Analysis of the efficacy and prognostic factors of gemcitabine combined with oxaliplatin in non-Hodgkin lymphoma

XIAOBO ZHANG, GUANG LI, FENG LIU, RUI SHI, JING WEN, WEN WU and JINQIAN DAI

Department of Hematology, Xi'an Central Hospital/Xi'an Institute of Hematology, Xi'an, Shaanxi 710000, P.R. China

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Abstract. Non-Hodgkin lymphoma (NHL), a heterogeneous malignancy accounting for ~90% of lymphomas, often requires chemotherapy as the primary treatment for patients unsuitable for stem cell transplantation. This study aimed to analyze the therapeutic effects of gemcitabine combined with oxaliplatin on NHL and examine the prognostic factors affecting patients with NHL. A total of 106 patients with NHL were retrospectively selected and divided into a control group (CG; n=50 received oxaliplatin treatment) and an observation group (OG; n=56 received oxaliplatin combined with gemcitabine treatment) based on the differences in treatment measures. Clinical data, therapeutic efficacy, adverse reactions, improvement in B symptoms, post-treatment levels of lactate dehydrogenase (LDH) and TGF-β1 and post-treatment Karnofsky Performance Status (KPS) scores were collected from patients in both groups. Prognostic factors for NHL were analyzed based on the results of a 2-year follow-up. In the OG, the complete remission rate (CRR) was 73.21% and the disease control rate (DCR) was 91.07%, whereas in the CG, the CRR was 52.00% and the DCR was 80.00%, demonstrating a significant intergroup difference (P<0.05). The OG had an overall survival (OS) of 13.6 months and a progression-free survival (PFS) of 8.9 months, and the CG had an OS of 11.3 months and a PFS of 6.1 months. After chemotherapy, the serum LDH and TGF-β1 levels in the OG were significantly lower compared with those in the CG, and the KPS scores were higher compared with those in the CG (all P<0.05). Multivariate logistic regression analysis indicated that the Ann Arbor stage and the International Prognostic Index score for lymphoma were independent prognostic risk factors for patients with NHL (both P<0.05). The combination therapy of gemcitabine and oxaliplatin was demonstrated to be safe for patients with NHL. This combination treatment demonstrated notable overall efficacy and improved functional improvement compared with oxaliplatin monotherapy.

Correspondence to: Dr Jinqian Dai, Department of Hematology, Xi'an Central Hospital/Xi'an Institute of Hematology, 65 Tangfang Street, Lianhu, Xi'an, Shaanxi 710000, P.R. China
E-mail: daijinqian263@yeah.net

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Introduction

Lymphoma is a malignant tumor caused by abnormal clonal proliferation of lymphocytes (1). Based on pathological characteristics, lymphomas can be divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), with NHL accounting for ~90% of cases and HL only 10% (2). NHL can be further classified based on cell origin into B-cell, T cell and natural killer (NK)-cell NHL (3,4). Clinical practice indicates that although lymphoid tissue is the common origin of most lymphomas, different types of lymphomas exhibit notable differences in clinical manifestations, molecular characteristics and case structures. Therefore, therapeutic approaches vary substantially. In recent years, emerging treatments such as programmed cell death protein-1/programmed cell death ligand-1 inhibitors, chimeric antigen receptor T (CAR-T) cell therapy and bispecific antibodies have been increasingly applied for the management of NHL, offering notable therapeutic potential compared with conventional chemotherapy (5). With the continuous advancement of modern medical knowledge, the classification and treatment of lymphoma have been consistently updated; while some lymphoma subtypes have achieved satisfactory outcomes with standard treatment protocols, a subset of patients still experience relapse or develop resistance (6).

For patients with NHL unsuitable for stem cell transplantation, chemotherapy remains the preferred treatment (7). Oxaliplatin, a third-generation platinum-based anticancer drug, is a platinum compound of diaminocyclohexane and it targets DNA, forming cross-links with DNA strands, thereby inhibiting tumor DNA replication and transcription. Multiple clinical studies have reported the positive impact of oxaliplatin on improving the prognosis of patients with NHL (8,9). However, clinical practice has indicated that traditional platinum-based chemotherapy drugs, such as oxaliplatin, have low treatment response rates and high incidence of adverse reactions (e.g., leukopenia, acute neurotoxicity, gastrointestinal reactions) (10). In recent years, novel anticancer drugs such as gemcitabine have entered clinical use (11). Gemcitabine, a novel cytidine analog, shares

a similar mechanism with cytarabine, primarily inhibiting ribonucleotide reductase to suppress deoxycytidine deaminase, thereby reducing the degradation of intracellular metabolites and enhancing self-potentiation (11). *In vitro* experiments have confirmed its efficacy against various solid tumors, such as pancreatic cancer and non-small cell lung cancer (12,13).

Currently, there is limited research on the combined use of oxaliplatin and gemcitabine in NHL. However, existing research has demonstrated the efficacy of this combination. Previous clinical data on patients with NHL treated with the two agents demonstrated that the majority of participants benefited from the regimen, with markedly improved overall response and disease control rates (DCRs) compared with monotherapy, while maintaining a favorable safety profile (14). The present study aimed to analyze the clinical value of the two-drug combination in patients with NHL and to explore the safety of their combined use, which will potentially provide more references for the clinical treatment of patients with NHL in the future.

Materials and methods

Study design and patient selection. The present study was a retrospective analysis, approved by the Xi'an Central Hospital/Xi'an Institute of Hematology Ethics Committee (approval no. 2024-JT-023; Xi'an, China). All study participants provided written informed consent prior to participation in the present study. The clinical data of patients with NHL treated at Xi'an Central Hospital/Xi'an Institute of Hematology from August 2018 to April 2022 were collected. Cases were screened according to the following inclusion criteria: i) All cases confirmed as NHL through pathological examination; ii) patients treated with oxaliplatin or oxaliplatin combined with gemcitabine in Xi'an Central Hospital/Xi'an Institute of Hematology; iii) patients who received at least two cycles of chemotherapy (with the option to include >2 cycles); iv) patients with complete baseline data [sex, age, pathological type, Ann Arbor stage and International Prognostic Index (IPI) score for lymphoma (15)]; v) patients with blood samples collected before and after chemotherapy and examined for serum lactate dehydrogenase (LDH) and TGF-β1 levels; vi) patients with Karnofsky Performance Status (KPS) score assessed before and after chemotherapy (16); and vii) patients with definitive follow-up results by the end of the follow-up period (case inclusion ended in April 2022, with a follow-up duration of 2 years ending in April 2024). The exclusion criteria were as follows: i) Patients with other malignant tumors; ii) patients with incomplete clinical data; and iii) patients with infectious diseases.

After screening the patients according to the inclusion and exclusion criteria, a total of 106 patients were included, comprising 68 men and 38 women, with an age range of 37-69 years and a median age of 48 years. Based on the differences in treatment regimens, patients were divided into a control group (CG; n=50), who received oxaliplatin treatment and an observation group (OG; n=56), who received a combined treatment of oxaliplatin and gemcitabine.

Observation indices. Differences in baseline clinical data between patients in the OG and CG were collected and compared.

According to the Lugano classification criteria published in 2014 for malignant lymphoma response assessment (17), the clinical efficacy of patients after chemotherapy was categorized as progressive disease (PD), stable disease (SD), partial remission (PR) and complete remission (CR). The complete remission rate (CRR) was calculated as (PR + CR)/total cases x100% and the DCR was calculated as (PR + CR + SD)/total cases x100%. The clinical efficacy differences of chemotherapy between the two groups were compared and their overall survival (OS) and progression-free survival (PFS) were recorded through follow-up. OS was defined as the duration from the first administration to mortality or the follow-up endpoint, while PFS was defined as the duration from the first administration to tumor progression, mortality or follow-up endpoint.

According to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria (18) for adverse reaction evaluation, chemotherapy adverse reactions were classified into grades 0-5, with 0 indicating no adverse reaction, 1 indicating mild adverse reaction, 2 indicating moderate adverse reaction, 3 indicating severe adverse reaction, 4 indicating life-threatening or disabling adverse reaction and 5 indicating a fatal adverse reaction. The present study analyzed the incidence of leukopenia, liver and kidney dysfunction and toxic side effects of gastrointestinal reactions in the OG and CG.

The serum LDH levels and TGF-β1 levels of two groups of patients were measured before and after chemotherapy using enzyme-linked immunosorbent assay (cat. nos. EH0287 and EH0198; Wuhan Saipei Biotechnology Co., Ltd.). Although TGF-β1 is not a standard biomarker in routine NHL treatment, previous studies have demonstrated its involvement in tumorigenesis and progression through modulation of the tumor microenvironment, which justifies its inclusion in the present analysis (19,20).

The differences in KPS scores before and after chemotherapy for the two groups were also collected. The KPS scores, evaluated as a percentage, indicated the health status of the individual, with higher scores representing improved functional status of the subjects.

Based on the 2-year follow-up clinical outcomes of 106 patients with NHL, they were divided into a death subgroup (n=15) and a survival subgroup (n=91). Multivariate logistic regression analysis was used to identify the risk factors affecting the prognosis of patients with NHL.

Statistical analysis. Data collection for the present study was performed using Excel 2021 (version no. 16.0.14332.20255_x64; Microsoft Corp.) and data analysis was performed with SPSS (version 26.0; IBM Corp.). The measurement data were normally distributed according to the Shapiro-Wilk test and are expressed as the mean ± SD, and intergroup differences were assessed using an independent-samples t-test. The count data were expressed as rates and intergroup differences were analyzed using a χ^2 or Fisher's exact test. The risk factors were analyzed using univariate and multivariate logistic regression analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Comparison of general clinical data between the OG and the CG.

General clinical data	OG (n=56)	CG (n=50)	t/χ^2/Fisher	P-value
Sex			0.001	0.976
Male	36	32		
Female	20	18		
Age, years	49.63±7.83	50.26±6.39	0.450	0.653
Pathological type			0.709	0.400
B cell	38	30		
T cell	18	20		
Ann Arbor stage			2.083	0.347
II	16	12		
III	26	30		
IV	14	8		
International Prognostic Index score for lymphoma, points			1.156	0.628
0-1	16	12		
2-3	39	38		
4-5	1	0		

Values are expressed as the mean ± standard deviation or n. OG, observation group; CG, control group.

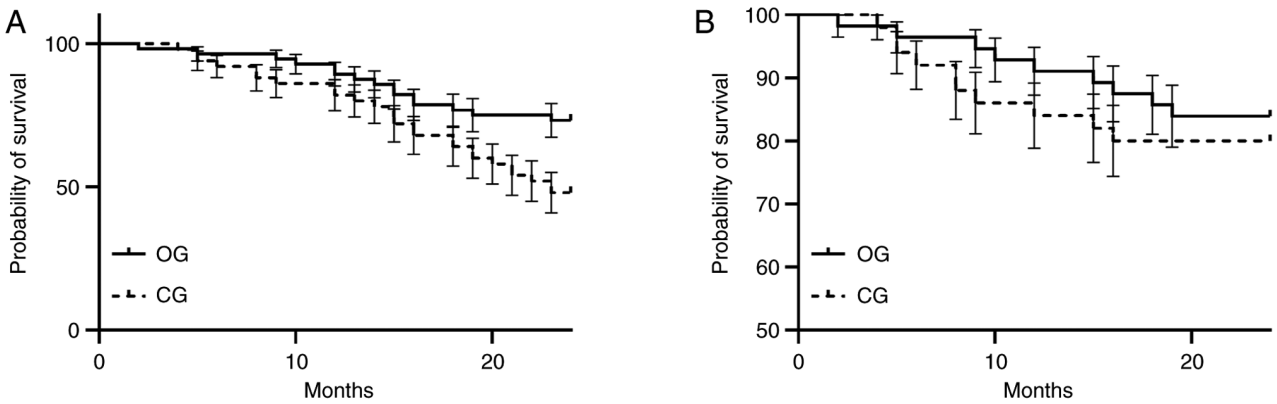

Figure 1. Comparison of survival time between the two groups. The OG had (A) an OS of 13.6 months and (B) a PFS of 8.9 months. The CG had (A) an OS of 11.3 months and (B) a PFS of 6.1 months. OG, observation group; CG, control group; OS, overall survival; PFS, progression-free survival.

Results

Comparison of general clinical data between the OG and the CG. Based on the inclusion and exclusion criteria, a total of 106 patients were selected for the present study, with 56 patients receiving oxaliplatin combined with gemcitabine treatment and 50 patients receiving oxaliplatin treatment alone. Baseline clinical data such as sex, mean age, pathological type, Ann Arbor stage and IPI score for lymphoma were collected in both groups. Comparative analysis revealed no statistically significant differences between the two groups (all P>0.05; Table I).

Comparison of clinical efficacy between the two groups. All enrolled patients underwent a 24-month follow-up, which concluded in April 2024. The assessment revealed that the OG had a CRR of 10.71%, a PR rate of 62.50%, an SD rate of 17.85% and a PD rate of 8.93%, with a complete remission rate (CRR) of 73.21% and a DCR of 91.07%. The CG had a CRR of 4.00%, a PR rate of 48.00%, an SD rate of 28.00% and a PD rate of 20.00%, with a CRR of 52.00% and a DCR of 80.00%. Comparisons between groups indicated that the CRR and DCR of the OG were significantly higher compared with those of the CG (P=0.024, P=0.031). The OG had an OS of 13.6 months and a PFS of 8.9 months and the CG had an OS of 11.3 months and a PFS of 6.1 months (Fig. 1).

Comparison of toxic side effects between the two groups. According to the CTCAE v4.03 criteria, two groups of patients undergoing chemotherapy were assessed for the incidence of various toxic side effects (leukopenia, gastrointestinal reactions, and liver and kidney damage) and intergroup comparisons were performed. The results indicated that there were no statistically significant differences between the groups in terms of leukopenia-related toxic side effects (Fig. 2A), gastrointestinal reactions (nausea, vomiting, diarrhea, and loss of appetite) (Fig. 2B), and liver and kidney damage (abnormal liver and kidney function) (all P>0.05) (Fig. 2C).

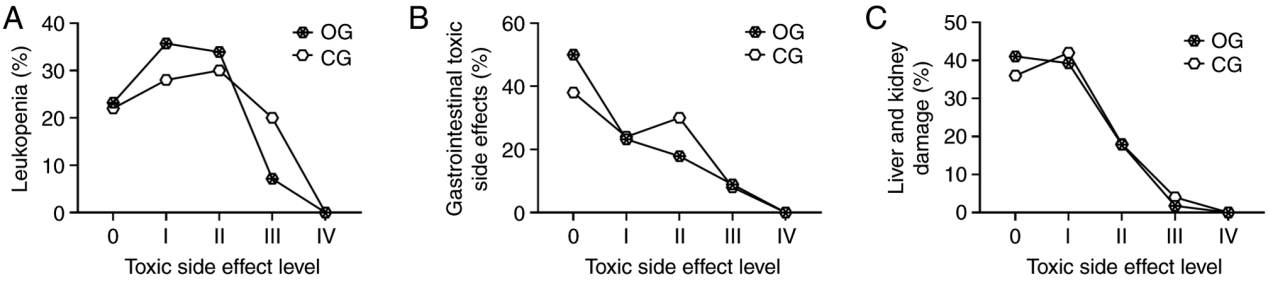

Figure 2. Comparison of incidence of toxic side effects between the two groups. There were no statistically significant differences between the groups in terms of (A) leukopenia-related toxic side effects, (B) gastrointestinal reactions and (C) liver and kidney damage (all P>0.05). OG, observation group; CG, control group.

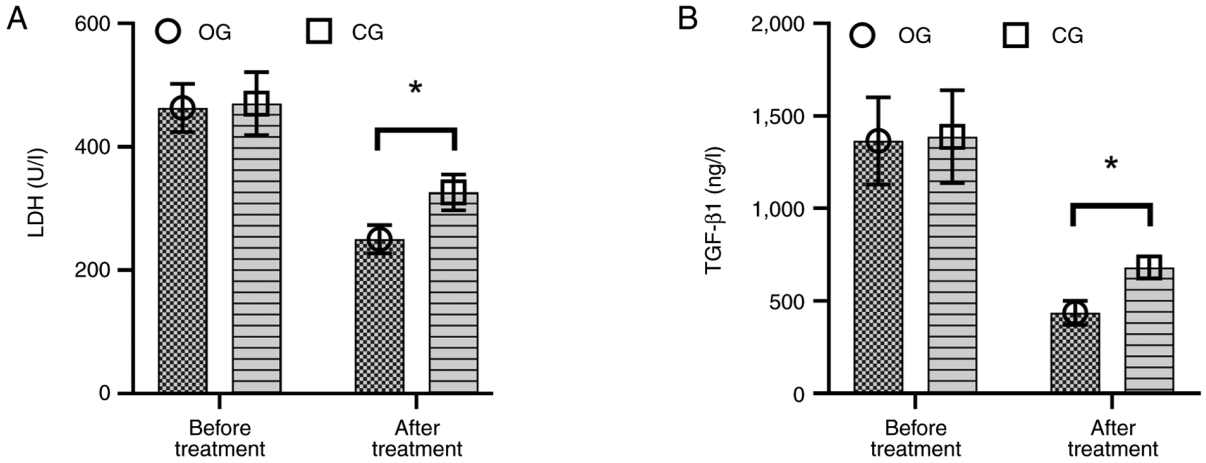

Figure 3. Comparison of LDH and TGF-β1 levels between the two groups before and after chemotherapy. Before chemotherapy, there was no significant difference in serum (A) LDH and (B) TGF-β1 levels between the two groups (both P>0.05). Upon discharge after chemotherapy, patients in the OG demonstrated significantly lower serum (A) LDH and (B) TGF-β1 levels compared with that of CG. *P<0.05. OG, observation group; CG, control group; LDH, lactate dehydrogenase.

Comparison of LDH and TGF-β1 levels between the two groups before and after chemotherapy. Before chemotherapy, there was no statistically significant difference in serum LDH and TGF-β1 levels between the two groups (P>0.05). However, upon discharge after chemotherapy, patients in the OG exhibited significantly lower serum levels of LDH (Fig. 3A) and TGF-β1 (Fig. 3B) compared with the CG (P=0.008, P=0.003).

Comparison of KPS scores between the two groups before and after treatment. Before treatment, there was no statistically significant difference in KPS scores between the two groups (P>0.05; Fig. 4A). After treatment, KPS scores in the OG were significantly higher compared with those in the CG (P<0.001; Fig. 4B).

Analysis of prognostic factors in patients with NHL. Univariate analysis revealed that the Ann Arbor stage and the IPI score for lymphoma were significantly associated with the prognosis of patients with NHL (P<0.001, P=0.002; Table II). Furthermore, using patient prognosis as the dependent variable and the Ann Arbor stage and IPI score for lymphoma as independent variables, a multivariate logistic regression analysis was performed, which indicated that these indicators were independent prognostic risk factors for patients with NHL (P=0.005, P=0.008; Table III; Fig. 5).

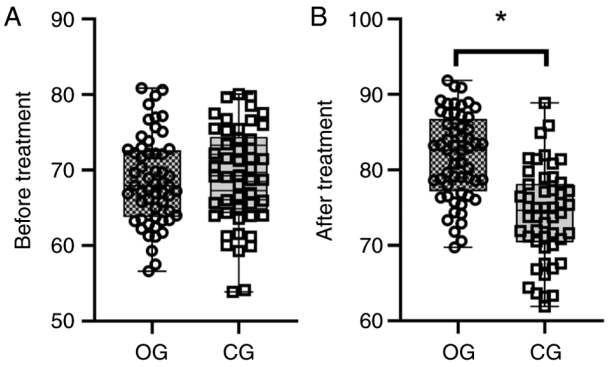

Figure 4. Comparison of KPS scores between the two groups before and after treatment. (A) Before treatment, there was no statistically significant difference in KPS scores between the two groups (P>0.05). (B) After treatment, KPS scores in the OG were higher compared with those in the CG (P<0.05). *P<0.05. OG, observation group; CG, control group; KPS, Karnofsky Performance Status.

Discussion

Lymphoma is one of the most common types of malignant tumors. Data have indicated that the incidence of lymphoma has been increasing globally in recent years, which accounts for 3-4% of all malignant tumor cases (21). Epidemiological

Table II. Univariate analysis of prognostic factors in patients with non-Hodgkin lymphoma.

General clinical data	Survival subgroup (n=91)	Death subgroup (n=15)	t/χ^2/Fisher	P-value
Sex			2.323	0.128
Male	61	7		
Female	30	8		
Age, years	50.23±8.56	49.69±7.56	0.326	0.811
Pathological type			0.889	0.346
B cell	60	8		
T cell	31	7		
Ann Arbor stage			28.467	<0.001
II	28	0		
III	52	4		
IV	11	11		
International Prognostic Index score for lymphoma, points			10.892	0.002
0-1	28	0		
2-3	63	14		
4-5	0	1		
Therapeutic measures			2.665	0.103
Oxaliplatin combined with gemcitabine	51	5		
Oxaliplatin	40	10		

Values are expressed as the mean ± standard deviation or n.

Table III. Multivariate analysis of prognostic factors in patients with non-Hodgkin lymphoma.

Risk factors	B	SE	Wald χ^2	P-value	OR	95% CI
Ann Arbor stage	0.617	0.203	8.135	0.005	1.844	1.209-2.787
International Prognostic Index score for lymphoma	0.067	0.020	7.216	0.008	1.062	1.015-1.104

OR, odds ratio.

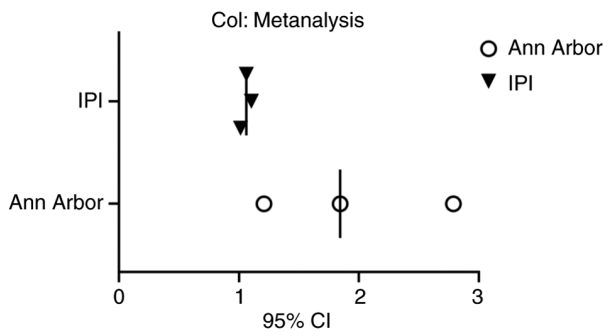

Figure 5. Analysis of prognostic factors in patients with non-Hodgkin lymphoma. Multivariate logistic regression analysis indicated that the Ann Arbor stage and the IPI score for lymphoma were independent prognostic risk factors for patients with non-Hodgkin lymphoma. IPI, International Prognostic Index.

studies have indicated that lymphoma ranks 12th in terms of incidence in China, with its mortality rate positioned 9th among malignant tumors in men and 15th in women (22). NHL is not a singular disease, rather a collective term for various lymphomas with diverse biological behaviors, 85-90% of which originate from B lymphocytes, with the remainder arising from T or NK lymphocytes. Due to its high heterogeneity, there are notable differences in treatment and prognosis (23). Currently, chemotherapy remains the primary treatment for NHL. Although the advent of drugs such as rituximab, alemtuzumab and oxaliplatin has improved the prognosis of patients with NHL, clinical practice indicates that some patients still experience poor efficacy and notable drug resistance with oxaliplatin treatment or notable toxic side effects during chemotherapy, adversely affecting their prognosis (24).

The present retrospective study compared the intervention effects of oxaliplatin alone vs. oxaliplatin combined with gemcitabine in patients with NHL. The results indicated that the combination therapy significantly improves the overall treatment efficacy and DCR compared with oxaliplatin monotherapy. A multicenter study involving 196 patients with NHL indicated that the combined use of oxaliplatin and gemcitabine

is effective, with 63% of patients benefiting from the treatment, 33% achieving CR, a PFS of 5 months and an OS of 10 months (25). Although oxaliplatin has a stronger DNA inhibitory effect compared with traditional cisplatin chemotherapy drugs (26), oxaliplatin still belongs to the conventional platinum-based chemotherapy category and carries a risk of resistance, thereby reducing its efficacy. Gemcitabine is a novel nucleoside analogue that primarily acts on S-phase cells, which inhibits DNA synthesis and thereby induces apoptosis, and this mechanism endows gemcitabine with broad-spectrum antitumor activity (27). Furthermore, the mechanisms of gemcitabine and oxaliplatin are distinct, and their combination produces a synergistic effect. Therefore, combination therapy is more effective compared with monotherapy, as reflected in the serological indicators and KPS scores of the two groups of patients in the present study.

The present study further compared the safety differences in chemotherapy between two groups of patients, which indicated that the addition of gemcitabine did not significantly increase the incidence of various toxic side effects, including leukopenia and abnormal liver and kidney function. This may be attributed to the reduction in the dosage of oxaliplatin due to the addition of gemcitabine. This finding has also been corroborated in previous studies. Qu *et al* (28) administered a salvage chemotherapy regimen of decitabine combined with oxaliplatin to 14 patients with relapsed NHL and the results indicated a 2-year OS rate of 42.7%, markedly higher compared with previously reported levels; the most common toxic side effect during treatment was hematologic toxicity, but all adverse effects were reversible, suggesting a favorable safety profile for the combination therapy. The advantage of gemcitabine over conventional chemotherapeutic agents lies in its self-potentiation mechanism, which enhances the efficacy of combination therapy, allowing for a reduced dosage of other chemotherapeutic drugs and thereby ensuring the safety of the combined treatment (29).

The results of the present study indicated that there were no statistically significant differences in serum LDH and TGF-β1 levels between the two groups before chemotherapy; however, after chemotherapy, the OG exhibited significantly lower levels of both serum LDH and TGF-β1 compared with the CG. LDH, a key glycolytic enzyme widely distributed in tissues, is often elevated in patients with lymphoma, reflecting increased tumor burden and heightened proliferative activity of malignant cells (30). In the present study, the post-treatment LDH levels in the OG were significantly reduced compared with the CG, which suggests that the combination therapy of gemcitabine and oxaliplatin more effectively suppressed the metabolic activity and proliferation of tumor cells, thereby reducing tumor burden. This finding aligns with the higher CRR and DCR observed in the OG, further substantiating the advantage of the combined regimen (19). TGF-β1, a multifunctional cytokine, serves a complex role in tumorigenesis and progression (31). While TGF-β1 may inhibit cellular proliferation during early tumor development, it promotes tumor progression and metastasis in advanced stages through mechanisms such as angiogenesis, immunosuppression and epithelial-mesenchymal transition (20). The significant post-treatment reduction in TGF-β1 levels observed in the OG suggests that gemcitabine combined with oxaliplatin may exert a synergistic antitumor effect by modulating the tumor microenvironment and inhibiting the TGF-β1 signaling pathway.

Lastly, multivariate logistic regression analysis was performed to investigate the risk factors affecting the prognosis of patients with NHL and the results indicate that both the Ann Arbor stage and the IPI score for lymphoma are independent prognostic risk factors for patients with NHL, inconsistent with the expected outcomes. We hypothesized that differences in treatment regimens would impact the prognosis of patients with NHL. The observed phenomenon may be attributed to the small sample size of enrolled patients and the relatively short follow-up period. Furthermore, the follow-up outcomes of the present study were only survival or mortality, whereas recurrence rate, which serves as another key indicator for evaluating NHL prognosis, was not explored due to limitations in follow-up data.

Although the present study offers notable insights into the treatment and prognostic analysis of patients with NHL, it has certain limitations: i) The present study is a retrospective analysis with a relatively small sample size; however, the inability to randomize patient grouping may introduce some bias in the results; ii) due to the retrospective design in nature, the selection of certain variables was limited. For instance, prognostic factor analysis may be influenced by elements such as molecular biomarkers and gene mutations; however, these factors could not be assessed in the present study; iii) in assessing the prognosis of patients with NHL, the present study only used OS as the primary evaluation criterion; however, factors such as quality of life and disease recurrence may also exert a considerable influence on patient prognosis; and iv) due to the limited number of cases, it was not possible to comprehensively classify all NHL subtypes in accordance with the 2016 WHO classification. The intrinsic heterogeneity of NHL may impact the findings. Furthermore, even within the same NHL subtype, notable variations may exist in genetic background, immune status and treatment response. These differences warrant further elucidation of the molecular heterogeneity of NHL through genomic, immunohistochemistry and other advanced techniques, thereby informing and guiding personalized therapeutic strategies.

Due to the aforementioned limitations of the present study, future research directions may include the following. First, the design of prospective randomized controlled trials is warranted. Future studies should be performed as multicenter, large-sample, randomized prospective studies to further validate the efficacy and safety of the gemcitabine-oxaliplatin regimen in the treatment of NHL, thereby enhancing the level of evidence. Second, considering the potential impact of heterogeneity of NHL on treatment outcomes, future studies should strictly classify NHL subtypes according to the WHO 2016 classification criteria and evaluate the differential responses of various subtypes to combination therapy, thereby providing a foundation for precision treatment. Third, prognostic analyses should incorporate a broader range of molecular biomarkers and genetic mutations, such as Myc, Bcl-2 and Bcl-6 rearrangements or expression, p53 mutations and CD20 expression levels, combined with clinical staging and

the IPI to construct a more accurate prognostic evaluation model. Fourth, in recent years, the therapeutic landscape of NHL has undergone profound transformation with the emergence of various immunotherapeutic strategies, including immune checkpoint inhibitors, CAR-T cells and bispecific antibodies. These novel therapies hold notable potential, particularly in certain NHL subtypes, particularly among patients with relapsed or refractory NHL. Future studies may compare the efficacy of the gemcitabine-oxaliplatin regimen with these emerging immunotherapies or explore the optimal sequencing or combination strategies integrating chemotherapy with immunotherapy.

In conclusion, the combination therapy of gemcitabine and oxaliplatin was confirmed to be safe for patients with NHL. This treatment demonstrated notable overall efficacy and improved functional improvement compared with oxaliplatin monotherapy. The Ann Arbor stage and the IPI score for lymphoma are independent prognostic factors for patients with NHL.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XZ and FL designed the present study. XZ, GL, FL, RS, JW, WW and JD performed the research and analyzed the data. XZ and GL contributed towards novel methods in the present study and wrote the manuscript. WW and JD confirm the authenticity of the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Xi'an Central Hospital/Xi'an Institute of Hematology ethics committee (approval no. 2024-JT-023; Xi'an, China). All study participants provided written informed consent before participating in the present study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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