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The effect of doxorubicin curcumin co-loaded lipid nanoparticles and doxorubicin on osteosarcoma before surgery

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Abstract

Background: The research aims to observe the difference in the effect of preoperative doxorubicin curcumin co-loaded lipid nanoparticles (DOX+CUR LPNs) and doxorubicin (VAD) in the treatment of osteosarcoma.

Methods: 68 patients with osteosarcoma who visited the hospital from January 2020 to December 2022 are chosen. They are separated into VAD group and DOX+CUR LPNs group, with 34 cases in each group. VAD and DOX+CUR LPNs groups VAD chemotherapy, and DOX+CUR LPNs treatment, respectively. All patients receive tumor resection. Comparison is made between the two groups before chemotherapy, at the end of chemotherapy and 1 week after surgery on the changes of vascular endothelial growth factor (VEGF), angiopoietin-2 (Ang-2), galectin-3 (Gal-3), renal function indicators cystatin-C (Cys-C), serum creatinine (Scr), blood urea nitrogen (BUN) in the peripheral blood. The clinical efficacy and adverse reactions are determined by observation and follow-up for 1 month.

Results: The VEGF, Ang-2, and Gal-3 in both groups were significantly lower at 1 week after chemotherapy and surgery compared to before chemotherapy ($P < 0.05$). The VEGF and Gal-3 in the DOX+CUR LPNs group were lower than those in the VAD group in the same period, with $P < 0.05$. The Cys-C, Scr, and BUN in both groups of patients after chemotherapy and surgery increased compared to before chemotherapy, with $P < 0.05$. The Cys-C, Scr, and BUN in the DOX+CUR LPNs group were lower than those in the VAD group during the same period, with $P < 0.05$. Following up for 1 month, the ORR of the DOX+CUR LPNs group was 94.12% (32/34) higher than that of the VAD group, with $P < 0.05$. The incidence of adverse reactions in the DOX+CUR LPNs group was 47.05% lower than that in the VAD group, with $P < 0.05$.

Conclusion: Preoperative application of DOX+CUR LPNs enables effective drug delivery to the tumor section by combining the antibacterial, antioxidant and anti-inflammatory effects of curcumin, which is co-wrapped in nanoparticles. It has the effect of promoting angiogenesis and damage repair, inhibiting inflammation-related factors, and protecting renal function, while adriamycin alone has drug resistance problems and toxic side effects, which can damage the patient's liver and kidney. Therefore, DOX+CUR LPNs are more effective than adriamycin alone, indicating that it

can improve the therapeutic effect of the drug and reduce the side effects, which is of great significance for improving the survival rate and quality of life of patients.

Keywords: Drug-loaded lipid nanoparticles, Osteosarcoma, VAD, Curcumin

Background

Osteosarcoma is a malignant tumor originating from interstitial tissue, which can occur lung or bone metastasis and has a high mortality rate (Tang and Liu 2023). According to the survey, about 2.3% of 3438 patients with osteosarcoma will develop into second primary malignancies (SPMs). The estimated standard incidence rate per 10,000 people is 2.84, and the absolute risk increase is 44.96 (Freedman et al. 2023). The treatment effect of osteosarcoma determines the later life quality of patients. Osteosarcoma is usually treated with comprehensive therapy in clinic, and chemotherapy is a commonly used treatment. VAD is an important drug for clinical chemotherapy of osteosarcoma. In particular, VAD chemotherapy is a commonly used clinical treatment (Pilavaki et al. 2023). Curcumin and some potential analogues and infusion formulas are important strategies to improve the currently feasible treatment for osteosarcoma (Sun et al. 2022). However, curcumin has poor water solubility, absorption and metabolic stability. Some studies believed that the polymeric thermosensitive hydrogel of VAD and curcumin can produce anti-tumor effect when used in the tumor focus of osteosarcoma (Yang et al. 2020). Some scholars have designed and developed DOX+CUR LPNs and successfully used them in animal experiments. Its pharmacokinetic background information mainly includes the fact that the absorption of lipid nanoparticles receives the influence of nanoparticle size and surface properties, and drug metabolism also affects the activity and concentration of the drug. The results showed that DOX+CUR LPNs can be used as a nano preparation that can combine VAD and curcumin to play a synergistic role in the treatment of osteosarcoma (Wang et al. 2016; Angulo et al. 2017). Some scholars even used nanorods made of hydroxyapatite as a carrier of curcumin for therapeutic detection of the viability and number of osteosarcoma cells. The results showed that curcumin nano-formulation could significantly reduce osteosarcoma cell viability and had a good adjuvant effect on the assessment of biological performance of osteosarcoma treatment (Marinho et al. 2023; Lu et al. 2023). The above experiments illustrate that DOX+CUR LPNs inhibit the growth of cancer cells through synergistic anti-tumor activity, i.e., interfering with DNA replication and cell division. Meanwhile, combining drugs under this coordinated mechanism enhances bioavailability and therapeutic targeting, thus overcoming the limitations of adriamycin and curcumin alone and improving solubility and stability. The mechanism of action of targeted delivery is used to increase the local concentration of the drug and reduce the side effects. Therefore, on the basis of previous studies, this study applies it to the clinical treatment stage, to verify the difference between its clinical effect and VAD chemotherapy, and to promote the improvement of surgical treatment effect of osteosarcoma.

Methods

Research objects

Sixty-eight patients with osteosarcoma who visited the hospital from January 2020 to December 2022 are chosen. They are randomly separated into VAD and DOX+CUR LPNs groups, 34 cases in each group. Inclusion criteria: ① patients are diagnosed as osteosarcoma by histopathological examination. ② The tumor is the primary lesion with no metastasis and no history of other malignant tumors. ③ The patient did not undergo any chemotherapy or radiotherapy before receiving surgical treatment. ④ Expected survival time $\geq$ 6 months, and Karnofsky life condition score $\geq$ 70 points. ⑤ Sign an informed consent form and voluntarily participate in this study. Exclusion criteria: ① the tumor is secondary or has undergone distant metastasis. ② Patients who have received chemotherapy or radiation therapy in the past complicated with severe infection, liver and kidney dysfunction or severe cardio-cerebral vascular disease. ④ Those who cannot tolerate surgical treatment. ⑤ Patients with poor compliance and inability to cooperate with clinical research. ⑥ History of serious cardio-cerebral vascular disease. A total of 20 males and 14 females are included in the VAD group, aged 6–27 years, with an average age of (15.18 $\pm$ 5.72) years, a course of 2–13 years, and an average course of (6.26 $\pm$ 2.60) years. The maximum diameter of the tumor is 4-11 cm, with an average maximum diameter of (7.59 $\pm$ 1.58) cm. The ECCG physical activity score is 0 in 19 cases, 1 in 9 cases, and 2 in 6 cases. The DOX+CUR LPNs group includes 21 males and 13 females, aged 6–23 years, with an average age of (15.76 $\pm$ 4.55) years, a disease course of 2–14 years, and an average disease course of (6.50 $\pm$ 2.97) years. The maximum diameter of the tumor is 5-11 cm, with an average of (8.21 $\pm$ 1.59) cm. The ECCG physical activity score is 0 for 18 patients, 1 for 9 patients, and 2 for 7 patients. It has no statistical significance difference between the two groups in gender, age, disease course, maximum diameter of the tumor, and ECOG score ($P < 0.05$). The study was approved by the hospital ethics committee and informed consent was obtained from the patients or their families. Blinding of patients, researchers and outcome assessors was also ensured in order to avoid the effect of testing for chance factors. The study had a double-blind design, i.e., neither the patients nor the researchers knew whether the patients were receiving actual medication or non-pharmacological treatment, and this process could be achieved by using numbered labeled medications or by having medications dispensed by an independent pharmacist.

Treatment methods

Therapeutic principles

Treatment principles The selection of dose and frequency of agents in the VAD group and DOX+CUR LPNs group in the experiment is based on clinical trials and experience accumulation. The optimal dose and schedule are then based on a combination of several factors, including treatment goals, patient's physical condition, tumor type and stage. Criteria for dose adjustment or modification include factors such as patient tolerability, response to treatment, and achievement of treatment goals. If the patient cannot tolerate the existing dose or experiences significant adverse effects, the dose may need to be adjusted or reduced. If the patient does not have a significant therapeutic response to the existing dose or the therapeutic goal is not achieved, the dose may need

to be increased or modified. In addition, any adverse events or complications associated with treatment need to be promptly recognized and managed. This may include measures such as dosage adjustments, suspension of treatment, use of supportive therapeutic measures, and medications to manage complications. Specific methods and measures to manage adverse events or complications may vary depending on the situation and need to be determined on a patient-specific basis and clinical judgment. During the course of treatment, the patient's hematology, biochemistry, electrocardiogram, imaging, and other indicators are regularly monitored, as well as the patient's subjective feelings and discomfort are asked about, in order to detect and manage any adverse events or complications in a timely manner.

AVD group

Before surgery, VAD chemotherapy, namely vincristine, VAD and dexamethasone, is applied. On the first to 4th days, vincristine (produced by Gismex Wuhan Pharmaceutical Co., Ltd.) is administered intravenously at a dose of 1 $mg{\cdot}d^{-1}$, and VAD (produced by Shanghai Yuanmu Biotechnology Co., Ltd.) is administered at a dose of 15 $mg\ m^{-2}\ d^{-1}$. Oral dexamethasone (produced by Zhangfeng Pharmaceutical Factory in Longchuan County, Yunnan Province) 20 $mg\ d^{-1}$ is administered on days 1–4 and 9–12. Every 4 weeks is a cycle.

DOX + CUR LPNs group

The patients are treated with DOX+CUR LPNs before operation.

(1) Preparation of DOX + CUR LPNs: matrix preparation: weigh appropriate amount of VAD and curcumin, respectively, and dissolve them in ethanol to prepare VAD solution and curcumin matrix solution. Oil phase preparation: 50 mg of VAD and 100 mg of curcumin are weighed and dissolved in 10 ml of dichloromethane and 500 ml of poly(lactic acid) poly(glycolic acid) copolymer solution, fully stirred evenly, completing the oil phase preparation. Aqueous phase preparation: a certain amount of 50 mg lecithin, 50 mg cholesterol and 600 mg lauroyl phosphatidylcholine are weighed and dissolved in phosphate buffer with pH 7.4 to prepare lipid aqueous phase solution. Emulsification process: using the optimized emulsification technology and parameters, the oil–water liposome lotion is prepared by dropping the oil phase solution into the aqueous phase solution. Nanoization: stir the uniformly dispersed ultrasonic suspension under magnetic force, set the rotating speed at 600r/min, and remove the residual dichloromethane in the liquid. Separation and purification: after the removal of dichloromethane, the remaining suspension is centrifuged at 4 ℃ at 10,000r/min, and the centrifugation time is set at 10 min. DOX+CUR LPNs are collected and kept at 4 ℃. Storage and quality inspection: before use, the particle size, drug loading, and in vitro drug release behavior of the sample are tested. This experimental study is conducted when the sample particle size is between 100 and 500 nm, the drug loading is $\geq$ 10%, the in vitro drug release duration is > 24 h, and the cell survival rate is > 70%. To ensure the safety of experimental drug use, DOX+CUR LPNs are prepared into an injection with a concentration of 10 mg: 5 ml in a strictly sterile environment with normal saline as the solvent, and the sterility and bacterial endotoxin tests are conducted to ensure the safety of injection in vivo. (2) Application of DOX+CUR LPNs: before chemotherapy, blood

routine, biochemical, electrocardiogram, and other examinations are conducted to evaluate chemotherapy tolerance. On the 1st day, DOX+CUR LPNs injection 5 mg m^{-2} is taken. On the second to 4th days, it is changed to 10 mg m^{-2}. The chemotherapy cycle is referred to the control group.

After completing one cycle of chemotherapy, two groups of patients undergo imaging examinations again. According to the Enneking classification of the patient, and following the principle of complete extracapsular resection of solid tumors and surrounding normal tissues > 5 cm, radical or extensive resection surgery is performed. Limb preservation is performed with reconstruction surgery for in vitro inactivation before implantation or prosthetic replacement surgery.

Observation indicators

Peripheral blood VEGF, Ang-2, and Gal-3 levels

Before and at the end of chemotherapy, and 1 week after surgery, 5 ml of fasting elbow vein blood is extracted from the patient. The centrifugation time, radius and speed are 5 min, 8 cm and 4000 r/min, respectively. After centrifugation, the serum is taken and stored in a − 80 ℃ refrigerator. Among them, VEGF and Ang-2 use enzyme-linked immunosorbent assay (ELISA), and the kit is provided by Santa Cruz Company in the United States. It takes anti-human VEGF or Ang-2 antibody and coats it on the enzyme plate. 100 μl corresponding standard and sample are added, incubating at room temperature for 2 h. 100 μl biotinylation anti-human VEGF or Ang-2 are added into the enzyme hole, incubating again in dark for 0.5 h. Horseradish peroxidase-labeled streptomycin, avidin and biotin are combined and added to 100 μl substrate working solution to develop color, and 50 μl sulfuric acid is used as terminator. The absorbance value of the sample is measured using an ELISA, with a wavelength set at 450 nm. The concentration of VEGF and Ang-2 is calculated using the standard curve method. Gal-3 shall be measured with the ELISA kit provided by Wuhan Yiaibo Technology Co., Ltd. The dilution ratio of serum samples is 1:4. The concentration of Gal-3 shall be measured strictly according to the instructions of the kit. It determines the absorbance value using an ELISA, sets the detection wavelength to 450 nm, draws a standard curve for Gal-3, and calculates the concentration of Gal-3 using the standard curve method.

Clinical efficacy

The evaluation is divided into 6 indicators: CR, PR, SD, PD, ORR, and DCR. Among them, CR is the case where the target lesion completely disappears. PR refers to partial relief when the total diameter of the lesion decreases by ≥ 30%. PD represents an increase of ≥ 20% in the total diameter of the lesion. And SD is between PR and PD. ORR is CR + PR/total number of cases × 100% and DCR is CR + PR + SD/total number of cases × 100% (Marinho et al. 2023).

Renal function indicators

The changes of serum Cys-C, Scr, and BUN are used as renal function indicators before treatment, 1 week after chemotherapy (hereinafter referred to as after chemotherapy),

and 1 week after surgery (hereinafter referred to as after surgery). Among them, Cys-C is measured using immunoturbidimetry. Scr and BUN are measured using enzyme methods using Abbott Laboratories' relevant reagent kits. Specific concentrations are determined using standard curve and enzyme methods.

Adverse reactions after injection

Bone marrow suppression, infection, digestive tract reaction and adverse reaction of heart damage are collected during the treatment period.

Statistical methods

Data analysis is conducted using Medcalc 21.0 statistical software, and relevant visualization images are drawn using GraphPad software. Data conforming to normal distribution are expressed as mean ± standard deviation ($\bar{x} \pm s$), while measurement data of non-normal distribution are expressed as median (quartile). The overall comparison is performed by repeated measurement ANOVA, the pairwise comparison is performed by SNK-q test, and the categorical variable between groups are compared by χ^2 inspection. Statistical testing level $\alpha = 0.05$.

Results

Comparison of peripheral blood VEGF, Ang-2, and Gal-3 Levels between two groups of patients

As shown in Fig. 1, the two groups' VEGF, Ang-2, and Gal-3 after chemotherapy and surgery were less than before chemotherapy, with $P < 0.05$. The VEGF and Gal-3 in the DOX+CUR LPNs group were lower than those in the VAD group during the same period, and with $P < 0.05$. Overall comparison: there were statistical differences in PGE2 and Gal-3 between the two groups of patients in inter group, time, and interaction ($F_{time} = 53.28$, 42.57, $P_{group} < 0.001$. $F_{time} = 144.26$, 489.88, $P_{time} < 0.001$. $F_{interaction} = 12.54$, 26.43, $P_{interaction} < 0.001$). There was a statistical difference in Ang-2 between the two groups of patients in terms of time effect ($F_{group} = 0.015$、$P_{group} = 0.903$; $F_{time} = 254.94$、$P_{time} < 0.001$; $F_{interaction} = 0.088$、$P_{interaction} = 0.916$).

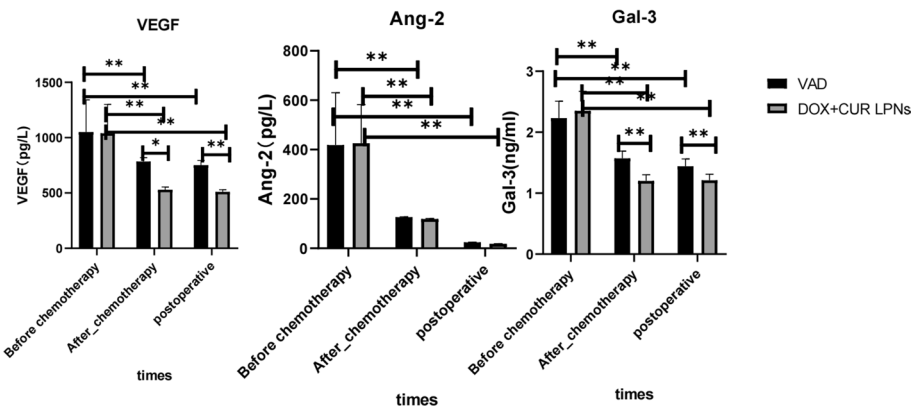

Fig. 1 Changes in VEGF, Ang-2, and Gal-3 concentrations in two groups of patients

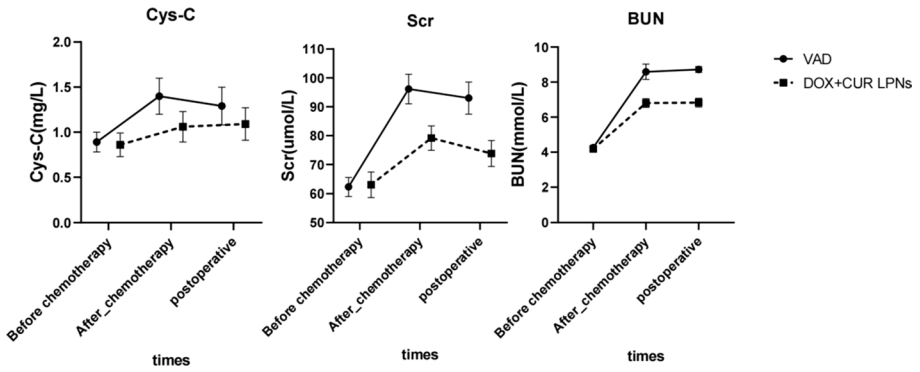

Fig. 2 Comparison of renal function indicators between two groups of patients

Table 1 Comparison of clinical efficacy between two groups of patients (d, x ± s)

Group (*n*)	CR	PR	SD	PD	ORR	DCR
VAD group (34)	17 (50.00)	5 (14.71)	7 (20.59)	5 (14.71)	22 (64.71)	29 (85.29)
DOX + CUR LPNs group (34)	25 (73.53)	7 (20.59)	1 (2.94)	1 (2.94)	32 (94.12)	33 (97.06)
χ^2	9.024				8.995	2.925
P	0.029				0.003	0.087

Comparison of renal function indicators between two groups of patients

As shown in Fig. 2, the Cys-C, Scr, and BUN in both groups of patients after chemotherapy and surgery increased compared to before chemotherapy, with $P<0.05$. The Cys-C, Scr, and BUN in the DOX+CUR LPNs group were less than those in the VAD group, with $P<0.05$. Overall comparison: there were statistical differences in Cys-C, Scr, and BUN between the two groups of patients in inter group, time, and interaction ($F_{group}=62.49$、343.23、865.93, $P_{group}<0.001$; $F_{time}=90.87$、583.56、3082.53, $P_{time}<0.001$; $F_{interaction}=14.05$、97.95、195.96, $P_{interaction}<0.001$)。

Comparison of clinical efficacy between two groups of patients

Following up for 1 month, the CR and PR rates of the DOX+CUR LPNs group were 73.53% (25/34) and 20.59% (7/34), significantly higher than those of the VAD group ($P<0.05$). The ORR of the DOX+CUR LPNs group was 94.12% (32/34) higher than that of the VAD group, with $P<0.05$ (see Table 1 for details).

Adverse reactions in two groups of patients

In the DOX+CUR LPNs group, there were 6 cases of hair loss, 5 cases of vomiting, 4 cases of leukopenia, and 1 case of hair loss accompanied by vomiting with leukopenia. The VAD group was composed of 10 cases of leukopenia, 7 cases of nausea and vomiting, and 7 cases of hair loss. The occurrence of adverse reactions in the DOX+CUR LPNs group was 47.05%, which was lower than that in the VAD group, and the difference was statistically significant ($\chi^2=17.934$, $P=0.003$).

Discussion

According to statistics, the current treatment of osteosarcoma includes surgical removal of all visible lesions combined with systemic chemotherapy to control micrometastasis. Because of the micrometastasis and diffusion of osteosarcoma, simple radical surgery is rarely cured. However, the introduction of combination chemotherapy in the 1970s greatly increases the overall survival rate, from 20% to around 70% (Watanabe et al. 2009). Unfortunately, in recent decades, large-scale clinical trials aimed at enhancing treatment have not achieved high cure rates. Therefore, improving the cure and survival rates of osteosarcoma is still an urgent problem for clinicians. Based on the fact that surgical resection is still the main treatment method for osteosarcoma, because of the rapid growth of osteosarcoma, preoperative chemotherapy is an important means to improve the surgical resection rate and reduce tumor recurrence, which can improve the excellent prognosis rate (Harrison et al. 2018). VAD can inhibit tumor cell proliferation and improve surgical resection rate, but its toxic side effects, especially severe cardiorenal toxicity, limit its chemotherapy dose and efficacy (Lilienthal and Herold 2020; Wang et al. 2017). How to improve the efficacy of chemotherapy while reducing toxic side effects has always been a challenge faced by clinical physicians.

The occurrence of osteosarcoma is closely related to angiogenesis. VEGF and Ang-2 are important factors to promote angiogenesis. High expression is related to tumor progression, metastasis and bad prognosis, and is a crucial serological marker of osteosarcoma prognosis (Smrke et al. 2021; Armstrong and Dass 2018). Some scholars also emphasized that inhibiting angiogenesis is one of the important means for the treatment of osteosarcoma (Xin and Wei 2022). Gal-3 is an active inflammatory factor, which is related to tumor proliferation, metastasis and chemotherapy resistance. Its elevated level is also a prognostic marker of osteosarcoma disease progression (Liu et al. 2021). At the same time, VAD, a chemotherapy drug, has a certain degree of nephrotoxicity, which limits its clinical application dosage and scope to a certain extent. Curcumin is a natural antioxidant, which can inhibit angiogenesis, reduce inflammation and anti-tumor activities, enhance the efficacy of chemotherapy drugs and reduce their side effects (Tabone et al. 2017). Although there are some targeted drugs or immunotherapeutic drugs for the treatment of osteosarcoma (Zhou et al. 2014), due to the uneven distribution of these drugs in the body, it is difficult to give full play to the efficacy, resulting in adverse reactions of chemotherapy drugs. The drug delivery system selectively aggregates drugs to the lesion site through nanotechnology to achieve controlled release, enhance clinical treatment effectiveness, and reduce systemic toxicity and side effects. Therefore, inhibition of angiogenesis, enhancement of effective distribution of chemotherapeutic agents, and reduction of renal impairment during chemotherapy are important strategies for the treatment of osteosarcoma. DOX+CUR LPNs synergize the chemotherapeutic effect of adriamycin, the inhibitory angiogenic effect of curcumin, and the reduction of renal impairment, and are encapsulated using lipid nanoparticles, which enable the drugs to enter the tumor tissues and have a controlled release, producing a more efficient antitumor effect. This result is in agreement with Jiacong H et al. who found that the combination of drugs with lipid nanomaterials can trigger a biomorphic response in cancer cells and reduce toxicity (Jiacong et al. 2023). The innovative drug delivery system in this

study provides a new strategy for improving the efficacy and safety of chemotherapy for osteosarcoma, which is worth further verification and application in a wider range.

This study hypothesized that DOX+CUR LPNs can play a synergistic effect of VAD chemotherapy, curcumin angiogenesis inhibition and enhanced chemotherapy effect, and play a better role in the treatment of osteosarcoma. The clinical application value of the new co-loading drug delivery system was verified through clinical experiments, which provided a better choice for improving the efficacy and safety of osteosarcoma chemotherapy (Zheng et al. 2022). The research approach was clear, the research hypotheses were in line with clinical treatment principles, and had operability. From the implementation results, the DOX+CUR LPNs group showed a more significant decrease in VEGF and Gal-3 levels, milder renal function damage after chemotherapy, higher clinical efficacy, and lower incidence of adverse reactions. This result was similar to the research results of Gota scholar (Gota et al. 2010). Many scholars have found that Curcumin inhibits PI3K/AKT/mTOR pathway, and its liposomes can protect renal function (Abe et al. 2016; Bulboacă et al. 2021). It is suggested that DOX+CUR LPNs has stronger angiogenesis inhibition effect than VAD, better protection of renal function, and promotes the improvement of chemotherapy efficacy, providing a new preoperative chemotherapy scheme for patients with osteosarcoma. In addition, the comparison of the incidence of adverse reactions between the two groups of patients revealed that the incidence of adverse reactions in the DOX+CUR LPNs group was 47.05% lower than that in the VAD group, and the difference was statistically significant ($\chi 2 = 17.934$, $P = 0.003$). The results of this data are consistent with the results of endoplasmic reticulum expression test in osteosarcoma cells conducted by Chiu K W et al. in which the probability of adverse reactions in the experimental group was lower than that of the control group by about 50% (Chiu et al. 2023). This study was a small sample randomized controlled study. It was preliminarily confirmed that DOX+CUR LPNs can more effectively inhibit angiogenesis, reduce nephrotoxicity, improve chemotherapy efficacy, and provide a better choice for patients with osteosarcoma. However, the number of research cases was limited, the follow-up time was short, and long-term survival analysis and tumor histological testing have not been conducted, making it difficult to directly evaluate the long-term impact and direct mechanism of DOX+CUR LPNs on tumor progression and prognosis. In the future, it is necessary to carry out multi center large sample RCT, extend the follow-up time, and comprehensively evaluate the clinical effect, mechanism of action and safety of DOX+CUR LPNs in combination with animal experiments and clinical tumor histology research to determine their true value in the treatment of osteosarcoma. At the same time, clinical research on other solid tumors is also needed to explore the broad-spectrum anti-tumor potential of DOX+CUR LPNs.

Conclusion

To sum up, this study systematically compared the difference between DOX+CUR LPNs and VAD chemotherapy schemes. The results support that DOX+CUR LPNs can enhance the chemotherapy effect, reduce the side effects, reduce the degree

of renal function damage caused by chemotherapy, and provide a new strategy for improving the efficacy and safety of preoperative chemotherapy for osteosarcoma.

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Author contributions
XL, PZ, JL, YZ, BW and ZL contributed to the investigation, participated the design, supervision and editing, and resources, edited tables and figures and data statistics and analysis, revised the manuscript and wrote the manuscript. All authors read and approved final manuscript.

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Availability of data and materials
The datasets used and/or analyzed in the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the local ethics committee of the Xiangyang Central Hospital. All experiments were performed in accordance with relevant guidelines and regulations such as the Declaration of Helsinki and the patients signed the informed consent form and agreed to be published.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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