisplatin, gemcitabline, pegaspargase (DDGP), and performed related research.

In our previously prospective and retrospective studies, Li and colleagues (7) showed that patients with newly diagnosed stages II–IV ENKL who were initially treated with a DDGP regimen had a complete remission (CR) rate of 83.3% and partial remission (PR) rate of 16.7%. Zhou and colleagues (8) conducted a study and showed that 17 relapsed/refractory ENKL patients treated with DDGP regimen had an overall response rate (ORR) of 88.2%.

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Translational Relevance

Natural killer/T (NK/T)-cell lymphoma is a distinct lymphoid neoplasm with aggressive course and poor outcomes. Optimal treatment strategies for advanced NK/T-cell lymphoma have not been fully defined. We carried out a randomized, open-label, multicenter clinical trial enrolled patients with newly diagnosed in stage III–IV NK/T-cell lymphoma to compare the safety and efficacy of DDGP and SMILE. In this study, DDGP chemotherapy resulted in significant improvement in progression-free survival and overall survival, higher complete remission rate and overall response rate, and better tolerability compared with SMILE chemotherapy for newly diagnosed patients with advanced NK/T-cell lymphoma.

Currently, there are no articles comparing the efficacy, toxicity, and survival analysis of DDGP versus SMILE regimens in patients with newly diagnosed advanced stage NK/T-cell lymphoma. On the basis of our previous studies, we designed this randomized controlled trial.

Materials and Methods

Study design and patient eligibility

This randomized controlled, open-label, multicenter study compared the efficacy and safety of DDGP regimen with SMILE in patients with newly diagnosed ENKL in III–IV stages. The trial was registered on the Clinicaltrials. gov website in 2011 (Reg. No. NCT01501149). Patients were selected in the study from March 2011 to June 2014, whose date of diagnosis was no later than September 2013. Diagnosis of ENKL based on clinical features, histopathologic morphology, immunohistology (CD2+, CD3ε+, CD43+, CD56+ CD20−, TIA-1+, perforin+, granzyme B), and Epstein-Barr virus (EBV) by *in situ* hybridization. All biopsies were independently reviewed and confirmed by more than two pathologists in accordance with WHO 2008 morphologic, immunophenotypic, and genetic criteria.

The inclusion criteria were: (i) 14 to 70 years of age and had satisfactory performance scores (0–2). (ii) Granulocytes $\geq 1.5 \times 10^9$ cells/L, platelets $\geq 100 \times 10^9$/L, hemoglobin ≥ 90 g/L, AST and ALT levels $\leq 2\times$ the upper limit of normal, total bilirubin $\leq 1.5 \times$ the upper limit of normal, serum creatinine $\leq 1.5 \times$ the upper limit of normal and serum albumin ≥ 30 g/L. (iii) Primary tumor sites were extra nodal sites. (iv) Never accept chemotherapy or radiotherapy. Patients were excluded if they had CNS involvement or a prior malignancy.

The pretreatment staging procedures included physical examination, tests for complete blood cell count, β2-microglobulin, lactate dehydrogenase (LDH), liver and kidney functions, blood coagulation function, urinalysis, electrocardiography, and computed tomography scans of the head, neck, thorax, and abdomen. Bone marrow aspiration and biopsy were also carried out to determine whether the bone marrow was involved or not.

Six cycles of DDGP or SMILE chemotherapy were randomly assigned to the patients based on a computer-generated randomization schedule. The specific details of the DDGP and SMILE regimens are shown in Table 1.

The study was carried out with Good Clinical Practice Guidelines and the Helsinki Declaration. This work was approved by the Local Ethics Committee of Zhengzhou University and the Scientific Council of Faculty of Medicine. All patients were fully informed about the nature and possible toxicities of the treatment protocol and submitted written informed consent.

Table 1. The DDGP and SMILE regimens

Agents	Dose	Route	Timing of treatment
DDGP			
PEG-Asp	2,500 IU/m^2	IM	Day 1
Gemcitabine	800 mg/m^2	IV	Days 1 and 8
Cisplatin	20 mg/m^2	IV	Days 1–4
Dexamethasone	15 mg/m^2	IV	Days 1–5
SMILE			
Methotrexate	2 g/m^2	IV (6 hours)	Day 1
Dexamethasone	40 mg/m^2	IV	Days 2–4
Ifosfamide	1,500 mg/m^2	IV	Days 2–4
Mesna	300 mg/m^2 × 3	IV	Days 2–4
Etoposide	100 mg/m^2	IV	Days 2–4
L-Asp	6,000 U/m^2	IV	Days 3–9

NOTE: Cycles of DDGP and SMILE regimen were repeated every 21 days.
Abbreviations: IM, intramuscularly; IV, intravenously; L-Asp, L-asparaginase; PEG-Asp, pegaspargase.

Staging and response evaluation

Clinical stage based on the modified Ann Arbor new staging system for NK/T-cell lymphoma. Stage I: lesions confined within nasal cavity or nasopharynx without local invasiveness (paranasal sinuses or bony or skin invasion); stage II: localized disease with local invasiveness; stage III was defined localized disease with regional lymph node involvement (cervical lymph nodes); and stage IV: disseminated disease (lymph nodes on both sides of diaphragm, multiple extranodal site; ref. 9).International Prognostic Index (IPI) scores were used to determine the classification of risks (10). Performance status was evaluated on the basis of the Eastern Cooperative Oncology Group scale (11). Treatment responses, including CR, PR, stable disease (SD), and progressive disease (PD), evaluated according to response criteria of Cheson and colleagues (12). Evaluation was conducted every two cycles.

Assessment of adverse effects

Adverse reactions were monitored by biochemistry and hematological tests, urinalysis, electrocardiogram, and routine physical examination. They were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 and assessed from the first cycle of the regimen until 1 month after terminal treatment (13).

Statistical analysis

The primary endpoint was PFS, which was defined as the interval from date of randomization to the date of disease progression or date of death, whichever occurred first, irrespective of the use of subsequent antineoplastic therapy. Patients who were progression-free and alive were censored at the time of their last disease assessment, and patients who were alive with no post-baseline disease assessment were censored at randomization. Secondary endpoints included ORR (CR and PR), OS, and safety.

We compared the clinical and laboratory data, response rate, and adverse effects between DDGP and SMILE groups by χ^2 test and Mann–Whitney U test. OS and PFS were estimated with the Kaplan–Meier method. Survival rates were compared by the long-rank test. Prognostic risk factors were estimated with univariate

analysis. Statistical significance was determined at a level of $P < 0.05$. SPSS version 17.0 was used for the statistical analysis.

Result

Baseline characteristics of patients

Forty-two patients were enrolled from March 2011 to June 2014. Their baseline characteristics are listed in Table 2. The median age was 42 years (range, 14–64 years) and the male: female ratio was 1.625:1. Ninety percent of the patients were diagnosed as upper aerodigestive tract ENKL. Thirty-eight percent of the cases had newly diagnosed stage IV disease. Systemic B symptoms were present in 20 patients (48%), and the elevation of LDH level was observed in 19 patients (45%). Between the DDGP (21 cases) and SMILE (21 cases) groups, there were no obvious differences in the baseline characteristics of patients.

Treatment

The mean cycles of chemotherapy for patients receiving DDGP was 5.57 cycles (range, two to six cycles), whereas for those receiving SMILE, it was 3.9 cycles (range, 1–6 cycles). In the DDGP arm, 17 patients received six cycles, and two cases received four cycles. One case received five cycles, and one case received two cycles. In the SMILE arm, nine patients received six cycles, and three cases received four cycles. Two cases received three cycles. Four patients completed less than one cycle because of the severe methotrexate-related mucositis and myelosuppression-related septic shock, and three of them died within 15 days. Three cases in the SMILE group received two cycles because of tumor progression and upper gastrointestinal hemorrhage, and one of them died within 12 days.

Table 2. Baseline patient characteristics

Characteristic	Number of patients ($n = 42$) DDGP ($n = 21$)	SMILE ($n = 21$)	P
Age, y			
Median	40	43	
Range	17–64	13–64	
Sex			0.525
Male	12	14	
Female	9	7	
Site of involvement at diagnosis			0.293
UAT	20	18	
Nasal	17	16	
Extra-nasal	3	2	
NUAT	1	3	
Stage at enrollment			0.525
III	14	12	
IV	7	9	
B symptoms present	11	9	0.537
Elevated serum LDH	9	10	0.757
IPI			0.747
0–2	8	7	
3–4	13	14	
PS			0.603
0	3	2	
1	13	16	
2	5	3	

NOTE: P, χ^2 test.

Abbreviations: IPI, International Prognostic Index; LDH, lactate dehydrogenase; NUAT, non-upper aerodigestive tract; PS, performance status; UAT, upper aerodigestive tract.

Table 3. Response rates of DDGP and SMILE regimens

Response	Number of patients (%) DDGP	SMILE	P
	$N = 21$	$N = 21$	
CR	15 (71)	6 (29)	0.005
PR	5 (24)	8 (38)	—
SD	0 (0)	0 (0)	—
PD	1 (5)	3 (14)	—
ORR	20 (95)	14 (67)	0.018

NOTE: P, χ^2 test.

Abbreviations: CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Response

The ORR in the DDGP group was obviously better than the SMILE group (95% vs. 67%, $P = 0.018$), with CR and PR rates of 71% and 24% for DDGP whereas 29% and 38% for SMILE (Table 3).

OS and PFS

At a median follow-up of 14 months (range, 1–39 months) for overall patients, four patients died of disease progression. One patient died of cerebral hemorrhage, and one patient died of gastrointestinal hemorrhage. Two patients died of septic shock, and one patient died of infection combined with hemorrhage. Two patients died of the methotrexate–related mucosa reaction, and three patients died of unknown reasons.

The DDGP arm had a significantly better OS and PFS than SMILE arm: 90% versus 57% for 1-year OS, 74% versus 45% for 2-year OS and 86% versus 38% for 1-year PFS, respectively (Fig. 1).

The univariate analysis of OS (Table 4) showed that only site of involvement at diagnosis was predictor of OS in the 42 patients.

Adverse events

Adverse events were assessed in all patients (Table 5). Adverse events included hematologic and non-hematologic adverse reactions. Compared with the DDGP arm, the SMILE arm had more instances of grade 3/4 leukopenia ($P = 0.030$) and grades 3/4 allergy ($P = 0.015$). Moreover, three cases underwent grade 3 diarrhea, and two cases underwent grade 4 mucositis, which led the patients to death in the SMILE arm. At the same time, two patients had a grade 4 heart failure, and one patient had a grade 3 arrhythmia in the SMILE group. However, there were more instances of grade 3/4 anemia ($P = 0.039$) in the DDGP arm than the SMILE arm.

Discussion

ENKL was labeled with high invasiveness, easy to develop drug resistance, low curative effect, dismal prognosis, and short survival time. Though physicians conducted many clinical trials, there was no optimal treatment modality before (14). Kim and colleagues (4) found a low CR rate and 2-year OS rate for 59 ENKL patients receiving anthracycline-based chemotherapy as an initial treatment. Lee and colleagues (15) showed that 26 patients with early-stage ENKL receiving ifosfamide, methotrexate, etoposide, and prednisolone (IMEP) chemotherapy as first-line treatment had a CR rate of 13% and median OS of 2.7 months, which was also unsatisfactory. Bortezomib, which was considered to induce the apoptosis in NK cell lymphoma, plus cyclophosphamide, doxorubicin, vincristine, and prednisolone, was undertaken by

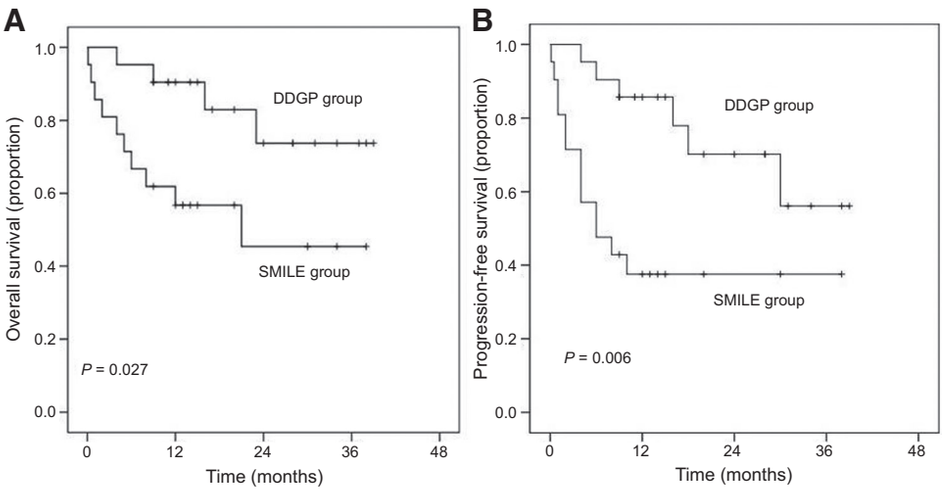

Figure 1.
A, overall survival is shown for all patients, showing that the DDGP group has a better OS than the SMILE group ($P = 0.027$). **B,** progression-free disease is shown for all patients, showing that the DDGP group has a better PFS than the SMILE group ($P = 0.006$).

patients with NK/T-cell lymphoma, and only 33.3% of the patients achieved CR (16).

The mechanisms of ENKL resistance to conventional chemotherapy were not fully understood, but it related to the frequent expression of P-gp by lymphoma cells, which was the product of the multidrug resistance gene (2). L-Asp was not affected by multidrug resistance of ENKL and had an original antitumoral mechanism. L-Asp hydrolyzes serum asparagines and deprives some cells of the required amino acid to yield anticancer effects in lymphoma cells lacking L-asparagine synthetase (17). Studies demonstrated that L-Asp could reduce the activity of normal NK cells *in vitro* and induced the apoptosis of tumoral NK cells (18, 19).

In recent years, the L-Asp–based chemotherapy (SMILE) was considered as an optimal treatment for patients with ENKL. In a retrospective study developed among patients with stage IV, relapsed or refractory ENKL, 20 patients receiving SMILE had significant higher CR and ORR and longer OS and PFS than patients receiving the CHOP regimen (20). But Yamaguchi and colleagues (6) found that in the 38 stage IV, relapsed/refractory ENKL patients treated with SMILE, grade 3/4 neutropenia occurred in all patients and that transferred into serious infections in 61% of

Table 4. Univariate analysis of OS in the 42 patients

	Number of PATIENTS ($n = 42$)		
Characteristic	**Univariate analysis**	**95% CI of OS**	***P***
Age			0.510
<60	28.314 ± 2.692	23.038–33.590	
≥60	22.000 ± 4.571	13.041–30.959	
Sex			
Male	28.536 ± 3.387	21.897–35.174	0.597
Female	26.368 ± 3.396	19.712–33.024	
Site of involvement at diagnosis			0.040
UAT	28.832 ± 2.571	23.793–33.870	
NUAT	12.775 ± 6.351	0.328–25.222	
Epstein-Barr virus infection			
Positive	28.355 ± 3.340	21.808–34.902	0.532
Negative	25.701 ± 3.612	18.621–32.780	
Stage at enrollment			0.195
III	29.622 ± 2.996	23.750–35.493	
IV	21.225 ± 3.597	14.175–28.275	
B symptoms present			0.123
Yes	32.150 ± 3.074	26.124–38.176	
No	23.026 ± 3.401	16.360–29.693	
Elevated serum LDH			0.481
Yes	23.382 ± 3.876	15.785–30.980	
No	28.902 ± 3.189	22.651–35.153	
IPI			0.896
0–2	26.781 ± 4.110	18.726–34.837	
3–4	27.311 ± 3.105	21.224–33.398	
PS			
0–1	27.634 ± 2.807	22.132–33.136	0.721
2	18.750 ± 3.217	12.445–25.055	

Abbreviations: IPI, International Prognostic Index; LDH, lactate dehydrogenase; NUAT, non-upper aerodigestive tract; PS, performance status; UAT, upper aerodigestive tract.

Table 5. Adverse effects between DDGP and SMILE groups

Toxicity	Grade of adverse reaction						*P*
	DDGP ($n = 21$)			SMILE ($n = 21$)			
Grade	0	1–2	3–4	0	1–2	3–4	
Hematologic							
Leukopenia	0	8	13	0	2	19	0.030
Neutropenia	0	6	15	0	3	18	0.259
Anemia	0	10	11	5	10	6	0.039
Thrombocytopenia	4	4	13	3	7	11	0.569
Non-hematologic							
Hypofibrinogenemia	9	12	0	13	8	0	0.217
Prolonged APTT	9	12	0	14	7	0	0.121
Hyperbilirubinemia	15	5	1	18	1	2	0.195
ALT elevation	6	15	0	9	9	3	0.078
AST elevation	10	11	0	12	7	2	0.215
Creatinine	21	0	0	17	3	1	0.110
BUN	20	1	0	17	3	1	0.326
Nausea	0	16	5	0	16	5	1.000
Vomiting	0	16	5	0	16	5	1.000
Diarrhea	21	0	0	18	0	3	0.072
Mucositis	21	0	0	18	1	2	0.199
Baldness	9	9	3	5	12	4	0.424
Allergy	21	0	0	14	5	2	0.015
Heart failure	21	0	0	19	0	2	0.147
Arrhythmia	21	0	0	20	1	0	0.311

NOTE: *P*, Mann–Whitney test.

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen.

the patients. Kwong and colleagues (5) showed SMILE regimen brought a good therapeutic effect in 43 newly diagnosed and 44 relapsed/refractory ENKL patients, but 73% of them had a grade 3/4 neutropenia. In addition, 50% of the patients underwent the allergy. The acute allergic reactions were induced by L-Asp and characterized by circulating antibodies and rapid clearance of the enzyme from the blood (21).

To ensure the efficacy and avoid the severe toxicity in treating with ENKL, a novel regimen was formulated by our center. PEG-Asp was a modified type of native *E coli* asparaginase, in which the enzyme was covalently linked to polyethylene glycol. The binding preserved the enzymatic activity of the drug and decreased the immunogenicity of the protein, which reduced the risk of hypersensitivity reactions (22). Another advantage of PEG-Asp was its prolonged half-life of elimination compared with the L-Asp. The elimination half-life of PEG-Asp was approximately 6 days, five times longer than L-Asp, which was important in improving the pharmacokinetic profile of the drug and alleviating the suffering of patients (21, 23, 24).

Currently, the safety and effectiveness of PEG-Asp against ENKL had been confirmed by some reports (7, 8, 25). Li and colleagues (7) reported that patients with newly diagnosed stages II–IV ENKL who were initially treated with a DDGP regimen had a CR rate of 83.3% and PR rate of 16.7%. The objective ORR was 100%. Zhou and colleagues (8) conducted a retrospective study and showed that 17 relapsed/refractory ENKL patients treated with the DDGP regimen had an ORR of 88.2% with 52.9% of the patients achieving CR and 35.3% of them achieving PR. Wen and colleagues found that for patients treated with PEG-Asp combination with CHOP ($n = 5$), EPOCH ($n = 7$), or GEMOX ($n = 7$), 25% of them achieved CR, and 35% of them achieved PR. No allergic reactions were detected, and no treatment-related death was reported (26).

Gemcitabine is a novel nucleoside analogue that inhibits DNA synthesis. Gemcitabine-containing therapy has shown promising results in patients with ENKL. Ahn and colleagues (27) showed that 20 patients with refractory or relapsed ENKL were given gemcitabine-containing regimen. The ORR was 40% with a CR rate of 20%. Four complete responders had a disease-free status for more than 7 months. A retrospective study showed that for the 93 patients newly diagnosed with stage IE to IIE ENKL, patients in GELOX (Gemcitabine, Oxaliplatin, and L-Asp) group had a higher CR rate and ORR than those in the EPOCH group (70.0% vs. 41.5%, $P = 0.007$ for CR rate; 87.5% vs. 67.9%, $P = 0.047$ for ORR). The GELOX regimen resulted in significantly superior 5-year PFS (79.0% vs. 46.5%, $P = 0.005$) and OS (78.9% vs. 50.4%, $P = 0.003$) rates. And the toxicity of both regimens was acceptable (28).

But until now, there have not been any prospective clinical trials to compare DDGP and SMILE regimens in the side effects and efficacy. Thus, we designed this randomized controlled trial and found that the DDGP group showed prolonged PFS and OS than the SMILE group. The ORR and CR rate in the DDGP group was also higher than that in the SMILE group.

Moreover, the SMILE group had a higher incidence of leucopenia, allergic reaction, nephrotoxicity, diarrhea, cardiotoxicity, and mucositis. The major side effects of DDGP regimen were myelosuppression and coagulation abnormalities. Though there was no drug-related death, we need careful handle the DDGP-associated anemia and thrombocytopenia.

In conclusion, our study demonstrated that the DDGP regimen can result in a higher CR rate, a longer survival time, and a lower toxicity than the SMILE regimen. This regimen offers a much safer and much more effective regimen for patients with ENKL stage III/IV.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: X. Li, W. Li, M. Zhang

Development of methodology: X. Li, X. Fu, F. Nan, M. Zhang

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): X. Li, Y. Cui, Z. Sun, L. Zhang, L. Li, X. Wang, J. Wu, X. Fu, W. Ma, X. Zhang, Y. Chang, F. Nan, W. Li, L. Su, J. Wang, H. Xue, M. Zhang

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Cui

Writing, review, and/or revision of the manuscript: X. Li, Y. Cui, W. Li

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X. Li, Z. Sun, L. Zhang, L. Li, X. Wang, J. Wu, X. Fu, W. Ma, X. Zhang, Y. Chang, F. Nan, W. Li, L. Su, J. Wang, H. Xue, M. Zhang

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