Progress in the chemotherapeutic treatment of osteosarcoma (Review)

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Abstract. Osteosarcoma (OS) is the most common type of primary bone tumor in children and adolescents and has been associated with a high degree of malignancy, early metastasis, rapid progression and poor prognosis. However, the use of adjuvant chemotherapy improves the prognosis of patients with OS. OS chemotherapy is based primarily on the use of adriamycin, cisplatin (DDP), methotrexate (MTX), ifosfamide (IFO), epirubicin (EPI) and other drugs. Previous studies have revealed that the survival rate for patients with OS appears to have plateaued: 5-year survival rates remain close to 60%, even with the use of combined chemotherapy. The most limiting factors include complications and fatal toxicity associated with chemotherapy agents, particularly high-dose MTX (HD-MTX), for which high toxicity and great individual variation in responses have been observed. Docetaxel (TXT) is a representative member of the relatively recently developed taxane class of drugs, which function to inhibit OS cell proliferation and induce apoptosis. Recently, more clinical studies have reported that TXT combined with gemcitabine (GEM) is effective in the treatment of OS (relapse/refractory and progressive), providing evidence in support of potential novel treatment strategies for this patient population. However, there is still no global consensus on this type of chemotherapy approach. The present review summarizes current studies surrounding progress in the chemotherapeutic treatment of OS and discusses the advantages and potential feasibility of TXT+GEM in the treatment of OS.

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Contents

1. Introduction

Osteosarcoma (OS) is derived from primitive bone-forming mesenchymal cells and represents the most common primary bone malignancy in children and adolescents, with an annual incidence rate of ~3 per 100 million, though this rate is ~50% higher in men than in women in the USA, 2016 (1,2). OS exhibits a high degree of malignancy and tends to metastasize early: Lung metastasis is frequently observed in newly diagnosed patients, and pulmonary symptoms may develop within one year without chemotherapy (3). The main cause of mortality in patients with OS is lung metastasis, and approximately 10-20% of patients are diagnosed with metastatic OS upon identification of the disease in the USA, 2015 (4). Consequently, prognosis is often very poor (5,6).

Prior to the 1950s, the treatment of OS depended primarily on surgical resection, with 5-year survival rates <20% in 1972 in the USA (7-9). Since the introduction of effective chemotherapeutic agents in the 1970s and subsequent developments in neo-adjuvant chemotherapy, prognosis for such patients has greatly improved. The main chemotherapeutic agents for OS include adriamycin (ADM), cisplatin (DDP), methotrexate (MTX), cyclophosphamide (CTX) and epirubicin (EPI). Although some novel insights have been offered for clinical and scientific relevance, minor progress has been made in OS treatment following a significant survival improvement in the late 1980s with the addition of chemotherapy to surgery. In addition, prognosis of patients with recurrent or refractory OS is particularly poor. The function of second-line chemotherapy for recurrent OS is much less well defined and there is no accepted standard regimen (10-20). The purpose of the

present article was to review the current state of the field and the opportunities for present and future treatment strategies in OS. Furthermore, informed consent was obtained from all individual participants included in the present study and all procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

2. Conventional OS chemotherapy

In the early 1950s, the primary treatment for OS involved surgical resection, with 5-year survival rates <20% in the USA (5,6). Sun *et al* (21) reported that the dose and intensity of MTX are associated with the survival of patients with OS. Prior to the 1970s, Jaffe (22) and Rosen *et al* (23-25) treated OS with bleomycin, CTX, HD-MTX, vincristine and ADM following surgery, providing the first reported evidence for postoperative adjuvant chemotherapy in this patient population.

Adjuvant chemotherapy is defined as chemotherapy directed toward the site of the primary tumor following radical resection or radical radiotherapy, also known as postoperative or radiation chemotherapy. Such therapy aims at improving cure rates by eliminating small metastases (26,27). In 1982, Eilber and Rosen (28) and Rosen (29) reviewed postoperative chemotherapy strategies in patients with OS, reporting a significant efficacy and thus forming the basis for neoadjuvant chemotherapy-important milestones in the history of OS treatment. Neoadjuvant chemotherapy was initiated prior to surgery according to the degree of the tumor response following chemotherapeutic treatment of the primary tumor. The T4 and T5 protocols were the first to incorporate neoadjuvant chemotherapy.

Current chemotherapy programs for OS have included the T protocols developed by Rosen (23) the Cooperative Osteosarcoma Study group protocol of the Germany and Austria OS Chemotherapy Collaborative Research Group and the treatment and investigation of osteosarcoma (TOIS) protocol developed by Jaffe *et al* (22) at the Rizzoli Institute of Chemotherapy in Italy. MTX, DDP, ADM and IFO are the four primary drugs used for OS chemotherapy (30). For almost 20 years, high-dose and multi-drug neoadjuvant chemotherapy has been the gold standard for OS treatment.

Currently, the majority of the scholars hypothesize that combined surgical removal of the tumor and systemic multi-drug chemotherapy consisting mainly of MTX, ADM and DDP (with or without IFO) represents the best strategy for the treatment of conventional OS. Two conventional chemotherapy regimens have been described: One involves the use of ADM (45 mg/m^2) in combination with DDP (100-120 mg/m^2), while the other involves the combined use of MTX (8-12 g/m^2 and 12 g/m^2), DDP (120 mg/m^2) and ADM (60 mg/m^2) (31).

3. Problems with chemotherapy

The most common side effects of chemotherapy include myelosuppression and gastrointestinal reactions, which typically manifest as lower blood, nausea and vomiting. The main side effect of anthracycline antibiotics (doxorubicin and EPI) is cardiotoxicity, and the incidence of heart failure increases to 25-30% when ADM doses exceed 550 mg/m^2 (32). Furthermore, the side effects of DDP include kidney damage, hearing loss, hypomagnesemia and peripheral neuropathy. The most severe side effect of IFO is bladder toxicity, as the IFO metabolite acrolein can result in hemorrhagic cystitis.

HD-MTX is associated with serious and sometimes fatal toxicity. Previous studies have reported that the grade III-IV gastrointestinal reaction rate for HD-MTX is 49.32% whereas the rate of grade III-IV neutropenia is 30.13% (33,34). Several adverse nervous system reactions have also been associated with HD-MTX chemotherapy. At present, the use of HD-MTX chemotherapy remains limited due to the risk of potentially fatal MTX poisoning or bone marrow suppression (35,36). A number of scholars have reported that patients exhibited adverse reactions of differing types and degrees following the use of the MTX-MTX-DDP/ADM regimen (37). Furthermore, certain studies have even reported a 100% rate of gastrointestinal reactions following MTX chemotherapy, mainly consisting of nausea and vomiting, as well as a 73.13% rate of oral mucositis; 80% rate of abnormal liver function [mainly associated with increases in alanine aminotransferase]; and a 17% incidence of leukopenia (38). Therefore, controversy remains regarding the use of multi-drug therapy involving HD-MTX for the treatment of OS. Thus, it remains crucial to elucidate whether such chemotherapeutic methods are both safe and effective.

In total, approximately 30-40% of patients are diagnosed with advanced stage OS upon clinical confirmation, with roughly 50% of patients experiencing postoperative recurrence (39). Although chemotherapy significantly improves the prognosis of patients with non-metastatic OS, patients are often forced to cease and modify chemotherapy regimens due to drug resistance, toxicity, and/or side effects. Furthermore, chemotherapy cannot effectively control tumor metastasis and progression. Almost 10 years of research has revealed that the survival rate for patients with OS has reached a plateau: The 5-year survival rate remains ~60%, even when combined chemotherapy is used (40). The 5-year survival rate for patients with pulmonary metastases in the early stage of treatment, however, remains lower than 20%. In total, approximately 25-50% of patients experience lung metastasis even during chemotherapy. Therefore, lung metastasis represents the main roadblock for improving survival rates in patients with OS (41).

With the advent of adjuvant and neoadjuvant chemotherapy, the survival rate of patients with OS has gradually increased, although 20-40% of patients still experience local recurrence or distant metastasis. Therefore, it is necessary to develop novel chemotherapeutic agents for the treatment of OS and to establish standards for second-line OS chemotherapy, which also remains controversial (42). Such developments may aid in improving the prognosis of patients with recurrent, metastatic or resistant OS.

Therefore, continuing research into novel treatment and all types of developed therapeutic forms is required (Fig. 1).

4. Second-line treatment of OS

OS is characterized by an onset during childhood or adolescence, a high degree of malignancy, early metastasis, rapid progression and poor prognosis (43). Multiple investigators

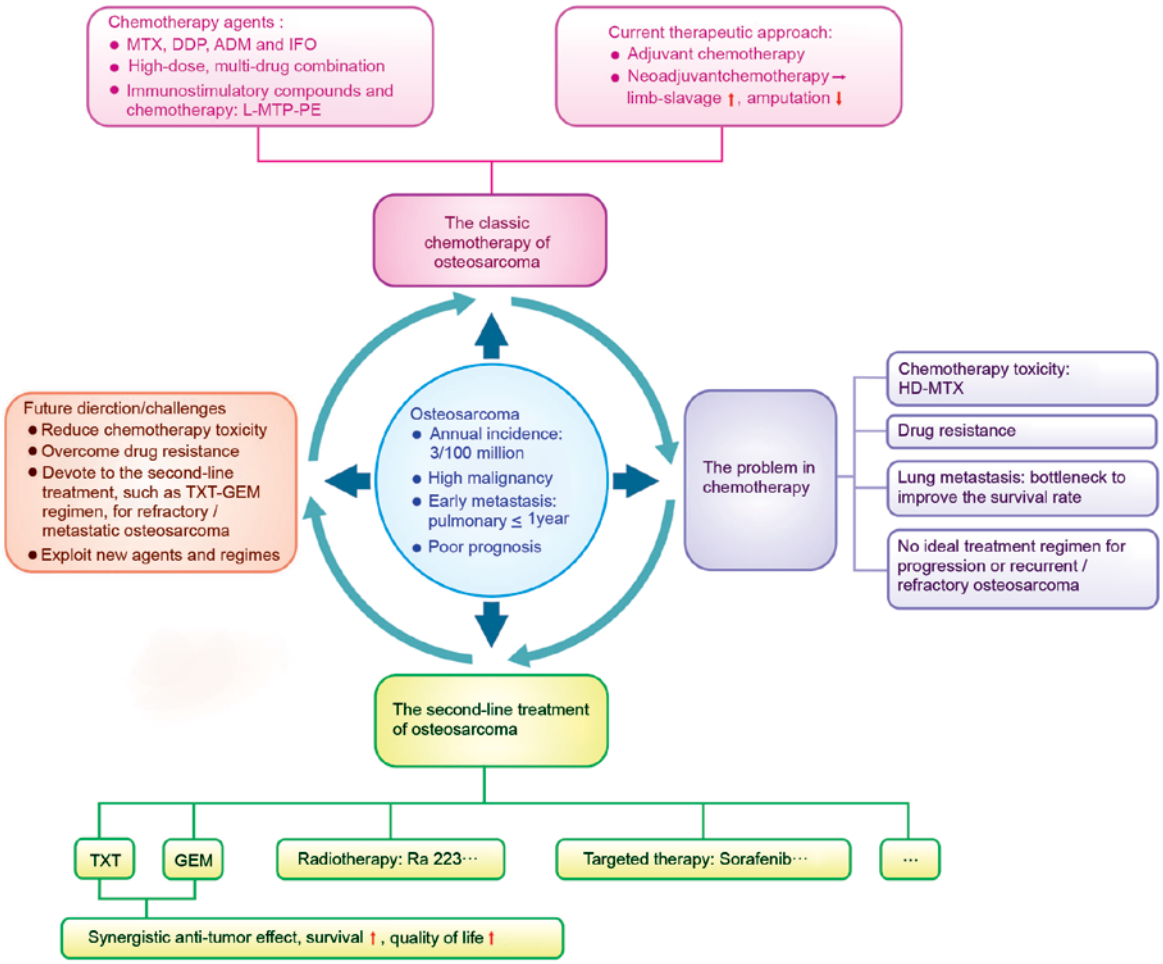

Figure 1. A synopsis model of osteosarcoma: Questions to be answered and future challenges. MTX, methotrexate; DDP, cisplatin; ADM, adriamycin; IFO, ifosfamide; L-MTP-PE, liposomal muramyl tripeptide phosphatidyl ethanolamine; TXT, docetaxel; GEM, gemcitabine; HD, high-dose.

have indicated that patients receive second-line therapy in the event of recurrence or metastasis (44,45). Furthermore, the National Comprehensive Cancer Network (NCCN) guidelines (version 2.2016) recommend that second-line therapy include TXT, GEM, CTX, etoposide (VP-16), topotecan (TPT), carboplatin, samarium lexidronam (^{153}Sm-EDTMP), Ra223, sorafenib and everolimus (46). Recent studies have focused mainly on the use of GEM, TXT or a combination of the two for second-line OS treatment (Tables I and II).

Docetaxel (TXT). TXT is a non-cytotoxic precursor derived from the needles of Taxus specimens that has been chemically modified to yield a taxol-type antitumor agent that is threefold higher in intracellular concentration than paclitaxel. TXT also exhibits long residence time in the cell (42). It acts mainly through the promotion of stable microtubule polymerization and the inhibition of depolymerization, thereby significantly reducing the number of free microtubules, inhibiting spindle separation at the two poles, blocking the G and M phases and ultimately inhibiting tumor cell mitosis and proliferation (47).

Certain scholars have reported that TXT can inhibit the proliferation of OS cells and induce apoptosis, and that such inhibition is time- and dose-dependent (48,49). Combination therapy using TXT and gemcitabine (GEM) has also been reported to enhance antitumor effects (50,51). A number of scholars (52) have used chemotherapy-related drug target gene detection via the application of second-generation high-throughput sequencing technology in patients with OS undergoing surgical resection. The results of such studies indicate that TXT induces OS cell apoptosis, and that OS cells can achieve moderate TXT sensitivity (53.3%).

Palmerini *et al* (53) used TXT chemotherapy for 14 cases of recurrent OS, 1 case of partial remission, and 1 case involving a patient in stable condition. Zwerdling *et al* (54) used single-drug TXT chemotherapy, reporting 1-year and 5-year overall survival rates of 24 and 6%, respectively. These observations indicate that such approaches may be useful in the treatment of metastatic and relapsed/refractory OS, and OS that is unresponsive to first-line treatment.

GEM. GEM is a fluorinated analog of the nucleoside deoxycytidylic acid, which is converted into active diphosphate and nucleoside triphosphates by the action of nucleoside kinases in the cell. Diphosphate inhibits ribonucleotide reductase and is involved in deoxycytidine triphosphate competition as a nucleoside triphosphate. Ribonucleotide reductase inhibition can activate self-generating mechanisms, thereby increasing the entry of nucleotides into cells. DNA synthesis terminates when the GEM triphosphate metabolite enters the DNA to produce additional nucleotides. This mechanism can develop

Table I. Osteosarcoma systemic therapy agents of the NCCN guidelines.

Agent	(Refs.)
First-line therapy (primary/neoadjuvant/adjuvant therapy or metastatic disease)	
Cisplatin and doxorubicin	(36-38)
MAP (high-dose methotrexate, cisplatin, and doxorubicin)	(39,40)
Doxorubicin, cisplatin, ifosfamaide, and high-dose methotrexate	(41)
Ifosfamide, cisplatin, and epirubicin	(42)
Second-line therapy (relapsed/refractory or metastatic disease)	
Docetaxel and gemcitabine	(30)
Cyclophosphamide and etoposide	(43)
Cyclophosphamide and topotecan	(18)
Gemcitabine	(44)
Ifosfamide (high dose)+/- etoposide	(26,28)
Ifosfamide, carboplatin and etoposide	(29)
High-dose methotrexate, etoposide and ifosfamide	(45)
^{153}Sm-EDTMP for relapsed or refractory disease beyond second-line therapy	(40)
Ra223	(41,46,47)
Sorafenib	(48)
Sorafenib+everolimus	(49)

NCCN, National Comprehensive Cancer Network; ^{153}Sm-EDTMP, samarium lexidronam.

resistance to DNA repair enzymes, which may represent a mechanism for overcoming drug resistance (55). The results of a small-sample phase II clinical trial have indicated that the effective rate of GEM monotherapy is <10%. Recent studies (47,53,56,57) have also indicated that TXT can increase the expression of thymidine phosphorylase in tumor tissue, thereby enhancing the antitumor activity of GEM, resulting in synergistic antitumor effects ranging from 17-30% (58). He *et al* (51) reported that 80% of patients [median OS duration: 13 months; median progression-free survival (PFS): 6-7 months] receiving GEM in combination with TXT as second-line therapy experienced 12- and 24-month survival rates of 66 and 80%, respectively.

Qi *et al* (48) treated 18 patients with relapsed/refractory OS using TXT combined with GEM, reporting a tumor control rate of the rate [(CR+PR+ stable disease (SD)] of 22.3% and a median overall survival of 8 months. Furthermore, Mora *et al* (59) used the same chemotherapy protocol, reporting a remission rate (CR+PR) of 50% and a median remission duration of 10 months. O'Day and Gorlick (60) reported that the overall response rate of patients with OS was 43% following combined TXT+GEM chemotherapy. Song *et al* (55) also reported a response rate (CR+PR) of 23.5% and a control rate (CR+PR+SD) of 41.2%, with a 1-year overall survival rate of 53.6% and a median remission duration of 11.2 months in patients receiving TXT+GEM for recurrent/refractory OS. Certain scholars have also applied this strategy for the treatment of patients undergoing limb-salvage surgery, reporting remission rates of 13.0% and a median overall survival period of 9 months (51). Additional studies have added arsenic trioxide (As_2O_3) to the TXT+GEM combination regimen for the treatment of first-line chemotherapeutic drug resistance in patients with OS lung metastasis, reporting an overall effective rate (CR+PR) of 34.6%, along with 1-,2-, and 4-year survival rates of 61.5, 38.4 and 15.4%, respectively (55). Additional studies have also reported disease control rates between 28.5-41.2% (55,58) and median overall survival times of 7-11 months following TXT+GEM treatment in patients with refractory/metastatic OS (53). Therefore, the TXT+GEM regimen, for which a relatively larger amount of evidence has been reported relative to other recommended regimens, was the first to be recommended (51) (as shown in Table II).

Targeted therapy. Sorafenib acts to inhibit a variety of kinases present in the cell and at the cell surface, including RAF kinase, vascular endothelial growth factor receptor-2, vascular endothelial growth factor receptor-3, platelet derived growth factor receptor-β, KIT Proto-Oncogene Receptor Tyrosine Kinase (KIT) and Fms Related Tyrosine Kinase 3 (FLT-3). A recent phase II study revealed that the median PFS was 4 months for sorafenib-treated patients with first-line failure and unresectable OS, with a clinical benefit rate of 29 and a 17% increase in clinical benefit after 6 months (61). Such observations provide the first evidence for the efficacy of small-molecule agents targeted toward the second-line treatment of lung metastasis in OS.

Everolimus. Everolimus is a derivative of sirolimus (also known as rapamycin), which is a classical inhibitor of the mechanistic target of rapamycin target and a novel macrolide immunosuppressive agent. Rapamycin prevents T lymphocytes and other cells from transitioning from the G_1 to S phases via blockage of signaling pathways involving various cytokines, which serve an important role in immunosuppression. Grignani *et al* (61,62) speculate that sorafenib and combined therapy using sorafenib and everolimus are promising for

Table II. Evidence which support the Docetaxel+Gemcitabine regimens are recommended to osteosarcoma.

Authors	Number of patients	Drugs	Outcomes	(Refs.)
Yu *et al*	39	21 cases: Gemcitabine (675 mg/m^2 d1, d8)+docetaxel (100 mg/m^2 d8) 18 cases: Pemetrexed (500 mg/m^2 d1)+cisplatin (100 mg/m^2 d1)	The response rate was 25.0% in patients who received pirarubicin-based chemotherapy, while it was 13.0% in the gemcitabine-docetaxel group. Moreover, the median OS was longer in the pirarubicin-based chemotherapy group (14.0 vs. 9.0 months, P<0.05), particularly in the pirarubicin-ifosfamide (14.0 months) and pirarubicin-cisplatin (15.0 months) subgroups.	(58)
He *et al*	75	23 cases: Gemcitabine (675 mg/m^2 d1, d8)+docetaxel (100 mg/m^2 d8) 52 cases: THP-based chemotherapy (THP-CDDP, THP-IFO, or THP-PTX)	13 patients (25.0%) in the THP group and 3 (13.0%) in the GT group achieved a PR, while 23 patients (44.2%) in the THP group and 8 (34.8%) in the GT group showed SD. Thus, RRs in the 2 groups were 25.0 and 13.0% (P=0.414), and DCRs were 69.2 and 47.8% (P=0.127)	(51)
Qi *et al*	18	Gemcitabine (675 mg/m^2 d1, d8)+docetaxel (100 mg/m^2 d8)	The overall response rate was 5.6% and the disease control rate was 22.3%, with 1 partial response and 3 patients with stable disease. The median time to progression and overall survival time were 2 months (range: 2-6 months) and 8 months (range: 3-21 months)	(48)
Mora *et al*	10	Gemcitabine (675 mg/m^2 d1, d8)+docetaxel (100 mg/m^2 d8)	4 (40%) patients had a CR, 1 (10%) had a PR, 3 (30%) had SD and 2 (20%) had a PD, which provides an objective response rate (CR+PR) of 50%. Median duration of response (CR+PR+SD) was 10 months (range: 6 to 32+mo). 5 out of the 10 patients (50%) are alive, with a median follow-up of 48 months from diagnosis.	(59)
O'Day *et al*	35	Gemcitabine (675 mg/m^2 d1, d8)+docetaxel (100 mg/m^2 d8)	All response rate 43%; 29% (CR+PR); 2 out of 4 osteosarcoma achieve PR.	(60)
Palmerini *et al*	51	Gemcitabine (900 mg/m^2 d1, d8)+docetaxel (75 mg/m^2 d8)	Four-month PFS rate was 46%; 6 (13%) patients had a PR, 20 (43%) had SD and 20 (43%) had PD. The 1-year OS was 30%: 67% for PR, 54% for SD and 20% for PD (P=0.005).	(53)

OS, osteosarcoma; THP, Therarubicin; GT, Gemcitabine+docetaxel; CR, complete response; PR, partial response; CDDP, cisplatin; IFO, ifosfamide; PTX, Paclitaxel; SD, stable disease; RR, Relative risk; DCR, Disease control rate; CR, control rate; PD, progressive disease; PFS, progression-free survival.

the treatment of patients with advanced or unresectable OS, although they did not attain the prespecified target of 50% or greater PFS within 6 months.

CTX. CTX is a bifunctional alkylating and cell cycle nonspecific agent that interferes with the DNA and RNA function, exerting its most apparent effects during the S phase via DNA cross-linking and inhibition of DNA synthesis. CTX first transforms into aldehydes and phosphorus amide in the liver *in vitro* and without antitumor activity. However, aldehyde amide in tumor cells is transformed into amide nitrogen mustard and acrolein, which exert cytotoxic effects.

Etoposide. Etoposide is a cell cycle-specific antitumor drug that acts on DNA topoisomerase II to form the reversible complex of drug-enzyme-DNA stabilization, thereby hindering DNA repair. This complex can be reversed by cessation of drug treatment, so that the damaged DNA undergoes repair and cytotoxicity is reduced.

A phase II study reported that combined treatment using CTX and etoposide X2 arrested OS progression in a significant

Table III. Strategies for target treatment of osteosarcoma and its representative drugs/compounds.

Strategy	Drugs/compounds
Novel delivery mechanisms	SLIT cisplatin (aerosolized liposomal formulation)
Overcoming drug resistance	
Inhibition of cellular DNA synthesis and cell growth	Gemcitabine
Induction of apoptosis and cell cycle arrest	Doxetacel
Novel antifolates	Trimetrexate (does not require RCF for transport into cell)
Inhibition of drug efflux	Curcumin
Inhibition of signaling receptors and transduction	
IGF/IGF-1R pathway	Robatumumab, Figitumumab, Cixutumumab
mTOR pathway	Ridaforolimus, Everolimus
Src pathway	Sorafenib, Dasatinib, Saracatinib
HER2-overexpression	Trastuzumab
Altering the tumor microenvironment	
Inhibition of osteoclast-mediated bone destruction	
Bisphosphonates	Zoledronic acid, Pamidronate
RANKL inhibitors	Denosumab
Inhibition of angiogenesis	
VEGF inhibitors	Bevacizumab
Collagen XVIII-a 1	Endostar

SLIT, sustain release lipid inhalation targeting; RCF, reduced folate carrier; IGF-1R, insulin-like growth factor 1; mTOR, mammalian target of rapamycin; Src, src is a membrane-associated tyrosine kinase; HER2, human epidermal growth factor receptor 2; RANKL, receptor activator of nuclear factor-jB ligand; VEGF, vascular endothelial growth factor.

number of patients (54%), with a relatively good tolerability and self-limiting toxicity that was resolved in all cases (11).

TPT. TPT is an inhibitor of topoisomerase I, which binds to the topoisomerase I-DNA complex and prevents reconnection of these single strand breaks. TPT is an S-phase specific drug whose cytotoxicity influences the synthesis of DNA. Saylors *et al* (12) reported that the combination of CTX and TPT is effective in the treatment of rhabdomyosarcoma, neuroblastoma and Ewing's sarcoma. Stabilization of disease was also observed in patients with OS, although objective responses were rare. Furthermore, TPT therapy can be initiated within the range of acceptable hematopoietic toxicity with the use of filgrastim support.

IFO. IFO is a cell-cycle nonspecific drug that is mainly activated by hydrolysis of the first four carbons, following which 4-hydroxy-IFO automatically forms aldehyde IFO, which decomposes into phosphorus amide nitrogen mustard and acrolein. The cytotoxic effect of IFO influences cross-linking with DNA. The cell cycle increases in proportion to G_2+M, and the G_2 phase is delayed following administration of IFO. Magnan *et al* (63) conducted a retrospective chart review and reported that high doses of IFO resulted in a 4-year event-free survival (EFS) rate of 27% and an overall survival rate of 39%.

The combination of etoposide and high-dose IFO is effective for induction of chemotherapy in patients with metastatic OS (3). Le Deley *et al* (17) reported a 5-year EFS rate of 62% for the entire study population, which was slightly higher in the etoposide-IFO arm than in the doxorubicin arm. Furthermore, the 5-year overall survival rate of the entire population was 76%. In total, ~43% of patients in the etoposide-IFO arm were event-free at 3 years without having received any doxorubicin or DDP, thus avoiding the risk of long-term cardio- and cardiotoxicity.

Pemetrexed. Pemetrexed is a multi-target antifolate agent that significantly inhibits thymidylate synthase, dihydrofolate reductase and glycine ribonucleoside formyl transferase to interfere with folic acid metabolic pathways. Studies have revealed that such treatment may be effective as second-line chemotherapy in patients with MTX-resistant OS (45). Endostar has been combined with pemetrexed for the treatment of recurrent, drug-resistant OS and pulmonary metastases of OS. Furthermore, recent observations indicate that this treatment is effective and results in significant improvements in the quality of life without significant adverse reactions (64-67). Although trial results regarding second-line chemotherapy with pemetrexed for patients with OS lung metastases have been positive, further evidence regarding monotherapy and combination therapy using this agent is required.

Liposome-encapsulated muramyl tripeptide-phosphatidyl ethanolamine (L-MTP-PE). L-MTP-PE is an analog of muramyl dipeptide with the ability to activate macrophages and monocytes. Phase III clinical trials have indicated that L-MTP-PE can enhance immune system function (68). Mori *et al* (69) reported that infusion of L-MTP-PE can reduce

the recurrence of lung metastases following surgery, and that the survival rate was higher than that of patients in the concurrent chemotherapy group. In recent years, L-MTP-PE has gained attention for its effects on pulmonary metastasis of OS and may prove effective as a second-line chemotherapy agent.

Samarium-153 ethylenediaminetetramethylene phosphonate. The ^{153}Sm nuclide is ideal for the diagnosis and treatment in nuclear medicine and is mainly used in the preparation of therapeutic radiopharmaceuticals, including ^{153}Sm-EDTMP (ethylene diamine tetramethylene phosphonic acid ethylene diamine tetramethylene phosphonic acid), which has a high affinity for pro-tumor characteristics and bone. This agent has been used to treat bone metastases and relieve bone pain, although it can also be used for the treatment of primary bone cancer. Furthermore, bone-specific irradiation can be induced using ^{153}Sm-EDTMP with peripheral-blood progenitor-cell support (70).

Radium 223 chloride. Radium 223 chloride, an α-particle radioactive material, was the first particle to be used in radiation therapy drugs. The use of this agent is advantageous in that 95% of the decay can be released in the form of α-particles, resulting in less damage to normal cells. Radium 223 chloride simulates the main constituent of bone calcium, although the actual course of treatment requires 6 injections/month. Furthermore, the drug is transferred to sites with metabolically active cells and metastatic bone cancer cells following injection. α-particles are then released, resulting in the inhibition of bone metastases and cancer cell proliferation. Radium-223 is associated with low marrow toxicity and increased radiobiological effectiveness, particularly in bone-forming types of cancer, when compared with samarium-153-EDTMP (18,19). Radium 223 may have greater potential for widespread use against bone metastases in OS since it may achieve safe and effective decrease of tumor burden and facilitate improvements in surgery and/or radiotherapy in patients with unresectable, large or metastatic tumors.

Multiple molecular-based therapies have also been developed for the treatment of OS, including anti-C-X-C chemokine receptor type 4 drugs (71), matrix metalloproteinase inhibitors, selective cyclooxygenase-2 inhibitors (72), type 1 insulin like growth factor receptor, and osteoclast-targeted therapy (73) The main factors affecting the function of osteoclasts are receptor activator NF-κβ ligands, osteoprotective proteins, bisphosphonates and Src inhibitors (74) However, targeted therapies also produce resistance and adverse effects (Table III), thus necessitating further investigation (61,75-78).

5. Discussion

OS is the most common primary malignancy observed in children and adolescents (1). With the advent of adjuvant and neoadjuvant chemotherapy, the survival rate of patients with OS has gradually increased, although 20-40% of patients still experienced distant metastasis or local recurrence in 2014 (79). Despite major discoveries over the past 35 years, the survival rate for OS has plateaued, remaining at ~60% even when combined therapy is used in China in 2015 (80). A previous study revealed that multidrug-associated chemotherapy is superior to single-drug and high dose-intensity chemotherapy, although there is considerable agreement among experts regarding the cytotoxicity of these agents (81). The blind pursuit of high-intensity doses increases the cost and complications of chemotherapy, as well as the risk of fatal toxicity, which has been reported to be as high as 4.3% (32). In particular, HD-MTX is highly toxic and associated with great variation in individual responses. Furthermore, patients are often forced to terminate or modify their chemotherapy regimens due to drug resistance or intense side effects, thus making it difficult to gain definitive control over the progression and metastasis of tumors.

The stagnation in survival rates is principally associated to the fact that the arsenal of available effective chemotherapeutic agents has not changed substantially over the past decade. Therefore, novel agents and alternative strategies to combat this malignancy are required. Advances in research concerning tumor growth, chemoresistance, gene therapy and targeted molecular therapy will allow for the development of multidisciplinary approaches for the treatment of OS. Progress has also been made in the areas of antitumor angiogenesis therapy, tumor immunotherapy and tumor drug resistance (82). However, in 1993, 20-30% of all patients in USA exhibited clinically detectable metastatic OS when they were initially diagnosed (83). The great heterogeneity of these tumors often conveys resistance to drugs, giving rise to relapse and metastasis (84). Therefore, the requirement to develop novel drugs and treatment strategies for patients with OS relapse/metastasis remains urgent.

The NCCN recommends that patients receive second-line treatment in the event of disease progression during first-line treatment (44). At present, several novel chemotherapy agents are undergoing investigation, including GEM, TXT and a combination of the two. Studies have revealed that TXT may inhibit proliferation and induce apoptosis of OS cells, and that the sensitivity of OS cells to TXT is high, providing a novel method of treatment for patients with refractory OS or those in whom relapse or metastasis have occurred. Furthermore, a retrospective case study reported that TXT combined with GEM for the treatment of relapsed, refractory or metastatic OS is significantly effective (85), while other studies have revealed that patients benefit from such combination strategies, even when lower dosages are used (47).

Recent studies have revealed that TXT can increase the expression of thymidine phosphorylase in tumor tissue, thereby enhancing the antitumor activity of GEM, resulting in synergistic antitumor effects, and that such treatment is well-tolerated (55,86). These observations also represent a novel method for effective and comprehensive treatment of OS.

However, the most recent studies on these novel agents have been small, retrospective analyses, while phase III clinical data are lacking when compared with observations regarding conventional chemotherapy. Additional large, multicenter, randomized controlled trials and phase II trials are required in order to validate the efficacy and safety of TXT+GEM in the treatment of OS, as well as the appropriate chemotherapy regimens and doses. Finally, continuing research into novel treatment and all types of developed therapeutic forms is required.

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Availability of data and materials

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Authors' contributions

Study concept and design was the responsibility of YZ, YHZ and ZY. YZ, JY, NZ and CW searched references. NZ and CW acquired data and new ideas from references and analysed and interpreted this information Manuscript preparation was undertaken by YZ, YHZ, SK, YZ, ZH, JY, NZ, CW and BS. YZ, XS, LH, ZY performed a manuscript review. All authors read and approve the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

All authors declare that there have no competing interests.

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