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REVIEW

Advanced development of ErbB family-targeted therapies in osteosarcoma treatment

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Summary

Osteosarcoma (OS) is the most common primary aggressive and malignant bone tumor. Newly diagnostic OS patients benefit from the standard therapy including surgical resection plus radiotherapy and neoadjuvant chemotherapy (MAP chemotherapy: high-dose methotrexate, doxorubicin and cisplatin). However, tumor recurrence and metastasis give rise to a sharp decline of the 5-year overall survival rate in OS patients. Little improvement has been made for decades, urging the development of more effective therapeutic approaches. ErbB receptor family including EGFR, HER2, HER3 and HER4, being important to the activation of PI3K/Akt and MAPK signaling pathways, are potential targets for OS treatment. Genetic aberrations (amplification, overexpression, mutation and altered splicing) of ErbB are essential to the growth, apoptosis, motility and metastasis in a variety of cancers. Overexpression of ErbB family is associated with the poor prognosis of cancer patients. A number of monoclonal antibodies or inhibitors specific for ErbB family have entered clinical trials in a range of solid tumors including breast carcinoma, lung carcinoma and sarcoma. Here, we summarized the roles and expression of ErbB family in OS and the current development of ErbB-targeted therapeutic strategies including chemotherapies and immunotherapies for OS treatment.

Keywords Osteosarcoma · ErbB · Metastasis · Immunotherapy

Abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity
ATP	Adenosine triphosphate
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T cell immunotherapy
DAC	5-aza-2′-deoxycytidine
DLT	Dose-limiting toxicity
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ERα	Estrogen receptor α
H&N	Head and neck cancer
HB-EGF	Heparin-binding EGF
HRG	Heregulin
IFNγ	Interferon γ
IGF	Insulin like growth factor
IGF-IR	Insulin-like growth factor I receptor
IL	Interleukin
JM	Juxtamembrane
MAPK	Mitogen-activated protein kinase
MTD	Maximum-tolerated dose
NK	Natural killer
NSCLC	Non-small cell lung cancer
NRG	Neuregulin
OS	Osteosarcoma
PEA	Pseudomonas exotoxin A
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3-kinase
ROS	Reactive oxygen species

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RTK	Receptor tyrosine kinase
SH2	Src homology 2
TACE	Tumor necrosis factor-α-converting enzyme
TGFα	Transforming growth factor α
TIC	Tumor-initiating cell
VEGFR	Vascular endothelial growth factor receptor.

Introduction

Osteosarcoma (OS) is the most common primary aggressive and malignant bone tumor, which is the most prevalent tumor in children and adolescents, accounting for approximate 5% of paediatric tumors. It frequently occurs in the metaphyseal region of tubular long bones including femur, tibia and humerus, whereas it rarely arises in the skull, jaw and pelvis [1]. OS is characterized by malignant osteoblastic differentiation and osteoid production, that is composed of immature osteoblasts [2]. Currently, the standard therapy for OS includes surgical resection plus neoadjuvant chemotherapy and radiotherapy, but no other significant improvement has been made for decades. Since the introduction of MAP chemotherapy (high-dose methotrexate, doxorubicin, and cisplatin), the 5-year overall survival of OS patients maintains in approximate 60% [3]. However, osteosarcoma metastasis is common (15%–20%), more than 85% of which occurs in lung, while others occurs in the distant sites of bone [1]. OS patients underwent pulmonary metastasis often have poor prognosis with 20%–30% of 5-year overall survival rate, since this metastatic carcinoma acquires chemoresistance and results in more complications like lung calcification [4, 5]. Therefore, development of more effective therapeutic approaches is vital to improving the prognosis of advanced and metastatic OS.

Genetic aberrations in osteosarcoma include *TP53*, *RB1*, *ATRX*, *DLG2* and *BRCA* mutations, accounting for 29%–53% of all OS specimens [6, 7]. Dysfunction of phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR and insulin like growth factor (IGF) signaling pathways also drive the development and metastasis of OS [8, 9]. Identification of markers with prognostic and therapeutic significance may provide more possible therapies and benefit the OS patients. One of the possible targets is the ErbB family including HER1 (EGFR, ErbB1), HER2 (Neu, ErbB2), HER3 (ErbB3), and HER4 (ErbB4). The ErbB family of proteins belongs to the receptor tyrosine kinases (RTKs), consisting a modular glycosylated ectodomain that binds to the ligand, a single transmembrane domain and a cytoplasmic tyrosine kinase domain that contains a number of phosphorylation residues [10]. Receptor activation is initiated when the ligand binds to the extracellular domain of ErbB proteins, then two inactive ErbB monomers pair together to form an active homodimer or heterodimer, and undergoes conformational alteration and phosphorylation in the cytoplasmic domain. The phosphorylated tyrosine residues provide docking sites for downstream molecules, and subsequently initiate signal transduction, such as the PI3K/Akt and mitogen-activated protein kinases (MAPKs) signaling [10, 11].

ErbB family of proteins is involved in a variety of biological processes including growth, apoptosis, motility and metastasis in cancer cells. Evidence shows that EGFR and HER2 are membrane receptors widely expressed in all OS tissues and cell lines, while HER4 is distributed in OS cell nucleus, but HER3 is barely found [12]. Aberration of ErbB family is associated with the development and progression of OS, as well as the poor prognosis of OS patients [13, 14]. Therefore, targeting one or more members of ErbB family may lead to impaired growth and metastasis of osteosarcoma cells. Here, we summarized the roles of ErbB family proteins in OS, and the most recent preclinical and clinical studies of ErbB-targeted therapies for OS patients (Table 1).

Roles of ErbB proteins and ErbB-targeted therapies in osteosarcoma

ErbB1 (EGFR)

ErbB1, also named epidermal growth factor receptor (EGFR), can be activated by its specific ligands including epidermal growth factor (EGF) and transforming growth factor α

Table 1 Current clinical trials of ErbB family-targeted chemotherapies or immunotherapies for OS treatment

Therapeutic strategies	Targets	Tumor type	Phase	Reference
Gefitinib and Cediraninb	EGFR, VEGFR	Advanced solid tumors (renal cell carcinoma, colorectal cancer, lung cancer, OS, etc.)	I	[33]
Gefitinib and Irinotecan	EGFR	Refractory solid tumors (OS, neuroblastoma, sarcoma, etc.)	I	[34]
Erlotinib and Temozolomide	EGFR	Recurrent solid tumors (OS, rhabdomyosarcoma, neuroblastoma, glioma, medulloblastoma)	I	[35]
Erlotinib and Temozolomide	EGFR	Recurrent solid tumors (OS)	II	NCT00077454
Trastuzumab, plus cisplatin, doxorubicin, methotrexate, ifosfamide, and etoposide	HER2	HER2-positive and HER2-negative newly diagnosed metastatic OS	II	[57]
HER2-specific CAR-T	HER2	recurrent/refractory HER2-positive sarcoma	I/II	[58]
HER2-CD28 CAR-T and fludarabine	HER2	refractory HER2-positive sarcoma or metastatic HER2-positive OS	I	NCT00902044

(TGFα). Homodimerization of EGFR monomers gives rise to its autophosphorylation at tyrosine residues in the C-terminal domain, providing docking sites for proteins containing Src homology 2 (SH2) domains such as the regulatory subunit of PI3K to activated the PI3K/Akt signaling [15]. Studies show that overexpression (55%–60%) or copy number gains (15%) of EGFR are prevalent in OS samples, whereas expression of its activating EGFRvIII mutant is rare [16–18]. Moreover, microarray analyses show that compared with non-metastatic OS, EGFR is one of the core genes upregulated in metastatic OS samples [14, 19]. Although it is reported that EGFR expression has a dose-response correlation with prolong overall survival of OS patients, some studies demonstrate that it is not associated with the response of OS patients to chemotherapy or their survival, indicating that EGFR expression alone is not a reliable prognostic factor [20–22]. Nevertheless, EGFR may still be a druggable target for OS treatment.

Currently, therapeutic strategies targeting EGFR include monoclonal antibodies and tyrosine kinase inhibitors. The most widely used monoclonal antibodies are cetuximab (Erbitux™) and panitumumab (Vectibix™), both of which block ligand binding and prevent EGFR dimerization by targeting the extracellular domain of EGFR [23, 24]. Cetuximab and panitumumab are approved by FDA for the treatment of colorectal cancer with wild-type KRAS [25, 26]. Tyrosine kinase inhibitors such as gefitinib (Iressa™), erlotinib (Tarceva™) and canertinib are small molecules that reversibly or irreversibly compete with adenosine triphosphate (ATP) binding sites in the tyrosine kinase domain of EGFR. Gefitinib and erlotinib are reversible tyrosine kinase inhibitors that are approved for the treatment of non-small cell lung cancer (NSCLC) [27, 28]. Inhibition of EGFR by gefitinib suppressed OS cell colony formation, migration and the activation of downstream PI3K/Akt and MAPK signaling, with limited effects on cell viability. Gefitinib also increased the sensitivity of OS cells to doxorubicin and methotrexate [29]. Similarly, using the insulin-like growth factor I receptor (IGF-IR) antibody R1507 or the EGFR antibody cetuximab alone in human xenograft OS mouse model, OS cell motility and PI3K/Akt and MAPK signaling were inhibited, whereas no cytotoxic effect was observed. However, primary OS growth and pulmonary metastasis were blocked by the bispecific IGF-IR/EGFR antibody XGFR* [30]. These findings suggest that inhibition of EGFR alone is not sufficient to suppress OS cell survival in spite of the reduced PI3K/Akt and MAPK signaling, but has an inhibitory effect on cell motility and tumorigenesis. In addition, erlotinib alone inhibited colony formation and survival of canine OS cell lines, and enhanced the cytotoxic effects of radiation [31]. Against EGFR-expressing OS cell lines or primary culture cells, cetuximab-mediated cytolytic effects of dormant natural killer (NK) cells was augmented, whereas the cytolysis of NK cells was not elicited towards EGFR-negative OS cells, suggesting a potential EGFR-mediated immunotherapy for OS treatment [32].

Currently, EGFR-targeted therapies have entered phase I clinical trials for OS treatment. In a phase I study, gefitnib was combined with cediranib, a selective vascular endothelial growth factor receptor (VEGFR) inhibitor, in 90 patients with solid tumors including OS ($N = 2$). This drug combination was generally tolerated with the most common toxicities including diarrhea, anorexia and fatigue. Antitumor activity was observed in one OS patient with a partial response [33]. In a phase I dose-escalation and pharmacokinetic clinical trial, 19 children with refractory solid tumors including OS ($N = 5$) were co-treated with gefitinib and irinotecan. Dose-limiting toxicities (DLTs) included hypokalemia, anorexia, hypophosphatemia and diarrhea. During 20 therapeutic courses, 3 of 11 patients had stable disease, 1 patient maintained a complete response, and 2 patients had disease progression [34]. 46 children with recurrent solid tumor including OS ($N = 6$) were administrated with erlotinib alone or followed by co-administration of erlotinib and temozolomide in a phase I pharmacokinetic clinical trial. Erlotinib alone or in combination with temozolomide was well tolerated, and 17 of 43 patients had stable diseases after single erlotinib treatment. The most frequent DLTs included rash and hyperbilirubinemia, indicating a maximum-tolerated dose (MTD) of erlotinib [35]. Currently, a follow-up phase II study of erlotinib in combination with temozolomide for recurrent pediatric solid tumors including OS is ongoing (ClinicalTrials.gov Identifier: NCT00077454). Unfortunately, these clinical trials only cover a small number of OS patients, being lacking of enough evidence to support the efficacy of EGFR inhibitors or antibodies in OS treatment.

ErbB2 (HER2)

HER2 is a transmembrane glycoprotein receptor being short of a ligand-binding domain and has no identified ligand. It binds to a monomer of other ErbB receptors to form a heterodimer with high tyrosine kinase activity, and then actives the downstream pathways like PI3K/Akt and MAPK signaling [36]. HER2 is most investigated in breast cancer, in which its gene amplification in approximately 30% and protein overexpression is about 20% [37, 38]. Patients with breast cancer containing amplification or overexpression of HER2 would benefit from the HER2-targeted therapies [39]. Mutation of HER2 within the tyrosine kinase domain occurs in a small subset of breast cancer (3%), most of which is mutual exclusive with amplification or overexpression of HER2 (HER2-positive), leading to a more potent kinase activity than wild-type HER2 and resistance of tumor to anti-HER2 therapy [40]. Studies on the expression and prognostic value of HER2 in OS remain controversial, whereas its amplification and mutation in OS are rarely reported. A number of studies show that HER2 overexpression is found in approximately 80%, 72%, 32% and 43% of human OS specimens, and it is significantly correlated with reduced disease-

free or overall survival of OS patients [41–44]. On the contrary, some studies demonstrate the absence of membranous protein expression, mRNA expression or gene amplification of HER2 in human OS specimens [45–47]. Another study shows that although HER2 protein expression is present in 45.6% of OS samples, it is not correlated with distant metastatic potential or patients' survival [48].

In spite of the controversy on the prognostic value of HER2 expression in OS, the effort to develop molecular targeted therapy and immunotherapy against HER2 has been made. Studies showed that canertinib (CI-1033), a pan-ErbB inhibitor for EGFR and HER2, inhibited proliferation and induced apoptosis of OS cells through decreasing EGFR, HER2 and HER4 phosphorylation [49]. Transfection of immunocasp-6 protein consisting of a signal peptide, a single-chain HER2 antibody, a Pseudomonas exotoxin A (PEA) translocation domain and an active caspase-6 significantly induced apoptosis of primary OS cells, and inhibited tumor growth and metastasis in OS xenograft nude mice model [50]. However, because HER2 overexpression is not present in OS in some studies and HER2 expression is relative low in OS compared with breast cancer, HER2-targeted therapies using specific inhibitor or monoclonal antibody may be less responsive and beneficial to OS patients. Trastuzumab, a monoclonal antibody that specifically binds to the extracellular domain of HER2 and blocks its dimerization, has been approved for breast cancer treatment by FDA [51]. Evidence showed that although trastuzumab triggered an antibody-dependent cell-mediated cytotoxicity (ADCC) in osteosarcoma U2OS cell line, it had no effect on another OS cell line with low HER2 expression level [52]. Compared with breast cancer cell lines, trastuzumab alone displayed limited inhibitory effects on OS cell growth and colony formation [43]. Studies also showed that combination of trastuzumab and zoledronate significantly increased the Vγ9Vδ2 T cell-mediated cytotoxicity, suggesting that immunotherapy may be an attractive alternative for OS treatment [52]. Recently, chimeric antigen receptor T cell immunotherapy (CAR-T) specific for HER2 has been used for preclinical or clinical OS treatment, since the antigen with a relative low expression level is still sufficient to induce immunoresponse of effector cells. HER2-specific T cells with a HER2-specific chimeric antigen receptor (CAR) containing a CD28.ζ signaling domain could recognize and kill HER2-positive OS cell lines in spite of the low expression level of HER2, through releasing immunostimulatory cytokines like interferon γ (IFNγ) and interleukin (IL)-2 in vitro. In addition, adoptive transfer of CAR-T cells specific for HER2 caused regression of locoregional tumor and blocked the pulmonary metastasis in OS xenograft mouse models, resulting in a significantly improved survival [53]. HER2-specific CAR-T cells also blocked the sphere formation of OS tumor-initiating cells (TICs) with methotrexate resistance, impeded tumorigenesis and decreased the number of TICs in orthotopic OS xenograft [54]. Apart from the HER2-specific immunotherapy, nanomaterial which is able to augment HER2-binding capacity and activity of trastuzumab is also employed to overcome the challenge of the inefficacy of trastuzumab. Multivalent trastuzumab/graphene oxide complexes significantly induced oxidative stress and cell death in OS cells, whereas neither graphene oxide-induced reactive oxygen species (ROS) nor trastuzumab alone was sufficient to cause cell death. Regression of subcutaneous or lung metastatic OS xenograft was observed after the administration of trastuzumab/graphene oxide complexes [55]. In addition, a highly attenuated recombinant bacterial *Listeria monocytogenes* expressing a chimeric human HER2 fusion protein was intravenously administrated into dogs with appendicular HER2-positive OS. Compared with the historical control, the fusion protein induced HER2-specific IFNγ responses, reduced the tumor recurrence rate and increased the overall survival rate [56]. These findings indicate that immunotherapy especially CAR-T cell therapy specific for HER2 may be more effective than targeted therapy using inhibitor or monoclonal antibody on HER2-positive OS.

Currently, there are a number of phase I/II clinical trials using trastuzumab or HER2-specific CAR-T cells for OS treatment. In a phase II study, 41 patients with HER2-positive and 55 patients with HER2-negative newly diagnosed metastatic OS were all treated with cisplatin, doxorubicin, methotrexate, ifosfamide, and etoposide. Only patients with positive HER2 staining were concurrently administrated with trastuzumab. No significant short-term cardiotoxicity was observed due to the administration of dexrazoxane. However, there was no significance between HER2-positive and HER2-negative patients on the 30-month event-free and overall survival rates, suggesting a poor response of OS patients to trastuzumab [57]. A phase I/II dose-escalation clinical trial in 19 patients with recurrent/refractory HER2-positive sarcoma including OS ($N = 16$) showed that HER2-specific CAR-T cells was well tolerated with no dose-limiting toxicity, and long-term existed in peripheral blood and tumor sites. Plasma concentration of the chemokine IL-8 was persistently increased from 1 to 4 weeks after the T cell infusion. Among 14 evaluable OS patients, 3 patients had stable diseases for 12–15 weeks who then received surgical tumor resection, and remained in remission at 6, 12, and 16 months. 11 of 16 OS patients developed progressive diseases, and one of these patients who received salvage chemotherapy followed by second infusion of HER2-specific CAR-T cells had a partial response for 9 months. The median overall survival of all 19 patients was 10.3 months [58]. Another phase I study of patients with refractory HER2-positive sarcoma or metastatic HER2-positive OS is ongoing. Patients will receive HER2-CD28 T cells and fludarabine to evaluate the safety, in vivo persistence and anti-tumor activity of this CAR-T cell therapy (ClinicalTrials.gov Identifier: NCT00902044).

ErbB3 (HER3)

Unlike the other members of ErbB family, HER3 is short of a kinase domain which results in its impaired kinase activity. Therefore, the homodimer of HER3 fail to activate downstream signaling, instead HER3 is inclined to form the heterodimer with EGFR, HER2 or HER4 [59]. In the absence of the ligands including heregulin (HRG) or neuregulin (NRG), HER3 maintains a conformation that blocks dimerization. Ligand binding results in the phosphorylation of HER3 C-terminal domain and the activation of heterodimers like HER2-HER3 dimer, which is the most active ErbB family dimer [60]. Activated HER3 heterodimer allows the binding with PI3K regulatory subunit and then activates PI3K/Akt signaling network [61]. HER3 is overexpressed in a variety of cancers including breast cancer, ovarian cancer and lung adenocarcinoma, and is a significant prognostic predictor for these cancer patients [62–65]. However, a handful of studies on the expression and prognostic value of HER3 in OS are reported till now. Hughes et al. showed that HER3 was absent in human OS cell lines and tissue samples [12]. On the contrary, Jullien et al. found that compared with normal human primary osteoblasts or normal bone tissues, HER3 expression was increased in OS cell lines or tissues, and was further augmented in metastatic and recurrent OS samples. siRNA-induced silencing of HER3 not only significantly decreased mouse OS cell proliferation, migration and invasion in vitro, but also inhibited tumor growth in an allograft murine OS model [66]. These two controversial studies indicate an uncertain role of HER3 in the pathogenesis or clinical outcome of OS, and it requires further investigation and more evidence.

Due to the absence of appreciable kinase activity, using monoclonal antibody to block the dimerization seems to be the effective HER3-targeted strategy currently. Patritumab (U3–1287) and seribantumab (MM-121), fully monoclonoal antibodies that specifically bind to the extracellular domains of HER3, have entered into the phase I/II clinical trials for breast cancer, NSCLC, ovarian cancer and head and neck cancer (H&N) treatment. In a phase I study of 57 patients with solid tumors, the safety, tolerability, and pharmacokinetics of patritumab were evaluated. It was well tolerated and the most frequent adverse events were fatigue, diarrhea, nausea, decreased appetite, and dysgeusia [67]. A randomized phase II clinical trial, patients with platinum-resistant or -refractory ovarian cancer were administrated with seribantumab in combination with paclitaxel. Compared with paclitaxel alone, seribantumab plus paclitaxel did not significant increase the progression-free survival (PFS) of total patients. However, patients with detectable HRG and low-level HER2 had improved PFS [68]. Unfortunately, no preclinical or clinical study is reported on the treatment of OS using patritumab or seribantumab. There was only a preclinical study of patritumab alone or with erlotinib in combination with standard chemotherapy cisplatin, vincristine, and cyclophosphamide in pediatric sarcoma (Ewing sarcoma and embryonal rhabdomyosarcoma) xenograft mice. Patritumab or erlotinib alone, or their combination had limited anti-tumor activity and no significant inhibitory effect on tumor growth was observed. The activity of vincristine or cisplatin was augmented by the addition of patritumab, whereas this enhancement was eliminated by the combination of patritumab and erlotinib [69]. It suggests a limited activity of HER3-targeted therapy for sarcoma treatment.

ErbB4 (HER4)

HER4 is a ubiquitously expressed and unique member of the ErbB family. The ligands of HER4 include NRGs, heparin-binding EGF (HB-EGF), epiregulin and betacellulin. Alternative RNA splicing of *HER4* gene generates at least four different isoforms of HER4, which are determined and classified by the extracellular juxtamembrane (JM) and intracellular cytoplasmic (CYT-1 and CYT-2) domains. Activation by ligand binding leads to the proteolytic cleavage of HER4 JM-a domain by tumor necrosis factor-α-converting enzyme (TACE) or γ-secretase, and subsequent release of the soluble intracellular domain (4ICD) [70, 71]. It produces an 80 kDa protein fragment with constitutive tyrosine kinase activity that translocates to the nucleus and interacts with transcription factors [72]. HER4 expression was frequently found (67.7%) in breast cancer, among which the nuclear and cytoplasmic expression of HER4 was accounting for approximate 14% and 64%, respectively [73]. Owing to the functionally distinct isoforms of HER4, the role and prognostic value of HER4 in cancer remain controversial. Evidence showed that the intracellular domain 4ICD of HER4 was a potent estrogen receptor α (ERα) co-activator and was capable of inducing apoptosis of breast cancer cells. Nuclear expression of 4ICD increased the sensitivity of breast cancer cells to tamoxifen, and led to the clinical benefit of breast cancer patients from tamoxifen therapy [74]. Overexpression of CYT-1, not CYT-2, significantly increased anchorage-independent growth of ovarian cancer cells, and was associated with tumor grade and poor overall survival of ovarian cancer patients [75]. Overexpression of HER4 was associated with reduced 5-year distant relapse free survival of triple-negative breast cancer patients [76]. On the contrary, a DNA demethylating agent 5-aza-2′-deoxycytidine (DAC) restored HER4 expression and induced apoptosis in low-HER4 breast cancer cells, which was rescued by HER4-specific siRNA silencing. Further, HER4 promoter hypermethylation was common in patients with HER4-negative brease cancer, and it was significantly correlated with reduced disease-specific survival of breast cancer patients [77]. It suggests a potential tumor suppressor function of HER4 in cancer. In addition, a study showed that there was no significant correlation between HER4 expression

or localization and recurrence-free survival of patients with breast cancer [73].

Until now, there are limited studies investigating the role of HER4 in OS. The p80 fragment of HER4 was observed in the nuclei of OS cell lines and tissue specimens [12]. Constitutive HER4 phosphorylation was also observed in early passage OS cell lines [49]. Another study showed that HER4 mainly expressed in the cytoplasm and nuclei of OS cells, and the expression of soluble 4ICD was increased in response to stress. shRNA-induced knockdown of HER4 suppressed proliferation and anchorage-independent growth of OS cells through inducing cell senescence, and increased the chemosensitivity of OS cells to methotrexate and doxorubicin [78]. It suggests that HER4 plays an essential role in the survival of OS cells through mediating stress responses including cytotoxic agents, loss of attachment, and nutritional deprivation. Unfortunately, due to the lack of specific inhibitor or monoclonal antibody against HER4, there is no HER4-targeted clinical study for cancer treatment, let alone OS.

Conclusions

Given the importance of ErbB family in downstream signaling activation like PI3K/Akt and MAPK signaling pathways and in regulating cancer cell survival, metastasis and drug resistance, it may be a potential druggable target for OS treatment. However, ErbB-targeted therapy for OS has been proven to be a challenge due to the controversy on the expression and prognostic value of ErbB in OS patients. Currently, most studies focus on the roles of EGFR and HER2 and their targeted therapies in OS. The efficacy of targeting EGFR or HER2 for OS treatment by specific inhibitors or monoclonal antibodies fails to reach the expectation. Nevertheless, immunotherapies such as CAR-T cell therapy specific for HER2 seem to be tolerated and effective in HER2-positive OS patients. No clinical trial of HER3- or Her4-targeted agents is reported in OS patients, due to the lack of strong evidence that HER3 or HER4 play important roles in the pathogenesis of OS. Tumor recurrence or metastasis is the major cause of poor prognosis of OS patients. Therefore, investigation of the roles of ErbB family in the progression and metastasis of OS have guiding significance for improving the prognosis of OS patients. Overall, application of ErbB-targeted therapies in OS patients has a long way to go, and immunotherapy seems to a promising approach for OS treatment.

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Compliance with ethical standards

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