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Original Article

Thalidomide combined with ifosfamide significantly improves survival in patients with pulmonary metastatic osteosarcoma

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Abstract: Objective: To evaluate the efficacy and safety of thalidomide combined with ifosfamide (IFO) in the treatment of pulmonary metastatic osteosarcoma and to compare its outcomes with the IFO plus etoposide (ETOP) regimen, providing a reference for the clinical treatment of osteosarcoma. Methods: In this retrospective study, clinical data from 95 patients with pathologically confirmed osteosarcoma were analyzed. Of these, 55 patients received thalidomide + IFO (Observation group), and 40 patients received IFO + ETOP (Control group). Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and adverse reactions (ARs) were compared between the two groups. Results: After treatment, the maximum diameters of both primary tumors and lung metastatic (LM) lesions in the Observation group were significantly smaller than those in the Control group. The median PFS was 10 months in the Observation group and 7.5 months in the Control group; the median OS was 22 months in the Observation group and 14 months in the Control group. The ORR and DCR in the Observation group were 23.63% and 52.73%, both significantly higher than those in the Control group ($P<0.05$). The incidences of hematological toxicity, gastrointestinal reactions, and renal dysfunction were significantly lower in the Observation group than in the Control group ($P<0.05$). Multivariate Cox regression analysis identified number of pulmonary metastases (HR=1.256, $P=0.038$), T stage (HR=1.453, $P=0.033$), N stage (HR=1.389, $P=0.035$), receipt of radiotherapy (HR=1.589, $P=0.018$), and LDH levels (HR=1.356, $P=0.015$) as independent prognostic factors for pulmonary metastatic osteosarcoma. Conclusion: Thalidomide + IFO notably improves PFS and OS in patients with pulmonary metastatic osteosarcoma, demonstrating superior safety compared with the IFO-ETOP regimen.

Keywords: Thalidomide, IFO, ETOP, osteosarcoma, PFS

Introduction

Osteosarcoma is a highly aggressive malignant bone tumor with strong metastatic potential [1], predominantly arising in long bones, such as the femur, tibia, and humerus. Despite advances in surgical resection and chemotherapy, the 5-year survival rate remains poor, particularly in cases with lung metastases (LM) [2-4]. The lung is the most common site of distant spread, typically within the first two years after diagnosis, and the clinical results have obviously deteriorated. Approximately half of osteosarcoma patients experience lung metastasis at initial diagnosis, complicating treatment and increasing the risk of recurrence. Although traditional methods such as surgery and chemotherapy may prolong survival in some cases, their limited efficacy and potential risks underscore the urgent need for novel and more effective treatment methods [5].

The standard therapy for osteosarcoma includes radical surgical resection combined with adjuvant chemotherapy. However, the invasive nature and high metastatic potential of osteosarcoma often limit the efficacy of chemotherapy alone, and treatment-related toxicities remain a significant concern [6, 7]. To address these limitations, targeted therapy and immunotherapy have emerged as promising adjuncts to traditional treatment. Among these, thalidomide has attracted much attention for its multiple mechanisms of action, including immuno-

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modulation, anti-angiogenesis, and direct anti-tumor effects, demonstrating potential clinical benefits in osteosarcoma [8]. Ifosfamide (IFO), an alkylating agent with broad-spectrum anti-tumor activity, remains a cornerstone of various chemotherapy schemes for malignant tumors, including osteosarcoma. Its primary mechanism involves binding to DNA, inducing DNA strand breakage, and inhibiting cell division, thus playing an anti-tumor role [9]. IFO is used in the treatment of various malignancies, including reproductive system cancers, lymphomas, lung cancer, and osteosarcoma. In osteosarcoma, IFO is usually employed as part of a multidrug chemotherapy regimens in combination with agents such as etoposide (ETOP), cisplatin, and doxorubicin [10]. This combination has been reported to enhance therapeutic efficacy by inhibiting tumor cell proliferation, limiting metastasis, and improving survival [11]. Notably, IFO has been shown to considerably reduce tumor burden, especially in late chemotherapy cycles, thereby lowering the risk of local recurrence and distant metastasis of osteosarcoma [12]. Beyond its role in first-line treatment, IFO is also employed in the management of recurrent or metastatic diseases. Nevertheless, its therapeutic benefits are accompanied by prominent side effects, including hematologic toxicity (e.g., leukopenia), gastrointestinal symptoms (e.g., nausea and vomiting), hepatotoxicity, nephrotoxicity, and neurotoxicity. Sarbay et al. reported that IFO may induce reversible encephalopathy, for which prophylactic treatment with methylene blue can help maintain treatment continuity [13]. Additionally, de Oliveira et al. found that IFO resistance may be associated with aberrant gene expression involved in tumor cell migration and proliferation (*e.g.,* EFNB2, EPB41L3) [14].

To fulfill the research gap, this study investigated the synergistic effects of thalidomide combined with IFO, aiming to reduce treatment-related risks while preserving anti-tumor activity, thereby providing an ideal combination regimen for pulmonary metastatic osteosarcoma.

Materials and methods

Subjects

This retrospective study was approved by the Institutional Review Board of Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology. A total of 95 osteosarcoma patients with pathologically and radiologically confirmed LM who received treatment at Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology between January 2020 and December 2022 were included in this study. Their medical records, detailed treatment histories, and clinical outcomes were comprehensively reviewed. The patients was stratified into two groups according to their treatment regimen: the Observation group (thalidomide + IFO-based chemotherapy; n=55) and the Control group (ETOP + IFO-based chemotherapy; n=40).

Inclusion criteria: 1) a pathological diagnosis of osteosarcoma and definitive radiological evidence of LM; 2) patients aged 18 years or older, in good physical condition, and able to tolerate systemic drug treatment; 3) patients with complete clinical data, including initial diagnosis, treatment regimens, follow-up records, and imaging results.

Exclusion criteria: 1) a history of other types of malignancies; 2) severe cardiac, hepatic, or renal diseases, including heart failure (left ventricular ejection fraction <40%), advanced cirrhosis, or renal failure; 3) known allergy or intolerance to thalidomide, IFO, or ETOP chemotherapy drugs; 4) central nervous system metastasis or ineffective previous treatments; 5) women in pregnancy or lactation.

The study design flowchart is shown in **Figure 1** below.

Rationale for control regimen

The combination of ETOP and IFO for the treatment of osteosarcoma with LM aligns with current clinical practice guidelines. According to the *Chinese Society of Clinical Oncology (CSCO) Classic Osteosarcoma Treatment Guidelines 2018.V1*, this regimen is recommended as a standard treatment option for osteosarcoma patients, particularly those with LM. The specific treatment strategy and drug selection in this study adhered to the standards outlined in the guidelines. Details are available at https://book.qq.com/book-read/27611836/10.

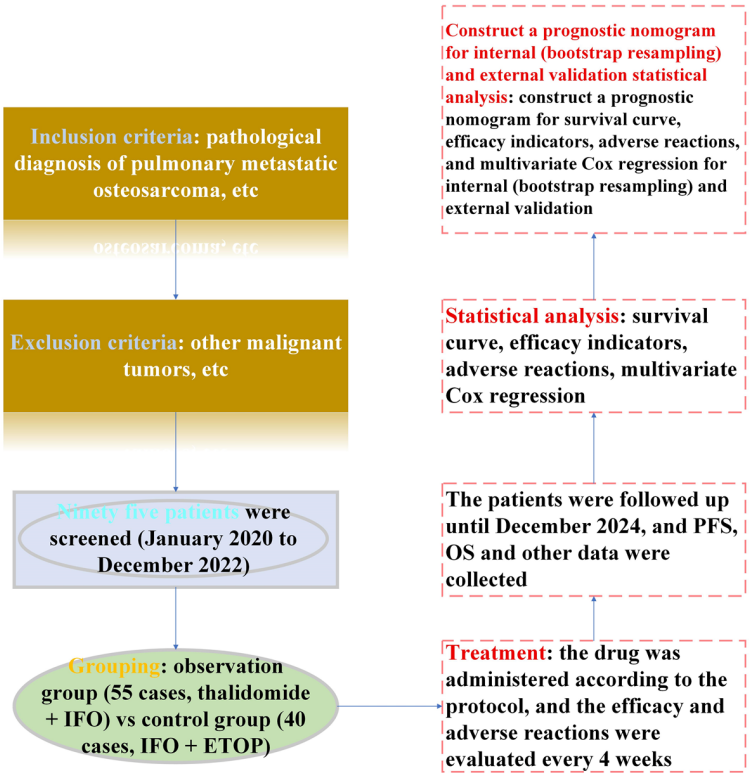

Figure 1. Research and design flow chart.

Treatment plan

Control group: ETOP + IFO regimen: ETOP: for patients with a body surface area (BSA) >1.5 m^2, 1.2 g/m^2, was administered intravenously every 3 weeks; for patients with a BSA ≤1.5 m^2, the dose was adjusted to 1 g/m^2, administered intravenously every 3 weeks.

IFO [15]: for patients with a BSA >1.5 m^2, 1.2 g/m^2 was administered intravenously every 3 weeks; for patients with a BSA ≤1.5 m^2, 1 g/m^2 was administered intravenously every 3 weeks.

In cases of intolerable adverse reactions (ARs), which was assessed every 4 weeks, the dose was reduced according to patient tolerance, typically to 0.9 g/m^2 or 0.8 g/m^2.

Observation group: Thalidomide + IFO regimen: Thalidomide: 50 mg/day, orally, administered continuously throughout the treatment. Efficacy and ARs were assessed every 4 weeks; dose adjustments or treatment suspension were made as necessary in response to ARs.

IFO: dosage and administration were the same as in the Control group, adjusted according to BSA, administered intravenously every 3 weeks.

Chemotherapy protocols: The Control group was treated with Cisplatin and Doxorubicin. Cisplatin 60 mg/m^2 was administered intravenously on Day 1, and Doxorubicin 37.5 mg/m^2 was administered intravenously on Days 1 and 2. Patients received six cycles of treatment, with each cycle lasting 3 weeks.

Observation group received Methotrexate and Cisplatin. Methotrexate 12 g/m^2 was administered intravenously in divided doses, with urinary alkalinization and leucovorin rescue following each dose. Cisplatin 60 mg/m^2 was administered intravenously on Day 1. Patients received six cycles of treatment, with each cycle lasting 3 weeks.

Observation indicators

Baseline data: Baseline data were collected for each patient. Demographic information included age and sex. Pathological data included the histological subtype of osteosarcoma. Tumor-related data encompassed the primary tumor site (*e.g.,* limb bones, pelvis, spine) and details of pulmonary metastases, including location, size, and number of lesions. Comorbidities were also recorded, along with the functional status of major organs, such as the heart, liver, and kidneys.

Time points of observation: Baseline data, including radiological examinations, were collected before treatment initiation. Follow-up assessments were conducted after treatment, with duration varying based on the patient's enrollment time. Follow-up time for each patient was calculated from the enrollment date to the study cutoff date (December 2024).

Primary outcome measures: Progression-Free Survival (PFS): defined as the time from disease progression after first-line chemotherapy to radiological confirmation of new pulmonary lesions or enlargement of existing lesions. Chest CT scans were conducted every 3-6 months after treatment initiation, with earlier assessments if prompted by symptoms or other clinical indications. Radiologists independently evaluated each CT scan to determine progression status and record the time point of progression.

Overall survival (OS): Defined as the time from disease progression after first-line chemotherapy to death from any cause or treatment discontinuation for any reason. OS was the primary endpoint of the study.

Secondary outcome measures: Clinical efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

Complete response (CR): Complete disappearance of all target lesions, sustained for more than 4 weeks; Partial response (PR): reduction in target lesion size by more than 50%, sustained for more than 4 weeks, with no new lesions; Stable disease (SD): no significant change in tumor size (neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD); Progressive disease (PD): increase in tumor size by more than 50%, or the appearance of new lesions. The Objective Response Rate (ORR) was calculated as the proportion of patients achieving CR or PR, and the Disease Control Rate (DCR) was calculated as the proportion achieving CR, PR, or SD.

Radiological evaluation included CT imaging of the primary tumor and pulmonary metastases before and after treatment, with measurement of the maximum diameters of the lesions.

All adverse reactions (ARs) occurring during the treatment period were recorded and graded according to the *Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0* [16]. ARs were categorized as follows: (1) Hematologic toxicity: abnormalities in parameters such as white blood cell count, red blood cell count, and platelet count; (2) Gastrointestinal reactions: nausea, vomiting, diarrhea etc.; (3) Renal dysfunction: elevated serum creatinine, proteinuria.

Follow-up duration and methods: The observation period extended from patient enrollment until the study cutoff data (December 2024). Individual follow-up duration varied according to enrollment time. All participants underwent scheduled clinical evaluations at our institution, including comprehensive physical examinations, imaging studies, and laboratory tests.

For patients unable to attend in person, follow-up was conducted through structured telephone interviews or telemedicine consultation. These remote assessments served the dual purpose of monitoring clinical status and providing psychological support. All data were recorded in detail and securely stored to ensure data integrity and research validity.

Quality control

To ensure methodological rigor, all participants were screened and treated according to the established clinical protocol, ensuring comparability between groups. Specially trained researchers collected all clinical data using standardized measurement techniques and uniform documentation procedures. Data collection was carried out in accordance with standardized operating procedures, and regular data audits were performed to ensure accuracy and completeness. Throughout the study, all procedures adhered to the principles outlined in international ethical standards.

Multivariate Cox regression analysis

To evaluate the independent association between treatment regimen and survival outcomes (PFS and OS), Cox proportional hazards models were constructed, incorporating relevant clinical variables. The analysis examined whether treatment protocols and other covariates (age, sex, pathological findings, and tumor features) independently predicted survival outcomes. Univariate analysis was first performed to identify potential prognostic factors for PFS and OS ($P<0.05$ threshold). Significant variables were subsequently entered into the multivariate model, with hazard ratios (HRs) and 95% confidence intervals (CIs) computed for each parameter to determine their independent prognostic value. This approach specifically tested whether treatment modality independently influenced survival outcomes after covariate adjustment. If the HR of the treat-

ment regimen was statistically significant and the *p*-value was less than 0.05, the treatment regime was considered an independent risk factor.

Internal and external validation

For internal validation, bootstrap resampling (1000 iterations) was employed to evaluate the model's stability within the original cohort. This involved calculating the average C-index, generating calibration curves via the Hosmer-Lemeshow test, and performing decision curve analysis (DCA) to assess discriminative ability, agreement between predicted and observed outcomes, and net clinical benefit.

For external validation, using independent patient data from tertiary medical institutions, the model's generalizability, predictive accuracy, and clinical utility were evaluated by computing the external C-index, calibration error, and DCA.

Statistical processing

All statistical analyses in this study were performed using *SPSS 27.0*. Normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared using independent samples t-test; non-normally distributed continuous data were presented as median (interquartile range) and compared with the Mann-Whitney U test; categorical data were described as frequency (percentage) [n (%)] and analyzed using the chi-square test; survival curves were plotted by the Kaplan-Meier method, and between-group survival differences were compared with the log-rank test; Cox proportional hazards regression models were applied to identify factors influencing outcomes, with results reported as hazard ratio (HR) and 95% confidence interval (CI); a nomogram was constructed using R software; all statistical tests were two-sided, and a *P*-value <0.05 was considered statistically significant.

Results

Comparison of baseline data between the two groups

In **Table 1**, there were no significant differences between the two groups in demographic characteristics (age, gender distribution), pathological features (number of osteosarcoma patients, number of soft tissue sarcoma patients), tumor characteristics (primary tumor site, number, location, and size of pulmonary metastases), comorbidities (heart disease, liver dysfunction, renal dysfunction, and other underlying conditions), pathological staging (T stage, N stage), radiotherapy status, or lactate dehydrogenase (LDH) levels ($P>0.05$ for all), indicating that the baseline characteristics of the two groups were comparable prior to treatment.

Comparison of PFS and OS between the two groups

The median PFS in the Observation group was 10.0 months, significantly longer than 7.5 months in the Control group ($P<0.01$; **Figure 2**). The median OS in the Observation group was 22.0 months, also significantly longer than 14.0 months in the Control group ($P<0.01$; **Figure 3**).

Comparison of clinical response between the two groups

As shown in **Tables 2** and **3**, in the Observation group, one patient achieved CR, 12 achieved PR, 14 achieved SD, and 26 had PD; in the Control group, the corresponding numbers were 0, 4, 8, and 28, respectively ($P<0.05$). The calculated ORR was 23.63% in the Observation group versus 10.00% in the Control group, and the DCR was 52.73% versus 30%, respectively ($P<0.05$ for all).

Comparison of maximum diameter of primary lesion and LM between the two groups before and after treatment

As shown in **Figure 4**, no visible distinction was noted in the maximum diameter of the primary lesion and LM between the two groups before treatment ($P>0.05$). Following treatment, lesion diameters decreased significantly in both groups, with the reduction in the Observation group being significantly greater than in the Control group ($P<0.05$).

Comparison of adverse reactions between the two groups

In terms of hematological toxicity, there were 0 cases of leukopenia, 1 case of thrombocytope-

Table 1. Comparison of baseline data between the two groups

Information	Observation group (n=55)	Control group (n=40)	t/χ^2	*P* value
Age (years old)	30±6.44	28±8.03	0.772	0.441
Sex (Male/Female)	31/24	23/17	0.000	0.912
Pathological type				
Osteosarcoma	37	28	0.091	0.953
Soft tissue sarcoma	18	12		
Primary tumor location				
Humerus	9	5	0.275	0.955
Femur	23	18		
Tibia	17	13		
Other sites	6	4		
Number of pulmonary metastases	15	10	0.031	0.856
Specific locations and sizes of pulmonary metastases	Two in the left upper lobe, three in the right lower lobe	One in the left lower lobe, two in the right upper lobe		
Comorbidities				
Heart disease	5	4	0.013	0.923
Hepatic dysfunction	4	3	0.000	0.905
Renal dysfunction	6	5	0.035	0.869
Others	8	7	0.010	0.943
Pathological staging				
T stage			0.592	
T1	13	8		0.746
T2	15	11		
T3	20	15		
T4	7	6		
N stage			0.715	
N0	32	25		0.634
N1	16	10		
N2	7	5		
Radiotherapy			0.166	
Yes	18	11		0.585
No	37	29		
LDH levels			0.054	
High (>240 U/L)	22	14		0.827
Low (≤240 U/L)	33	26		

Note: LDH: Lactate Dehydrogenase.

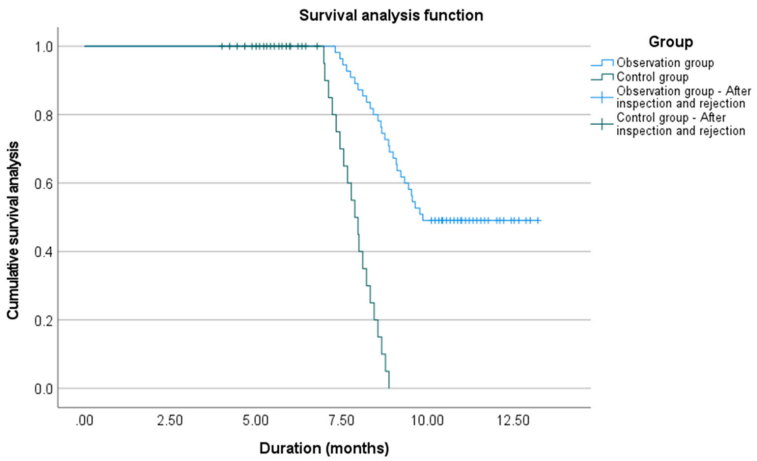

Figure 2. Comparison of progression-free survival between the two groups.

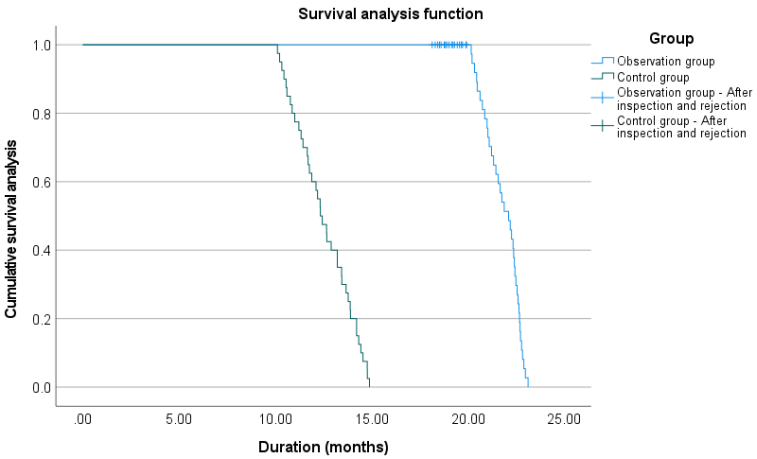

Figure 3. Comparison of overall survival between the two groups.

Table 2. Comparison of treatment outcomes between the two groups

Group	CR	PR	SD	PD	χ^2	*P* value
Observation group	1	12	14	26	7.982	0.046
Control group	0	4	8	28		

Note: CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease.

Table 3. Comparison of treatment response between the two groups

Group	ORR	DCR	χ^2	ORR-*P* value	ORR-*P* value	χ^2
Observation group	23.63	52.73	4.135	0.042	0.017	5.714
Control group	10#	30#				

Note: ORR: Objective Response Rate; DCR: Disease Control Rate. #: in contrast to the Observation group, *P*<0.05.

nia, and 2 cases of anemia in the Observation group; the corresponding numbers in the Control group were 1, 1, and 3, respectively. The overall incidence of hematological toxicity was 5.45% in the Observation group, significantly lower than 12.5% in the Control group (*P*<0.05; **Table 4**).

As for gastrointestinal reactions, there were 2 cases of nausea, 0 cases of vomiting, and 0 cases of diarrhea in the Observation group; in the Control group, the numbers were 3, 1, and 1, respectively. The overall incidence of gastrointestinal AR in the Observation group was 3.64%, notably lower than 12.5% in the Control group (P<0.05; **Table 5**).

In terms of renal toxicity, there was 1 case of elevated serum creatinine, 0 cases of proteinuria, and 0 cases of hematuria in the Observation group; in the Control group, there was 1, 1, and 1, respectively. The overall incidence of renal toxicity in the Observation group was 1.82%, markedly lower than 7.5% in the Control group (*P*<0.05, **Table 6**).

Results of multivariate Cox regression analysis

As shown in **Table 7**, compared with the ETOP + IFO regimen, the thalidomide + IFO regimen was associated with a significantly lower risk of death (HR=0.632, *P*=0.006), indicating a substantial survival benefit. Age, sex, tumor type (osteosarcoma *vs.* soft tissue sarcoma), and tumor location (femur vs. other sites) were not significantly associated with survival (P>0.05 for all). In contrast, the number of pulmonary

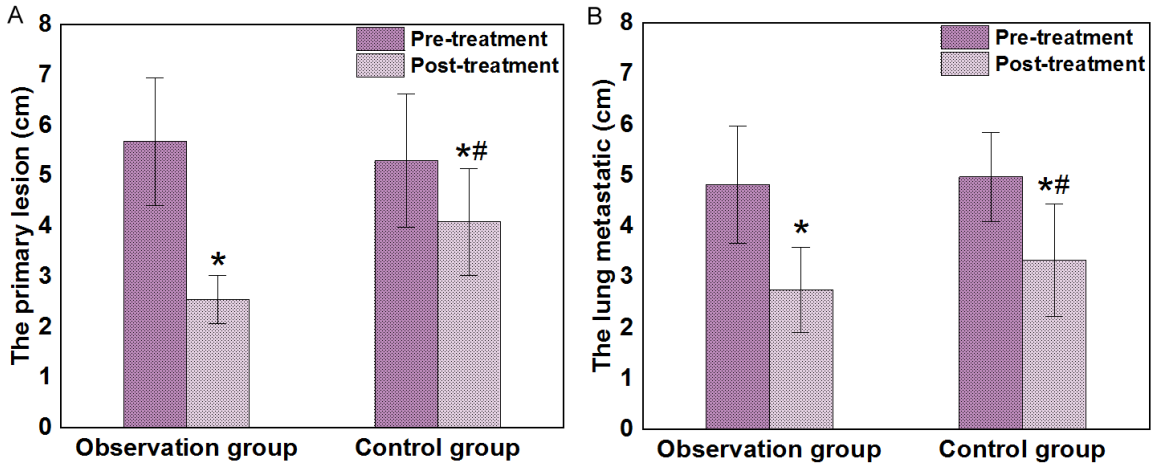

Figure 4. Comparison of maximum diameters of primary lesion and metastatic lesions between the two groups before and after treatment. Note: A: maximum diameter of primary lesion; B: maximum diameter of metastatic lesions. *P<0.05, compare with pre-treatment diameter; #P<0.05, compare with the Observation group.

Table 4. Comparison of hematological toxicity between the two groups

	Leukopenia	Thrombocytopenia	Anemia	Total incidence	χ^2 (Fisher)	P value
Observation group	0 (0.00)	1 (1.82)	2 (3.64)	3 (5.45)	4.333	0.038
Control group	1 (2.50)	1 (2.50)	3 (7.50)	5 (12.50)#		

Note: #: in contrast to the Observation group, P<0.05.

Table 5. Comparison of gastrointestinal reactions between the two groups

Group	Nausea	Vomiting	Diarrhea	Total incidence	χ^2 (Fisher)	P value
Observation group	2 (3.64)	0 (0.00)	0 (0.00)	2 (3.64)	4.762	0.047
Control group	3 (7.50)	1 (2.50)	1 (2.50)	5 (12.50)#		

Note: #: in contrast to the Observation group, P<0.05.

Table 6. Comparison of renal toxicity between the two groups

Group	Elevated serum creatinine	Proteinuria	Hematuria	Total incidence	χ^2 (Fisher)	P value
Observation group	1 (1.82)	0 (0.00)	0 (0.00)	1 (1.82)	4.167	0.041
Control group	1 (2.50)	1 (2.50)	1 (2.50)	3 (7.50)#		

Note: #: in contrast to the Observation group, P<0.05.

metastases (HR=1.256, P=0.038), T stage (HR=1.453, P=0.033), N stage (HR=1.389, P=0.035), receipt of radiotherapy (HR=1.589, P=0.018), and LDH level (HR=1.356, P=0.015) were identified as independent prognostic factors.

In summary, the multivariate Cox regression analysis identified pulmonary metastasis number, T stage, N stage, radiotherapy, and LDH level as significant prognostic factors (P<0.05), whereas age, sex, tumor type, and tumor location were not.

Nomogram development and validation

A prognostic nomogram (**Figure 5A**) was developed based on the multivariate Cox model. For each patient, the value of each predictor variable can be identified on the corresponding axis. The total score was obtained by summing individual scores and was then mapped to the Risk Probability axis to estimate survival risk. The specific point assignment for each variable is presented in **Table 8**.

The model demonstrated good discrimination, with a simulated C-index ranging from 0.78 to

Table 7. Multivariate Cox regression analysis of patient survival

Variables	HR	95% CI	*P* value
Treatment regimen (Thalidomide + IFO *vs.* ETOP + IFO)	0.632	0.456-0.879	0.006
Age	1.018	0.985-1.052	0.317
Sex (Male *vs.* Female)	1.203	0.742-1.952	0.457
Tumor type (Osteosarcoma *vs.* Soft tissue sarcoma)	1.457	0.836-2.541	0.178
Tumor location (Femur *vs.* Other)	1.312	0.846-2.033	0.268
Number of pulmonary metastases	1.256	1.011-1.557	0.038
Presence of heart disease (Yes *vs.* No)	1.567	0.623-3.928	0.348
T stage (High *vs.* Low)	1.453	1.029-2.043	0.033
N stage (High *vs.* Low)	1.389	1.022-1.887	0.035
Radiotherapy (Yes *vs.* No)	1.589	1.084-2.336	0.018
LDH level (High *vs.* Low)	1.356	1.061-1.730	0.015

Note: IFO: Ifosfamide; ETOP: Etoposide; LDH: Lactate Dehydrogenase.

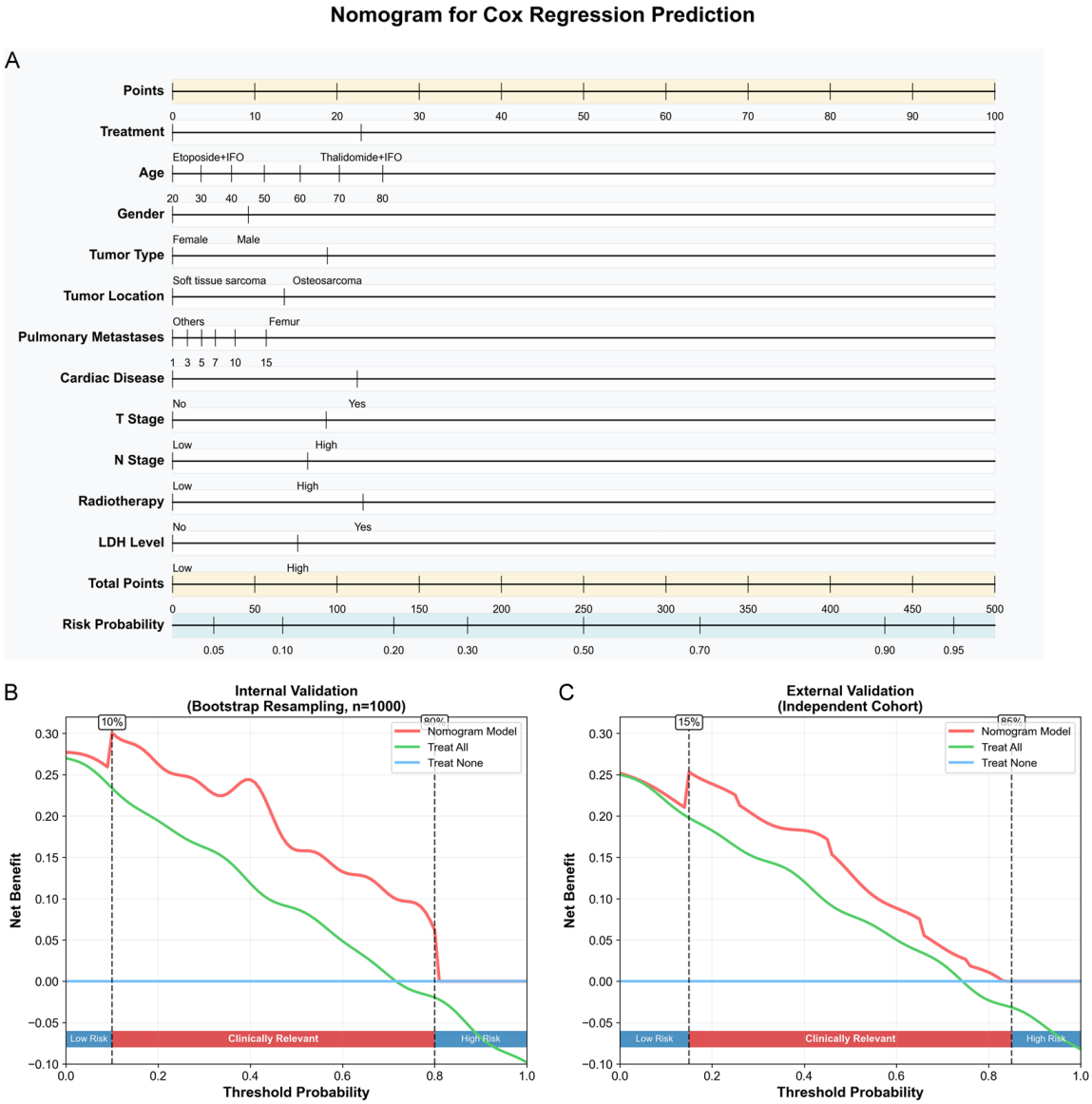

Figure 5. Model and Validation. Note: A: Model column chart; B: Internal validation; C: External validation.

Table 8. Score assignment for each variable

Variable	Category/range	Score range
Treatment mode	Etoposide + IFO	0-30
	Thalidomide + IFO	30-60
Age	20-80 years old	0-80
Sex	Female	0
	Male	20
Tumor type	Soft tissue sarcoma	0
	Osteosarcoma	40
Tumor site	Others	0
	Thighbone	25
Number of lung metastases	1-15 sites	0-150
History of heart disease	No	0
	Yes	30
T stage	Low	0
	High	35
N stage	Low	0
	High	25
Radiotherapy	No	0
	Yes	15
LDH level	Low	0
	High	50

Note: IFO: Ifosfamide; LDH: Lactate Dehydrogenase.

Table 9. Model verification indicators

Indicators	Outcome/range
C-index	0.80 (0.78-0.82)
Calibration slope	0.95 (0.90-1.05)
Time-dependent AUC (1 year)	0.79
Time-dependent AUC (3 years)	0.81
Brier score (1 year)	0.12
Brier score (3 years)	0.15

Note: AUC: Area Under the Curve.

0.82 (**Table 9**). In **Table 10**, the mean C-index was 0.80 (95% CI: 0.76-0.84), consistent with the simulated values. Calibration analysis showed good agreement between predicted and observed probabilities (χ^2=8.23, P=0.32, df=8). DCA indicated a net clinical benefit across a threshold probability range of 0.10-0.80 (**Figure 5B**).

Independent patient data from superior medical institutions were utilized for external validation. In **Table 11**, the external C-index was 0.79 (95% CI: 0.72-0.85), indicating good discriminative performance across cohorts. The calibration error was 0.92 (ideal value =1, 95% CI: 0.81-1.03), indicating minimal deviation between predicted and observed survival probabilities. The external DCA showed a net clinical benefit across a threshold probability range of 0.15-0.85, confirming the model's practical applicability (**Figure 5C**).

Discussion

Although multi-modality therapy such as surgery, chemotherapy, and radiotherapy has been widely used for osteosarcoma, therapeutic efficacy remains limited, particularly in cases with lung metastasis. LM is closely associated with poor prognosis and significantly impairs both quality of life and survival rate [17]. Therefore, exploring novel treatment strategies to improve patient outcomes has become a key focus of clinical research. In recent years, targeted therapies and immunomodulators have received great attention in osteosarcoma management. IFO, a classic chemotherapy agent, exerts its anti-tumor effect by inducing DNA crosslinking, thereby inhibiting tumor cell division and proliferation, and has demonstrated efficacy in treating osteosarcoma. Thalidomide, an immunomodulator, exerts dual anti-tumor effects through tumor microenvironment modulation and immune enhancement. Clinical evidence suggests that thalidomide, when combined with conventional chemotherapy, can produce synergistic effects, improving treatment response and prolonging survival [18]. Based on these pharmacological profiles, this study was designed to compare the clinical efficacy of thalidomide-IFO therapy with that of standard ETOP-IFO therapy in treating osteosarcoma.

The results showed that thalidomide-IFO therapy significantly improved PFS and OS compared with ETOP-IFO therapy. Specifically, thalidomide + IFO greatly prolonged the PFS, an important endpoint reflecting the ability of therapy to delay tumor progression. Thalidomide inhibits tumor growth and metastasis by modu-

Table 10. Internal validation metrics

Validation metric	Value/Result
Mean C-index	0.80 (95% CI: 0.76-0.84)
Calibration curve (Hosmer-Lemeshow Test)	χ^2=8.23, *P*=0.32 (degrees of freedom =8)
Decision curve analysis (DCA)	Net benefit higher than “treat all” or “treat none” strategies across a threshold probability range of 0.1-0.8

Table 11. External validation metrics

Metric	Value/Conclusion	Interpretation
External validation C-index	0.79 (95% CI: 0.72-0.85)	Indicates good discriminative ability across cohorts
Calibration error (Calibration slope)	0.92 (ideal value =1, 95% CI: 0.81-1.03)	Demonstrates minimal deviation between predicted and actual risks
Clinical net benefit	Net benefit >0 across threshold probability range of 0.15-0.85	Supports the model’s clinical utility in real-world applications

Note: 95% CI: 95% Confidence Interval.

lating the tumor microenvironment and enhancing T-cell-mediated immunity, thus delaying disease progression. IFO may further inhibit tumor angiogenesis, reducing blood supply and limiting tumor growth and metastasis [19]. These complementary mechanisms likely account for the synergistic effect observed in prolonging PFS. OS, as the gold standard for evaluating anti-cancer efficacy, was also significantly prolonged in the thalidomide-IFO group, indicating comprehensive clinical benefits, including better disease control and improved quality of life. The dual-agent regimen has demonstrated effective anti-metastatic properties by preventing tumor spread and organ infiltration, ultimately leading to survival advantages [20]. Clinical response analysis further supported these findings, with an ORR of 23.63% in the observation group *compared with* 10% in the control group, and a DCR of 52.73% versus 30%, respectively. ORR reflects the capacity to reduce tumor load, while DCR indicates the ability to achieve and maintain disease stability. The superior response rates highlight the therapeutic advantages of the thalidomide-IFO regimen in managing disease progress and altering tumor growth kinetics in osteosarcoma.

In addition, this study also evaluated the adverse reactions experienced during treatment. Regarding hematological toxicity, the incidences of leukopenia, thrombocytopenia, and anemia were relatively low in the Observation group. Hematotoxicity is a common AR in targeted therapy and chemotherapy, which can lead to immune suppression and increased risk of infection [21]. However, the low incidence of hematological toxicity in the thalidomide-IFO group suggests good treatment tolerability. Gastrointestinal reactions, including nausea, vomiting, and diarrhea, were also less frequent in the Observation group. Gastrointestinal toxicity is a common adverse effect of various anti-tumor treatments and can negatively affect treatment compliance. The lower AR rate in the Observation group may be related to the immunomodulatory properties of thalidomide and the tumor-inhibitory effects of IFO. Regarding renal function, the incidence of elevated serum creatinine, proteinuria and hematuria in the Observation group was dramatically lower compared to the Control group. Although thalidomide + IFO may still impact renal function, the low incidence of renal ARs in the Observation group indicates minimal nephrotoxicity.

Overall, thalidomide + IFO demonstrated superior treatment efficacy and lower incidences of ARs compared with the standard ETOP + IFO regimen. Nevertheless, this study has some limitations. First, as a retrospective study, it is subject to potential selection bias, which may limit the generalizability of the findings. Second, although the combination therapy of thalidomide-IFO has shown encouraging antitumor activity, its long-term efficacy and safety still need further investigation. Therefore, subsequent studies should include multicenter, prospective, randomized controlled trials to provide more reliable evidence of efficacy and safety.

Conclusion

This study demonstrated that thalidomide-IFO therapy markedly extends PFS and OS in osteosarcoma patients, while improving ORR and DCR with an acceptable safety profile. These findings propose a novel treatment approach for osteosarcoma, especially in cases with LM, where dual-agent therapy could offer clinical benefit. However, additional large-scale studies are warranted to evaluate its long-term efficacy and facilitate the translation of this regimen into standard practice.

Disclosure of conflict of interest

None.

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