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ORIGINAL ARTICLE

Effect of second-line chemotherapy in treating relapsed or refractory diffuse large B cell lymphoma and prognosis analysis

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Summary

Purpose: *To investigate the efficacy of second-line regimen in treating relapsed or refractory diffuse large B-cell lymphoma (DLBCL), and to analyze relevant prognostic factors.*

Methods: *The clinical data of 105 patients with relapsed or refractory DLBCL admitted and treated from July 2004 to June 2016 were retrospectively reviewed, the response rate after chemotherapy was assessed, and overall survival (OS) was calculated using Kaplan-Meier method. Moreover, Cox regression model was adopted for multivariate analysis, so as to find the independent prognostic factors influencing patient's OS.*

Results: *Among the 105 patients, there were 67 males and 38 females, with a median age of 57.54 years. There were 31 cases of CR and 21 cases of PR, and the objective response rate (ORR) was 49.5%. In addition, early progression or recurrence <12 months of relapsed or refractory DLBCL and high-risk international prognostic index (IPI) were the negative factors for response rate to chemotherapy. At the end of follow-up, the median OS of the patients was 14.7 months, and the median progression-free survival (PFS) was 12.4 months. Among the patients, the 1-year OS and 1-year PFS rates were 59.0% and 50.5%, respectively, the 2-year OS and 2-year PFS rates were 41.9% and 38.1%, respectively, and the 3-year OS and 3-year PFS rates were 30.5% and 27.6%, respectively. Multivariate analysis showed that high-risk IPI was an independent risk factor influencing the survival of patients, and response rate after chemotherapy was an independent prognostic indicator for improving the OS rate of patients.*

Conclusion: *Different chemotherapy regimens as second-line treatment for relapsed or refractory DLBCL are effective and safe. High-risk IPI is an independent risk factor influencing the survival of patients with relapsed or refractory DLBCL, and response rate after chemotherapy is an independent prognostic indicator for extending the OS of patients.*

Key words: *methotrexate, lymphoma, rituximab, central nervous system tumor, efficacy*

Introduction

Diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin's lymphoma (NHL), accounts for 30-40% of all NHL cases, and 40% of DLBCL patients have involvement of extranodal sites [1]. The complete response (CR) rate of standard first-line treatment regimen R-CHOP-21 (rituximab+cyclophosphamide + doxorubicin + vincristine + prednisone, with 21 days as one course of treatment) for DLBCL is up to 75-80%, but DLBCL still recurs in 30-40% of the patients, ultimately transforming into refractory DLBCL [2-4].

Clinically, it is still very difficult to treat relapsed or refractory DLBCL, and there is a lack of standard salvage treatment regimens for the disease at present. High-dose chemotherapy com-

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bined with autologous hematopoietic stem cell transplantation (Auto-HSCT) can improve the response rate and survival of relapsed or refractory DLBCL, but it is not suitable for all the patients due to conditions such as individual heterogeneity, performance status, age and induction treatment. The salvage treatment aims to alleviate disease, prolong survival and improve the quality of life of patients [5,6]. Both DHAP (dexamethasone+cytarabine+cisplatin) and ICE (ifosfamide+carboplatin+etoposide) are available second-line regimens in the clinic [7,8].

In this research, the efficacy of different second-line regimens in treating relapsed or refractory DLBCL was investigated, and relevant prognostic factors were analyzed, so as to provide a powerful basis for the selection of clinical treatment regimens for such patients.

Methods

Research subjects

The data of 105 patients with relapsed or refractory DLBCL who were admitted to and treated in our hospital from July 2004 to June 2016 were collected. Inclusion criteria: patients definitely diagnosed with DLBCL via biopsy, those who underwent unsuccessful standard chemotherapy regimen R-CHOP/CHOP or had relapse or progression in a short-term, those aged 18-80 years old, those with evaluable lesions and Karnofsky performance status (KPS) score >50 points, and those with a life expectancy >3 months. Exclusion criteria: patients with other types of NHL, severe organ dysfunction, chemotherapy contraindications, psychiatric diseases or immune system diseases. The diagnosis of all patients was in line with the criteria of 2008 World Health Organization (WHO) classification of lymphoid neoplasms, and the prognosis of patients was evaluated using the international prognostic index (IPI) score, including age, performance status, lactate dehydrogenase (LDH) level, number of involved extranodal sites and Ann Arbor clinical stage. Patients were assigned into low-risk group (IPI score: 0-1 point), medium-risk group (IPI score: 2-3 points) and high-risk group (IPI score: 4-5 points). The *Declaration of Helsinki* was followed, the duty of disclosure was performed, the research was reviewed by the Ethics Committee of Changzhou No.2 People's Hospital, and all the patients enrolled signed the informed consent form.

Therapeutic methods

A total of 57 patients were treated with R-ICE chemotherapy regimen (rituximab + ifosfamide + carboplatin + etoposide), 17 patients received GDP + V chemotherapy regimen (gemcitabine + dexamethasone + cisplatin + bortezomib), 12 patients were treated with R-Hyper-CVAD chemotherapy regimen (cyclophosphamide + vincristine + doxorubicin + dexamethasone/methotrexate + cytarabine + dexamethasone), 10 patients underwent R-DHAP chemotherapy regimen (rituximab + dexamethasone + cytarabine + cisplatin), and 9 patients received R-NAPD chemotherapy regimen (rituximab + vinorelbine + cytarabine + cisplatin).

The dose of chemotherapeutic drugs was decreased by 25-50% when the white blood cell count declined to 0.5-0.9×10^9/L during chemotherapy. Chemotherapy was delayed by 1 week when the white blood cell count declined below 0.5×10^9/L during treatment, and recombinant human granulocyte colony-stimulating factor (G-CSF) was administered when the blood cell count decreased to 3.0×10^9/L. As for the patients who manifested grade IV bone marrow suppression during chemotherapy, G-CSF and antibiotics were administered simultaneously to prevent infection. Granisetron was given routinely before chemotherapy to prevent gastrointestinal reactions.

Observation indexes

After chemotherapy, the efficacy was evaluated by means of PET-CT or enhanced CT of the neck, chest, abdomen and pelvic cavity according to the 2007 criteria of international working groups. The efficacy was classified as CR (The tumor focus and clinical signs and symptoms disappear for more than 4 weeks), partial response (PR) (PR: The volume of tumor focus is decreased by >50%, without new foci for more than 4 weeks), stable disease (SD) (The volume of tumor focus is decreased by ≤ 50%, without new foci for more than 4 weeks) and progressive disease (PD) or relapse (The volume of tumor focus is increased by >25%, or new foci emerge) [9].

The toxic and side effects of the drugs were assessed according to the WHO criteria for acute and subacute toxic reactions of anticancer drugs. The toxic and side effects of chemotherapy in the patients were observed and recorded, mainly including anemia, leucopenia, thrombosis, alopecia, peripheral neuritis and hepatic or renal function damage.

The survival conditions of the patients was followed up and recorded through telephone call and review of inpatient and outpatient medical records, and the follow-up ended on October 31, 2019. The overall survival (OS) is defined as the time interval from the definite diagnosis to death or the last follow-up. The progression-free survival (PFS) is defined as the time interval from the definite diagnosis to PD, relapse, death or the end of follow-up.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was utilized for statistical analysis. The measurement data were expressed by mean ± standard deviation (x±s), and two-sample t-test was performed for inter-group comparison. The enumeration data were presented as ratio (%) and compared via x^2 test or Fisher's exact test. The t-test was used for analyzing measurement data. Differences between two groups were analyzed by using the Student's t-test. Comparison between multiple groups was done using One-way ANOVA test followed by *Post Hoc* Test (least significant difference). The survival curves were plotted using the Kaplan-Meier method and compared

by log-rank test, and Cox regression models were used for univariate and multivariate analyses. P<0.05 suggested that the difference was statistically significant.

Results

General patient data

Among the 105 patients, there were 67 males and 38 females, with a median age of 57.54 years. 61 (58.1%) had Ann Arbor stage III-IV. 49 (46.7%) had ≥2 involved extranodal organs. Fifty-six (53.3%) patients had extranodal lesions at certain sites (bone marrow, central nervous system, liver, gastrointestinal tract or lung), including 43 (41.0%) cases of bone marrow involvement, 35 (33.3%) of of gastrointestinal tract involvement, 7 (6.7%) of skeleton, involvement, 5 (4.8%) of adrenal gland involvement and 6 (5.7%) cases of lung involvement. There were 66 (62.9%) cases of elevated serum LDH and 52 (53.1%) cases of anemia. Sixty-two (59.0%) patients had a time interval from initial diagnosis to progression or relapse <12 months, and 20 (19.0%) patients had high-risk IPI. As for the Hans's classification, 33 (31.4%) belonged to germinal center B-cell-like (GCB) subtype, and 72 (68.6%) belonged to non-GCB subtype. The cases of Ki-67 positive rate ≥70% and KPS score ≥70 points were 78 (74.3%) and 41 (39.0%), respectively (Table 1).

Efficacy in patients after chemotherapy

Of the 105 patients, 31 achieved CR and 21 PR, with an objective response rate (ORR) of 49.5% (52/105). The median number of treatment courses of R-ICE regimen was 3 (1-6) among the 57 patients, and the median number of treatment courses needed to reach response (CR or PR) was 3 (2-6). In GDP + V group, the median number of treatment courses among the 17 patients was 3 (1-6), and 3 (2-6) median treatment courses were needed to reach response. As for the 12 patients in R-Hyper-CVAD group, the median number of treatment courses of was 2 (1-5), and the median number of treatment courses needed to reach response was 2 (1-5). For the 10 patients in R-DHAP group, the median number of treatment courses of R-ICE regimen was 2 (1-4), and 2 (2-4) median treatment courses were required to obtain response. In the NAPD group, the median number of treatment courses among the 9 patients was 3 (1-6), and the median number of treatment courses needed to reach response was 3 (1-6). The ORR in R-ICE, GDP + V, R-Hyper-CVAD, R-DHAP and NAPD groups was 56.1% (32/57), 47.1% (8/17), 41.7% (5/12), 40.0% (4/10) and 33.3% (3/9), respectively. In addition, early progression or recurrence <12 months of relapsed or refractory DLBCL and high-risk IPI were negative factors for response to chemotherapy (p=0.029, p=0.035), while Ann Arbor stage as well as Hans's classification had no statistically significant impact on patient's response to chemotherapy (p=0.555, p=0.675) (Tables 2 and 3).

Incidence of adverse reactions

Bone marrow suppression was the major adverse reaction in patients after chemotherapy, manifested as leucopenia, febrile neutropenia, anemia

Table 1. Demographics and general clinical data of all studied patients

Parameters	*Cases (%) n=105*
Gender (Male/Female)	67/38
Age (years)	57.54±10.14
Ann Arbor staging	
I-II	44 (41.9)
III-IV	61 (58.1)
IPI	
Low-risk	38 (36.2)
Middle-risk	47 (44.8)
High-risk	20 (19.0)
Extranodal lesions	
0 or 1	56 (53.3)
≥2	49 (46.7)
LDH	
Normal	39 (37.1)
Elevated	66 (62.9)
Hemoglobin	
Normal	50 (47.6)
Reduced	55 (52.4)
Albumin	
Normal	68 (64.8)
Reduced	37 (35.2)
Progression or recurrence time, months	
<12	62 (59.0)
≥12	43 (41.0)
Hans classification	
Germinal Center B-cell-like	33 (31.4)
Non-germinal center B-cell-like	72 (68.6%)
Ki-67 positive rate	
<70	27 (25.7%)
≥70	78 (74.3%)
Karnofsky score	
70-90	41 (39.0%)
50-70	64 (61.0%)

LDH: Lactate dehydrogenase; IPI: International prognostic index

and thrombocytopenia, followed by gastrointestinal tract reactions and mild impairment of hepatic and renal function. There were fewer cases of thrombosis, alopecia and peripheral neuritis. Only 1 case of chemotherapy-related death due to cerebral hemorrhage occurred after grade IV thrombopenia. All the gastrointestinal tract reactions belonged to grade I-II, other adverse reactions were improved or eliminated after dose reduction or symptomatic treatment, and all the patients were tolerable to chemotherapy.

Table 2. Clinical effective rates of the studied patients

	Cases (n=105) n (%)
CR	31 (31.5)
PR	21 (50.0)
SD	34 (38.9)
PD	19 (18.5)
ORR	52 (49.5)

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Overall response rate

Follow-up results of patient's survival

All the patients were followed up for 5-36 months as of October 2019, with a median follow-up time of 22.6 months. The median OS of the patients was 14.7 months, and the median PFS was 12.4 months. Among the patients, the 1-year OS and 1-year PFS rates were 59.0% (62/105) and 50.5% (53/105), respectively, the 2-year OS and 2-year PFS rates were 41.9% (44/105) and 38.1% (40/105), respectively, and the 3-year OS and 3-year PFS rates were 30.5% (32/105) and 27.6% (29/105), respectively. The survival curves of the patients plotted via Kaplan-Meier method are shown in Figure 1.

Table 3. Factors influencing the response rate after chemotherapy in patients with DLBCL

Parameters	*Cases (n=105) n (%)*	*Response rate (n=52) n (%)*	*p value*
Ann Arbor staging			0.555
I-II	44 (41.9)	20 (45.5)	
III-IV	61 (58.1)	32 (52.5)	
IPI score			0.035
Low-risk	38 (36.2)	23 (60.5)	
Middle-risk	47 (44.8)	24 (51.1)	
High-risk	20 (19.0)	5 (25.0)	
Progression or Recurrence time			0.029
<12 months	62 (59.0)	25 (40.3)	
>12 months	43 (41.0)	27 (62.8)	
Hans classification			0.675
Germinal Center B-cell-like	33 (31.4)	15 (45.5)	
Non-germinal center B-cell-like	72 (68.6)	37 (51.4)	

DLBCL: Diffuse large B-cell lymphoma; IPI: International prognostic index

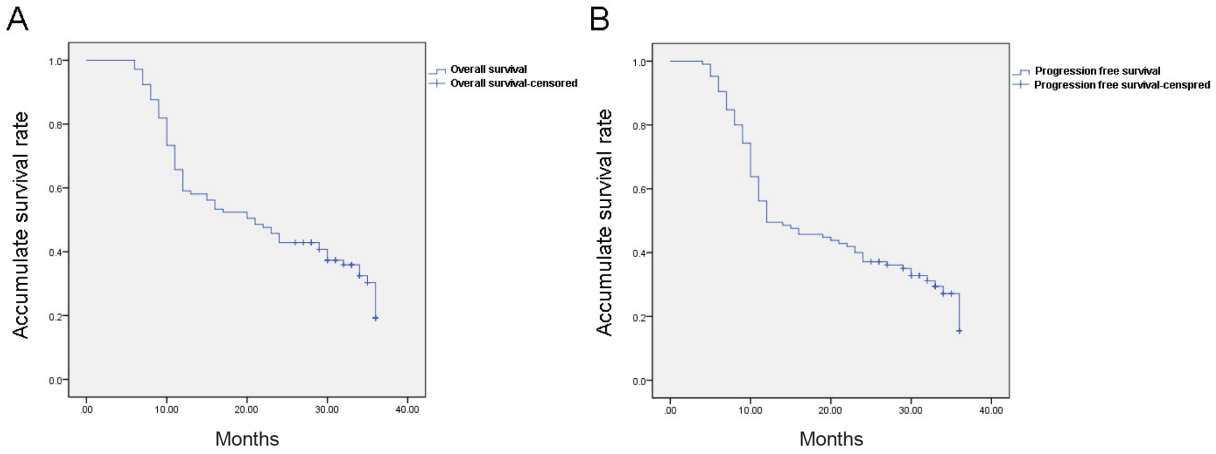

Figure 1. Kaplan-Meier survival curves of diffuse 1arge B-cell 1ymphoma patients. The overall survival rate **(A)** and progression-free survival rate **(B)** of studied patients are shown.

Analysis results of prognostic factors for survival of patients

The factors influencing the prognosis of patients such as gender, age, Ann Arbor stage, number of involved extranodal sites, specific sites of extranodal lesions, serum LDH, hemoglobin level, serum albumin, time of progression or recurrence, Hans's classification, Ki-67, IPI score, KPS score and response rate after chemotherapy were included into univariate analysis. The results indicated that the rise in serum LDH, serum albumin, early progression or recurrence (<12 months) and high-risk IPI were the negative factors for the OS of patients (p=0.009, p=0.021, p=0.031, p<0.001), and the response rate after chemotherapy was remarkably correlated with the prolongation of patient's OS (p<0.001). However, the gender (p=0.750), age (p=0.879), Ann Arbor stage (p=0.545), number of involved extranodal lesions (p=0.757), hemoglobin level (p=0.363), presence of germinal centers in Hans's classification (p=0.456), Ki-67 positive rate (p=0.247) and KPS score (p=0.592) had no prominent associations with the survival of patients (Table 4).

The aforementioned four factors exhibiting statistical significance in the univariate analysis were selected for multivariate analysis through Cox's proportional hazards regression model. The results revealed that high-risk IPI [hazard ratio (HR) =2.353, 95% confidence interval (CI): 1.349-3.594, p<0.001] was an independent risk factor influencing the survival of patients, and response rate after chemotherapy [HR=0.395, 95% CI: 0.351-0.690, p<0.001] was an independent prognostic indicator for improving the OS rate of patients (Table 5).

Discussion

DLBCL, a subtype of lymphoma that frequently occurs in people aged over 40 years, is characterized by invasiveness and rapid growth, with morbidity rate increasing by 3-4% every year. Its clinical manifestations, tissue morphology and prognosis are highly heterogeneous, seriously threatening the life of patients [10,11]. Chemotherapy combined with rituximab can distinctly improve the response rate and survival of DLBCL

Table 4. Univariate analysis of predictors for 3-year overall survival rate in patients with DLBCL

Parameters	*3-year overall survival rate* %	*HR (95%CI)*	*p value*
Male	40.3	1.154 (0.578-1.696)	0.750
Age ≥60 years	41.1	0.899 (0.610-1.475)	0.879
Ann Arbor III-IV staging	41.0	1.316 (0.818-1.890)	0.545
IPI High-risk	20.0	1.823 (1.720-4.792)	0.001
Extranodal tumor lesions ≥2	26.5	0.847 (0.590-1.471)	0.757
Elevated LDH level	21.2	2.235 (1.463-3.396)	0.009
Anemia	29.1	1.451 (0.766-2.282)	0.363
Reduced albumin level	21.6	1.820 (1.129-3.030)	0.021
Progression or recurrence <12 months	21.0	1.736 (1.293-3.080)	0.031
Germinal Center B-cell-like	30.3	1.344 (0.535-3.134)	0.456
Ki-67 positive rate ≥70%	41.0	0.606 (0.447-1.184)	0.247
Karnofsky Score ≥70	41.5	0.788 (0.585-1.670)	0.592
Response rate after chemotherapy	44.2	0.413 (0.266-0.731)	0.001

DLBCL: Diffuse large B-cell lymphoma; LDH: Lactate dehydrogenase; IPI: International prognostic index

Table 5. Multivariate Cox regression analysis of predictors for DLBCL patients

Parameters	*HR*	*95%CI*	*p value*
IPI High-risk	2.353	1.349-3.594	0.001
Elevated LDH level	2.012	1.478-2.672	0.229
Reduced albumin level	1.576	1.198-2.717	0.396
Progression or recurrence <12 months	1.934	1.367-2.370	0.448
Response rate after chemotherapy	0.395	0.351-0.690	0.001

DLBCL: Diffuse large B-cell lymphoma; LDH: Lactate dehydrogenase; IPI: International prognostic index; HR: Hazard ratio; CI: Confidence interval

patients. In recent years, first-line treatments represented by R-CHOP regimen have exact efficacy in DLBCL patients, and the overall response rate can reach 70-78%, but the proportion of short-term relapsed and refractory cases remains high [12,13]. In the current clinical practice, most patients with relapsed or refractory DLBCL undergo Auto-HSCT after salvage chemotherapy. The high-dose chemotherapy combined with Auto-HSCT is capable of raising the CR and OS rates of the patients [14]. However, as for the patients unsuitable for direct Auto-HSCT in the initial stage of relapse and progression because of the differences in individual heterogeneity, performance status, age and induction treatment, the second-line salvage treatment regimens are still the first choice for patients with relapsed or refractory DLBCL [15].

According to CORAL studies, the efficacy and prognosis of CD20+DLBCL patients who had the first relapse or were insensitive to first-line treatment regimens were compared between R-ICE and R-DHAP regimens. It was found that both regimens resulted in similar prognosis, and the ORR was 63.5% and 62.8%, respectively. Moreover, the differences in 3-year event-free survival (EFS), PFS and OS rates were not statistically significant between the groups, but R-DHAP group exhibited higher incidence rates of thrombocytopenia and renal toxicity [16]. For the patients with relapsed DLBCL who have been treated with chemotherapy combined with rituximab in China, R-ICE is still an effective salvage regimen, and its adverse reactions are manageable. In this research, the ORR of patients treated with R-ICE regimen was 56.1%, which may be related to the relapsed and refractory properties of the disease. Kuruvilla et al conducted a phase III clinical study on GDP and DHAP regimens for relapsed or refractory DLBCL patients in 2015, and the results revealed that both regimens had a similar response rate and no significant differences in the impacts on prognosis [17]. The ORR was 40.0% among the 19 patients in GDP+V group in this study, and the number of patients should be increased in the future to objectively evaluate the efficacy of GDP regimen. Besides, targeted drugs, such as lenalidomide, are expected to further ameliorate the prognosis of patients with relapsed or refractory DLBCL [18,19].

IPI is always a recognized evaluation criterion for prognosis of DLBCL, which consists of 5 clinical indicators, namely, age, ECOG score, Ann Arbor stage, LDH level and number of involved extranodal lesions [1]. Even in the era of rituximab, IPI serves as a powerful indicator of prognosis assessment, from which many optimized scoring methods are derived, including the revised IPI (R-IPI) and ALC/R-IPI [20,21]. In the PARMA study, 188 patients with first-relapse middle- and high-grade NHL were analyzed, and it was revealed that early relapse is a negative factor affecting patient's prognosis, and the patients with varying prognosis can be distinguished by the time interval from the first relapse to initial diagnosis (<12 months) ($p<0.001$), the time to the first CR (<6 months) ($p<0.001$) or the time to accomplish initial treatment (<5 months) ($p<0.001$) [22]. Furthermore, the CORAL study analyzed the CD20+DLBCL patients with first relapse or insensitivity to first-line treatment regimens for the first time, and the results demonstrated that early relapse (<12 months from initial diagnosis), medium-high-risk or high-risk IPI and no previous treatment with rituximab were the independent risk factors for response rate, EFS and OS [16]. Based on the results of univariate analysis in this research, the rise in serum LDH, serum albumin, early progression or recurrence (<12 months) and high-risk IPI were the negative factors for the survival of patients, which is consistent with literature reports. In the multivariate analysis, the high-risk IPI was an independent risk factor influencing patient's survival, and response rate after chemotherapy was an independent prognostic indicator for the improvement of the OS rate of patients.

Bairey et al [23] investigated the prognostic roles of laboratory indicators before treatment, and discovered through univariate analysis that the hemoglobin level (120 g/L) and serum albumin level (3.5 g/L) before treatment are correlated with patient's survival. Additionally, multivariate analysis via Cox regression model revealed that the serum albumin level before treatment serves as an independent prognostic factor for OS of the patients. According to another study on DLBCL, patients aged above 80 years and treated with R-miniCHOP elucidated that only the serum albumin level ≤35 g/L before treatment was an independent risk factor influencing patient's OS [24]. In this research, univariate analysis suggested that the serum albumin level had an association with the survival of patients, while its impact on patient's OS was not reflected in the multivariate analysis, which might be related to the relapsed or refractory property and the small number of patients.

As a retrospective study, this research enrolled a limited number of patients, the follow-up time was not long enough, and the follow-up content was not comprehensive enough. Besides, the effects of different chemotherapy regimens on the efficacy were not deeply analyzed, so it is necessary to design more rigorous multi-center, large-sample, prospective randomized studies to verify the conclusion of this research in the future.

Conclusions

Different chemotherapy regimens as second-line treatment for relapsed or refractory DLBCL are effective and safe. High-risk IPI is an independent risk factor influencing the survival of patients with relapsed or refractory DLBCL, and response rate after chemotherapy is an independent prognostic indicator for prolonging the OS of patients.

Conflict of interests

The authors declare no conflict of interests.

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