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Review

Tyrosine kinase inhibitors in osteosarcoma: Adapting treatment strategiesa

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ABSTRACT

Osteosarcoma (OS) is an aggressive primary bone malignancy that metastasizes rapidly. The standard of care has changed little over the previous four decades, and survival rates have plateaued. In this context, tyrosine kinase inhibitors (TKIs) emerge as potential treatments. A literature search was conducted to collect data related to receptor tyrosine kinase genetic alterations and expression in OS specimens. Gene amplification and protein expression of these receptors were linked to prognosis and tumor behavior. Relevant TKIs were evaluated as monotherapies and as parts of combination therapies. Certain TKIs, such as apatinib, regorafenib, and cabozantinib, present a potential therapeutic avenue for OS patients, especially when combined with chemotherapy. Producing long-lasting responses and enhancing quality of life remain key goals in OS treatment. To this effect, optimizing the use of TKIs by identifying biomarkers predictive of response and assessing promising TKIs in larger-scale trials to validate the efficacy and safety outcomes relative to these drugs reported in phase II clinical trials. To this effect, it is necessary to identify biomarkers predictive of response to TKIs in larger-scale trials and to validate the efficacy and safety of these drugs reported in phase II clinical trials.

1. Introduction

Osteosarcoma (OS) is a primary bone cancer that shares the same histological trait of malignant cells in association with osteoid matrix formation [1]. OS is the most frequent malignant bone tumor and it occurs most frequently in young males and typically develops in the long bones of the appendicular skeleton. In most cases, the cause of OS has remained unknown [2,3]. The association between OS and accelerated bone proliferation is suggested by the frequent occurrence of OS during the pubertal growth spurt phase and at the locations of greatest osteoformation. Other rarer causes of OS include exposure to radiation and alkylating compounds. Furthermore, OS is linked to hereditary diseases caused by germline mutations altering the function of tumor suppressor genes, such as familial retinoblastoma and Li-Fraumeni Syndrome [4].

Management of OS can be surgical as well as medical. En bloc resection of the lesion and limb salvage, if feasible, constitute the current surgical approach [5]. As for medical management, OS chemotherapy includes methotrexate, doxorubicin, and cisplatin (MDC), used both as neoadjuvant chemotherapy and adjuvant chemotherapy [6,7]. OS is characterized by rapid local growth and the early appearance of metastases, with well-documented local aggressivity [8].

Despite the adoption of multidrug chemotherapy, long-term OS survival rates for focal lesions have stagnated at >60 % since the 1980s [9]. Targeted therapies have recently emerged as drugs that target weaknesses more particular to malignant cells compared to standard chemotherapy [10], such as tyrosine kinase receptors (RTKs), which regulate a variety of processes, including cellular growth and differentiation. Tyrosine kinase inhibitors (TKIs) are a family of targeted therapy molecules that selectively target tyrosine kinase receptors and impede the binding of the ligand molecule, thus preventing the activation of downstream pathways [11,12].

In this comprehensive review, we looked at evidence of genetic mutations and protein expression of tyrosine kinase receptors in osteosarcoma patient samples. We then reviewed the effectiveness and safety of several tyrosine kinase inhibitors (TKIs) in the treatment of osteosarcoma.

2. Methods

An exhaustive search of the literature was conducted using the

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PubMed, Cochrane, and Google scholar (Pages 1–20) databases until August 2023. Using Boolean Operators, the MeSH term "sarcoma", with the keywords "osteosarcoma", and "VEGFR", or "PDGFR", "RET", "c-KIT", "c-MET","IGF1R", "FGFR", "AXL", "regorafenib", "anlotinib", "cabozantinib", "lenvatinib", "dasatinib", "sorafenib", "apatinib", "saracatinib", "pazopanib", "imatinib", "cediranib", and "axitinib" were applied, after an extensive familiarization with the available literature was undertaken to discover the tyrosine kinase receptors and inhibitors relevant to osteosarcoma.

In total, 738 publications were retrieved. After titles and abstracts of extracted papers were reviewed for eligibility, whole texts were assessed. Our goal is to review studies that contain data on the amplification, expression, and role of the most relevant RTKs in osteosarcoma patients, as well as trials and studies assessing the efficacy and safety of kinase inhibitors targeting these RTKs. Papers that focus on OS without data on RTK gene amplification, RTK protein expression or association of any of the latter with osteosarcoma were not included in our review. In vitro and in vivo studies, as well as reviews dating from before 2020 were additionally excluded from our analysis. Overall, 93 eligible articles were included in this review. The PRISMA diagram shown in Fig. 1 summarizes the process.

3. Results

3.1. Main pathways downstream of receptor tyrosine kinase inhibitors

Mitogen-activated protein kinase (MAPK), Phosphatidylinositol 3-kinase (PI3K) and Src family proteins are the main signaling mechanisms activated by RTKs [13].

Within the MAP/Ras/Raf/MEK/Erk pathway, after the RTK undergoes activation, rat sarcoma (Ras) activates rapidly accelerated fibrosarcoma (raf) kinases A, B and C, which trigger the ATP-dependent phosphorylation of Mitogen-activated protein kinase kinase 1 (MEK1) and MEK2. Phosphorylated MEK1/2 drives the activation of extracellular signal-regulated kinase 1 (Erk1) and Erk2. Once activated, Erk1/2 stimulate factors involved in the expression of genes associated with various cell functions, including differentiation, invasion and survival [14,15].

Moreover, activated RTK also recruits PI3K, which phosphorylates phosphatidylinositol biphosphate (PIP2) to generate PIP3 within the course of the PI3K/Akt/mTOR transduction pathway. PIP3 then phosphorylates 3-phosphoinositide-dependent kinase 1, resulting in the phosphorylation of protein kinase B (Akt). Akt controls several processes, including mammalian target of rapamycin (mTOR) activation, cell survival and proliferation, and the promotion of blood vessel development [16]. One study identified the PI3K/Akt/mTOR signaling mechanism as a key therapeutic target in the treatment of OS. [17].

RTKs are also upstream components of the activation of Src [18]. The activation of Src occurs through a recruitment mechanism [19], and involves Ras and Ras-like GTPases [20].

4. Main target receptors

4.1. VEGFR

Vascular endothelial growth factor (VEGF) stimulates blood vessel formation and growth, extracellular matrix disintegration, vascular permeability, and endothelial cell recruitment.

Angiogenesis constitutes one of the six key hallmarks of tumor formation, driving tumor development and potential for metastatic spread [21,22]. The expression of VEGFA and VEGF in OS was linked to worse disease-free survival [23] and overall survival [24]. According to one study conducted with next generation sequencing (NGS), more than 40 % of OS patients have malignancies with *VEGFA* or platelet-derived growth factor receptor A (*PDGFRA)* amplification [22]. Abnormalities in PTEN/PI3K/Akt/mTOR and the pathways downstream of the vascular endothelial growth factor receptor (VEGFR) reported to be two of the most common signaling system alterations in OS in an experiment utilizing whole genome sequencing (WGS), alongside other signaling pathways not directly regulated by RTKs. There was substantial intratumor RTK diversity, with some tumors showing alterations in numerous signaling pathways [25].

VEGFB linked to poor response to chemotherapy [26]. However, VEGFR3 did not reach significance as an indicator of OS prognosis [26,27]. A separate study using NGS to analyze the samples of 66 OS patients discovered that 24 % of tumors presented gains at 6p12–21. The subset of patients presenting gains at 6p12-21 showed significant *VEGFA* amplification and stronger metastatic potential [22].

Overall, the VEGFR family is heavily implicated in OS and constitutes an important possible target in OS.

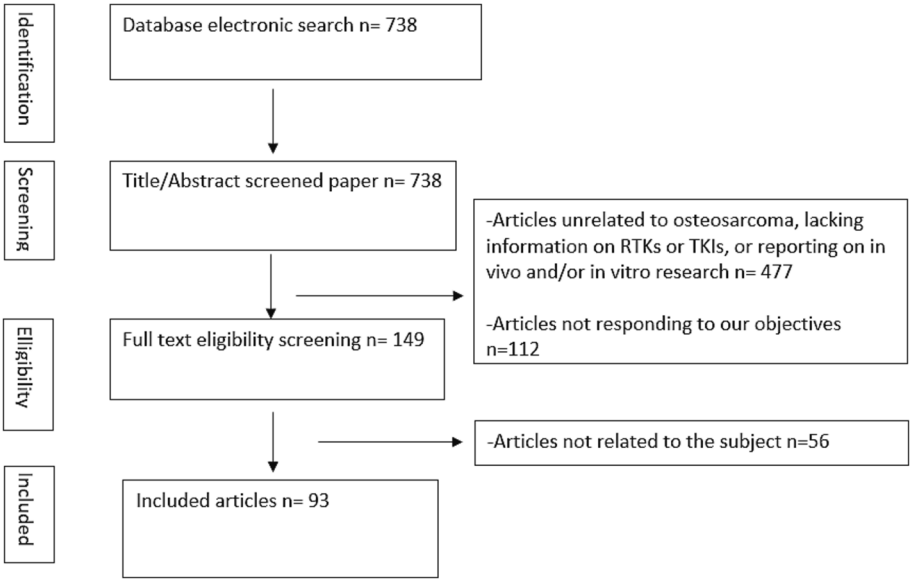

Fig. 1. PRISMA flowchart for article selection.

4.2. RET

Ligands from the GDNF (glial cell-derived neurotropic factor) family bind to GFRα (GDNF family receptor α) co-receptors, resulting in the activation of RET (rearranged during transfection) receptors. RET regulates several critical functions during embryonic development, including enteric nervous system [28], kidneys [29], and urinary tract development [30], among others [28]. Alterations in the *RET* gene are associated with various cancers, notably non-small cell lung cancer and medullary thyroid cancer [31]. It has been established that *RET* mutations are among the most frequent cancer-inducing alterations in the germline of OS patients, alongside mutations in *tumor protein 53 (TP53)* and *retinoblastoma protein 1 (RB1)* [32].

4.3. FGFR

Fibroblast growth factor receptors (FGFRs) are RTKs that regulate various functions, such as nervous system control, organogenesis, tissue repair, among others [33]. *FGFR* abnormalities are found in a wide array of tumors [34]. FGFR1 is expressed in 74 % of OS samples, and it was expressed in moderate to high levels in 83 % of FGFR1 positive OS specimens [35]. *FGFR1* amplification is frequent in certain rare OS histologies. Tumors displaying gains at the *FGFR1* gene were strongly linked to poor chemotherapy response, with 18.5 % of patients with FGFR1 amplification having a poor response to chemotherapy, and no good-responders having FGFR1 amplification [36]. Moreover, OS patients with *FGFR1* gene amplification and protein expression had significantly worse patient progression-free survival and overall survival [37].

4.4. PDGFR

Platelet-derived growth factor receptors (PDGFRs), are expressed on the surface of a wide variety of cells, including but not limited to platelets [38,39], vascular smooth muscle cells, fibroblasts [40], and many immune cells [41,42]. PDGFR regulates multiple functions, such as wound healing [43], embryonic development [44], and several roles in the central nervous system [45]. It has been shown that PDGFR and hypoxia, which facilitate the growth and metastatic potential of OS, are significantly correlated, with 15 out of 35 samples showing the co-expression of PDGFRβ, platelet-derived growth factor composed of two B subunits and hypoxia markers [46]. A study suggests that greater PDGFRα expression is associated with a more somber prognosis [47], while another claims that it is not [48]. Increased PDGFRβ is also significantly linked to lower overall survival in OS patients with metastatic disease at diagnosis. The value of PDGFRβ as a prognostic factor for event-free survival also reached significance in non-metastatic patients ($p = 0.01$) but not in the subset of patients with metastatic disease at diagnosis ($p = 0.13$) [27].

4.5. HGFR

Pathways downstream of HGFR (hepatocyte growth factor receptor) or c-MET (mesenchymal-epithelial transition factor) are implicated in the regulation of numerous functions, including cell mobility, infiltration, proliferative behavior, and cell death evasion. HGFR is also involved in the growth and metastasis of malignancies [49]. HGFR is significantly linked to the proliferative activity of OS. HGFR was expressed in 20 % of initial sites and in 50 % of metastases. It is important to note that 58 % of metastases displayed HGFR expression independently from the primary lesion [50]. While one analysis found HGFR expression in only two out of twelve OS samples [51], many studies have demonstrated substantial HGFR expression in OS samples [52–55]. *HGFR* genetic alterations were correlated with a poor prognosis [56]. Conflicting reports emerged regarding the status of HGFR as a prognostic factor. While one study showed that HGFR did not reach significance as an indicator of overall survival and event-free survival, another established that the recepteur d'Origine Nantais (RON), a transmembrane protein from the HGFR family, has a strong correlation with poor chemotherapy response and reduced survival times, making it a useful prognostic marker [57]. Furthermore, HGFR was found to be an important factor in the aggressive behavior of OS, as it showed greater staining with the MIB-1 cell proliferation marker (27.65 in HGFR-positive OS; 20.99 in HGFR-negative OS) and a non-significant trend toward expression at the site of metastasis (HGFR was in 50 % of metastatic lesions and 20 % of primary lesions) [50].

4.6. c-KIT

c-KIT (stem-cell factor receptor) regulates gene expression, cell survival, multiplication, and participates in carcinogenesis, tumor growth and metastasis [58]. One analysis determined that c-KIT was detected in 46 % of patients with OS. There was no association between c-KIT expression and mortality, recurrent or metastatic lesions at diagnosis. However, c-KIT expression was linked to poor response to chemotherapy [59]. Another French study discovered amplification at the 4q12 location, which comprises the *c-KIT* gene and is strongly linked to c-KIT overexpression, was frequent in a population consisting of pediatric high-grade OS patients (39 %). Significant c-KIT expression was detected in 57 % of the studied population. Like in the previous study, the role of c-KIT as an indicator for chemosensitivity was established [60]. The same team of researchers found *c-KIT* gene amplification in the entire study group, and c-KIT protein expression in 57 % of the population and amplification in a subsequent analysis with expansion of the previous cohort [61]. Another study discovered c-KIT immunoexpression in 62.5 % of patients and concluded that c-KIT expression was associated with tumor recurrence and decreased median survival, making it viable prognostic indicator [62]. However, in one analysis, c-KIT was found in only 20 % of tumors, and no correlation between c-KIT expression and survival could be established [63], while another study found c-KIT in 83 % of OS samples, with 39 % displaying strong expression [64].

4.7. IGF1R

Insulin-like growth factor 1 receptor (IGF1R) facilitates cell division, motility, and infiltration. IGF1R was also linked to cancer metastasis [65]. IGF1R supports the aggressiveness, adhesion, and migratory behavior of OS [66–68]. IGF1R is linked to a reduced apoptotic index in OS [69]. Furthermore, the role of *IGF1R* abnormalities in chemoresistance is well established [70]. Gains at the IGF1R gene are linked to high receptor protein expression and a poorer prognosis [37]. One analysis determined that 7.1 % of OS lesions carried amplifications at the *IGF1R* gene and protein overexpression [71]. Similarly, in another study using whole genome and whole exome sequencing, mutations in the distinct *insulin-like growth factor 1*, *IGF1R*, and *insulin growth factor binding protein 5* genes were found in 7 % of studied cases and in 27 % of cases if alterations affecting the Ras/Raf/MAPK or PI3K signaling pathways downstream of IGF1R were to be included. The same study, utilizing fluorescence in situ hybridization, detected high-level *IGF1R* amplification in 14 % of patients from a different cohort [72]. IGF1R is more expressed in high-grade, metastatic, and recurrent OS compared to low-grade, local, non-recurrent lesions [73]. It was also shown that pIGF1R (phosphorylated IGF1R) in the nucleus significantly correlates with poor overall survival [74]. A meta-analysis of the prognostic value of IGF1R in bone and soft tissue sarcomas included two studies on OS and found that high expression of IGF1R is significantly correlated with poor prognosis in OS ($p < 0.001$) [75].

4.8. AXL

Axl (anexelekto) is an RTK that binds to Gas6 (Growth arrest-specific) [76]. It supports various functions, including motility,

survival, and proliferation. Activated Axl (P-Axl) is substantially elevated in OS patient samples [70]. It has been established that P-Axl expression is positively associated with neoplasm recurrence and pulmonary metastasis, with 75 % of patients who had recurrent disease or developed lung metastasis showing high P-Axl expression. It was also shown that P-Axl expression is a valuable prognostic indicator in OS, as the 5-year survival rate was 40.7 % and 65.7 % in patients who had high and low P-Axl expression, respectively [77]. Furthermore, a substantial association was found between Yes-associated protein and transcriptional coactivator with the domain comprising the post synaptic density protein, Drosophila disc large tumor suppressor, and zonula occludens-1 protein -binding motif, which are regulated by Axl, and nuclear pIGF1R [74].

4.9. Intratumor receptor diversity

Multiple distinct RTKs have been documented to be expressed and/or amplified in OS, particularly in lesions with specific mutations. The amplification of a specific region located on the long arm of chromosome 4, or 4q12, is linked to several types of cancer. 4q12 amplification manifests by co-amplification of RTK genes (*KIT*, *PDGFRA* and VEGFR2). According to a study of 132,872 individuals with advanced malignant tumors, 6.5 % of osteosarcoma patients had 4q12 amplification, compared to 1.9 % of all sarcoma patients and 0.65 % of the total number of patients [78].

A separate study using NGS to analyze the samples of 66 OS patients discovered that 20 % and 24 % of tumors presented gains at 4q12 and 6p12–21, respectively. The subset of patients presenting gains at 4q12 showed *KIT*, *VEGFR2*, and *PDGFRA* amplification, and immunohistochemistry revealed substantial PDGFRA expression. The two patient subsets were mostly distinct [22].

A summary of the main RTKs implicated in OS is shown in Fig. 2.

5. Main tyrosine kinase inhibitors

5.1. Apatinib

Apatinib (also known as YN968D1) is an orally bioavailable multitarget tyrosine kinase inhibitor. It targets VEGFR2, c-KIT, RET, PDGFRβ and Src [69].A clinical trial evaluating the safety and effectiveness of apatinib monotherapy in refractory and inoperable OS patients observed 56.8 % progression-free survival at 4 months, 36.8 % progression-free survival at 6 months, a 43.2 % overall response rate, and a 35.1 % clinical benefit rate. Patients had a 4.5-month median progression-free survival and a 9.9-month median overall survival. The median duration of response was 5.1 months. Despite having a response length equivalent to lower-performing multi-targeted TKIs (MTKIs) and exhibiting substantial but acceptable levels of toxicity, apatinib clearly improved outcomes for OS patients [70]. In an ensuing trial, OS patients were treated with apatinib and camrelizumab. While this combination produced longer-lasting responses, the benefits of the bitherapy did not reach significance, and the study failed to reach the predefined level of activity for apatinib and camrelizumab to be assessed in a phase 3 trial. The combination resulted in a lower overall response rate, which can be explained in part by the fact that patients were given lower doses of apatinib. The safety of apatinib with camrelizumab was comparable to that of other MTKIs, such as sorafenib and regorafenib [71]. Another trial and numerous retrospective studies reported similar outcomes [72–78]. It was shown that pairing apatinib with chemotherapy significantly enhanced overall survival and progression-free survival compared to apatinib monotherapy [79,80]. The best outcomes were achieved in a study assessing apatinib in combination with ifosfamide and etoposide, with 90.9 % progression-free survival at 4 months and 78.5 % progression-free survival at 6 months. Patients achieved a 63.6 % overall response rate with an acceptable safety profile [80]. A meta-analysis analyzed the data of 356 OS patients across 11 studies and found a combined disease control rate, median progression-free survival, and median overall survival of 57 %, 5.2 months and 10.9 months [81], respectively. Despite one study reporting an insignificant difference in outcomes between high- and low-dose apatinib [73], the meta-analysis also demonstrated that patients who received doses ranging from 500 to 750 mg achieved better overall response rates and disease control rates, while patients who were given 500 mg had better median progression-free survival and overall survival durations. The analysis also found that apatinib produced fewer and less serious adverse events [81]. It was also suggested that apatinib at low doses is effective in reversing OS chemoresistance [82]. Furthermore, the occurrence of adverse events was shown to be indicative of more favorable outcomes in OS patients treated with apatinib [83,84].

5.2. Regorafenib

Regorafenib (BAY 73-4506) is an orally bioavailable MTKI that targets the MAP/Ras/Raf/MEK/Erk signaling pathway. RTKs inhibited by regorafenib include but are not limited to VEGFR1, 2, and 3, as well as RET, FGFR1, PDGFRβ and KIT [85]. Multiple trials have assessed the activity and safety of regorafenib in OS. A multicenter, double-blind clinical trial aimed to assess regorafenib in metastatic OS patients. The regorafenib group achieved a median progression-free survival of 3.6 months and progression-free survival values of 79 % and 44.4 % at 8 and 16 weeks, respectively. Overall survival was 11.1 months, and the partial response rate was 13.6 %. Adverse events were more common in the regorafenib group, although they were deemed tolerable [86]. A similar trial assessed regorafenib in advanced metastatic OS and other bone tumors; median progression-free survival durations were 16.4 and 4.1 weeks in the regorafenib group and in the placebo group, respectively. At 8 weeks, all patients in the placebo group had progressive disease, while 8 %, 58 %, and 35 % of patients in the regorafenib group achieved

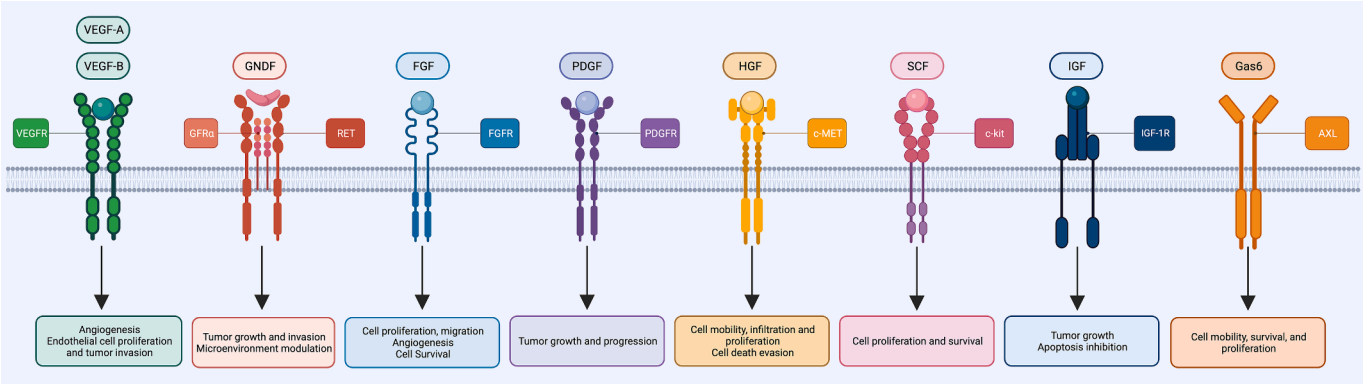

Fig. 2. A summary of the main RTKs implicated in OS.

partial response, stable disease, and progressive disease, respectively. At 12 weeks, 62 % of patients in the regorafenib subset were in progression-free survival, while 35 % remained in progression-free survival at 24 weeks. Those results demonstrate the activity of regorafenib in refractory and metastatic OS. The toxicity of regorafenib was well tolerated, even though dose adjustments were necessary in most patients [87]. In a retrospective study evaluating the activity and toxicity profile of multi-target kinase inhibitors in pediatric and young adult OS patients, patients who were treated with regorafenib monotherapy fared better than subsets of patients treated with sorafenib monotherapy and with sorafenib and everolimus bitherapy. Moreover, no serious adverse events were recorded [88]. Numerous reports identified regorafenib as the cause of congestive heart failure [89], acute pancreatitis [90], and asymptomatic pneumothorax [91].

Overall, regorafenib proved to be a viable option for patients with advanced and refractory OS with an acceptable safety profile.

5.3. Lenvatinib

Lenvatinib, or E7080, is an orally administered multitargeted kinase inhibitor. It inhibits VEGFR1, 2, 3, FGFR1, 2, 3, 4, PDGFRα, c-KIT, and RET [92]. In a clinical trial, patients who were treated with lenvatinib monotherapy achieved a 4-month progression-free survival of 37.8 %, a partial response rate of 6.7 %, and a disease control rate of 51.6 %. Median progression-free survival, median overall survival, and median duration of response were 3, 10, and 4.6 months, respectively [93]. A phase 1 trial of lenvatinib in combination with ifosfamide and etoposide showed substantially improved outcomes for patients, as progression-free survival at 4 months was 80 %, the partial response rate was 9 %, the disease control rate was 71 %, and the clinical benefit rate was 37 %. Patients achieved a partial response rate of 9 %; median progression-free survival was 8.7 months; and median overall survival was 16.3 months. The duration of the response could not be assessed. The adequate toxicity of this combination, along with encouraging outcomes, make it a promising therapeutic option for advanced and relapsed OS [94]. A phase 2 trial of lenvatinib with etoposide and ifosfamide (NCT04154189) is underway [95].

5.4. Anlotinib

Anlotinib is an orally administered tyrosine kinase inhibitor that targets the VEGFR, PDGFRα, PDGFRβ, c-Kit, and FGFR. [79,80].

A multicenter trial enrolled patients with different bone cancers, including osteosarcoma patients, with a main objective of assessing the efficacy and safety of anlotinib in the treatment of recurrent or metastatic primary malignant bone tumors. Among osteosarcoma patients, the study reported a median progression-free survival of 4.8 months and a 3-month progression-survival rate of 75.86 %. The median overall survival was not reached for osteosarcoma patients. Two osteosarcoma patients reached partial response with an objective response rate of 6.9 %. A disease control rate of 75.86 % was reported for osteosarcoma patients. The toxicity profile was considered manageable and seemed to be even more favorable compared to other orally administered anti-angiogenic tyrosine kinase inhibitors. The authors concluded that anlotinib displayed promising anti-tumor effectiveness and a manageable safety profile among patients with relapsed or metastatic primary malignant bone tumors. [81] Similar findings were reported in a retrospective study that analyzed the safety and efficacy of anlotinib in the treatment of patients with unresectable or metastatic bone sarcoma [82]. A retrospective study demonstrated that anlotinib had a modest therapeutic effect on patients with advanced osteosarcoma after standard treatment failure. In the study the median progression free survival was 9.8 months while the 6- and 10-months progression free survival rates were 73 % and 33 % respectively. The median overall survival was 11.4 months and there was no complete response. After 6 months of treatment, the disease control rate and objective response rate were 80 % and 13 % respectively. Most adverse events were manageable or relieved after treatment. [83] Another retrospective study assessed the efficacy and safety of anlotinib combined with gemcitabine/docetaxel (GD) in patients with metastatic osteosarcoma unresponsive to initial chemotherapy treatment and found that the combination and GD exhibited promising effectiveness with tolerable side effects compared to GD alone. [84] However, when comparing outcomes of patient treated with anlotinib with those of patients treated with anlotinib plus chemotherapy, no significant difference was found regarding the disease control rate or the median progression-free survival. [85].

A retrospective study comparing the efficacy and safety of patients treated with either apatinib or anlotinib concluded that both apatinib and anlotinib demonstrated their effectiveness in treating sarcomas. However, the efficacy of each drug varies depending on the histological type of sarcoma. Particularly in the case of osteosarcoma, apatinib appeared to have more effectiveness. Regarding adverse effects, they appeared to be more frequent in the apatinib group compared to the anlotinib group. [86].

5.5. Cabozantinib

Cabozantinib, or XL184 is an orally bioavailable multitargeted kinase inhibitor. It targets VEGFR2, HGFR, RET, and c-KIT [87]. Cabozantinib also inhibits MAPK/Ras/Erk and PI3K/Akt/mTOR transduction pathways [88].

A multicenter trial assessed cabozantinib in severe cases of OS. At 4 months, 71.4 % of patients were in progression-free survival, while at 6 months, 33.3 % of patients had non-progression, and 11.9 % had partial response. As best response, 19 % of patients had progressive disease. Median progression-free survival and overall survival were 6.7 months and 10.6 months, respectively. Cabozantinib is worth considering as a treatment option for advanced OS, and merits further study [89]. A retrospective analysis produced similar results [90].

5.6. Sorafenib

Sorafenib, or BAY 43–9006 is an orally administered multi-target kinase inhibitor. It inhibits VEGFR2, VEGFR3, FGFR1, c-KIT, PDGFRβ, and RET. Sorafenib also inhibits the MAP/Ras/Raf/MEK/Erk pathway [9192]. A clinical trial evaluating the efficacy of sorafenib was conducted. At 4 months, progression-free survival was 46 % and clinical benefit rate, partial responses, stable disease were 29 %, 8 %, and 34 %, respectively. No complete response was reported. Median progression free survival and overall survival were 4 and 7 months respectively. Overall, the most severe cases of OS benefitted from sorafenib, which demonstrated clinical activity and an adequate safety profile as a second- or third-line treatment [93].

Another clinical trial evaluated the safety and efficacy of sorafenib and everolimus in relapsed or advanced OS patients. At 6 months, 45 % of patients were in progression-free survival. While no complete responses were recorded, partial responses and minor responses were observed in 5 % of patients each, which translates to a 10 % overall response rate. Stable disease and progressive disease were recorded in 53 % and 37 % of patients, respectively. Disease control rate reached 63 %. Despite demonstrating clinical efficacy, the combination of sorafenib and everolimus failed to substantially enhance outcomes in refractory and unresectable OS patients [94].

A retrospective study reviewed the outcomes of OS patients treated with MTKIs. The subset of patients treated with sorafenib only achieved a progression-free survival of 1.7 months, while the subset of patients treated with a combination of sorafenib and everolimus achieved a 3.4 months progression-free survival. Drug induced toxicity was deemed acceptable [95]. A smaller-scale study assessed sorafenib in advanced and relapsed bone malignancies. With an overall response of 75 %, partial response was achieved in six OS patients, while the remaining two achieved stable disease. Median time to progression was 4 months.

Sorafenib tended to yield better outcomes when given earlier in the course of treatment, although this observation did not reach significance. The authors concluded that sorafenib only prolongs overall survival; additional treatments are needed to attain lasting remission [96]. Other assessments found comparable outcomes, including one that utilized sorafenib in conjunction with bevacizumab and cyclophosphamide. [97,98].

5.7. Pazopanib

Pazopanib (GW786034) is an orally administered tyrosine kinase inhibitor that targets VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor PDGFRα, PDGFRβ and c-Kit. [99].

A phase II study was conducted to assess the safety and efficacy of pazopanib in patients with inoperable, pulmonary metastatic osteosarcoma. The study was terminated prematurely because the sponsor withdrew financial support. Among the seven evaluable patients in the study, four exhibited stable disease for more than 4 months whereas the other 3 experienced progressive disease. Pazopanib was considered relatively well-tolerated as most adverse events were of grades 1 or 2 with no grade 4 or 5 adverse events. Pazopanib may therefore be considered a treatment option for adult patients who do not respond to chemotherapy. [100] A prospective phase II study was conducted to assess the efficacy of the combination of pazopanib with topotecan as a treatment for patients with metastatic unresectable soft tissue sarcomas, with the study comprising an exploratory arm targeting osteosarcoma. However, this combination did not achieve the predefined endpoints and was associated with a high degree toxicity profile [101] . Another study was carried-out with the aim of assessing the off-label utilization of pazopanib in patients with metastatic bone sarcomas who did not respond to standard chemotherapy. Most patients were diagnosed with osteosarcoma and an overall response rate of 35 % was reported. Median overall survival and median progression free survival were 11 months and 5.5 months respectively. It was concluded that pazopanib was well-tolerated and that it exhibits some activity against bone sarcomas. However, despite the evidence that pazopanib can stabilize the disease, progression free-survival and overall-survival outcomes remained unsatisfactory regarding patients with metastatic bone sarcoma. [102] A retrospective study had a primary objective of investigating the patterns of clinical benefit observed in patients who underwent pazopanib treatment within real-world community practice. Among the studied population, six patients had osteosarcoma among whom four reached progressive disease. Two patients had stable disease for 6 and 9 months respectively. However, no complete response or partial response were reported. [103]. Multiple clinical trials suggested that pazopanib may be effective as a treatment for metastatic osteosarcoma and may contribute to prolonging the survival of patients with osteosarcoma. [104–107].

5.8. Dasatinib

Dasatinib is an orally administered MTKI that targets proteins from the Src family, c-KIT, PDGFR [108,109]. Treatment with dasatinib failed to substantially enhance outcomes of advanced and relapsed OS, as clinical benefit rate only reached 13 %, objective response rate reached 6.5 %, with 4- and 6- months progression-free survival values only reaching 13 % and 11 % [110].

5.9. Saracatinib

Saracatinib (or AZD0530) is an orally administered selective inhibitor of Src family kinases [111].

The efficacy and safety of saracatinib were assessed in a clinical trial, and while it was shown to have acceptable safety, it had no discernible effect on OS, as there was no statistical difference between the median progression-free survival and median overall survival respective to the placebo group and the saracatinib group [112].

5.10. Imatinib

Imatinib (or STI571), is a tyrosine-kinase inhibitor that targets c-Kit and PDGFR [113,114]. A study was conducted to assess the efficacy and safety of imatinib in treating children and young adults diagnosed with refractory or relapsed solid tumors, with no complete response or partial response were recorded. [115] In another study, 21 patients had progressive disease while 5 patients had a clinical benefit response with no complete or partial responses. Median progression free survival for osteosarcoma patients was recorded at 1.92 months and the observed response rate was 19.2 %. Concerning all the sarcoma subtypes, after treating almost 200 patients, only 4 complete/partial response were recorded, which indicates that the drug provided very limited clinical benefit [116].

5.11. Cediranib

Cediranib is an orally administered molecule that acts as a highly potent inhibitor of the tyrosine kinase activity of vascular endothelial growth factor receptors: VEGFR1, VEGFR2 and VGFR3 [117].

Multiple phase I trials were conducted to evaluate the safety, efficacy, and impact on critical parameters of cediranib. In one such trial [118], one osteosarcoma patient had a minor response. The rest of the study did not present explicit findings specific to osteosarcoma patients. Similarly, another Phase I trial [119] explored the synergistic effects of cediranib, in combination with gefitinib—an epidermal growth factor receptor inhibitor—among patients with advanced cancers, including osteosarcoma. One osteosarcoma patient showed partial response. While the trial did not singularly concentrate on osteosarcoma, it did illuminate the effectiveness of cediranib in inhibiting the VEGFR signaling pathway in advanced malignancies. Nevertheless, future dedicated clinical trials targeting osteosarcoma patients are essential to completely assess the overall response rate, disease control rate, safety threshold, and therapeutic efficacy of cediranib in osteosarcoma treatment.

5.12. Axitinib

Axitinib is an orally administered tyrosine kinase inhibitor that targets the VEGFR receptors 1,2 and 3. [120].

A phase 1 trial [121] sought to comprehensively assess the safety and efficacy of axitinib within a pediatric patient population with diverse cancer histologies. The two included osteosarcoma patients had stable disease. In the rest of the study, explicit findings specific to osteosarcoma were not presented. The study provided invaluable insights into the safety profile of axitinib and its impact on overall tumor response patterns. Illuminating the potential therapeutic applications of axitinib, the research shed light on its ability to impede tumor growth and target angiogenesis through the inhibition of VEGF receptors. Nevertheless, to gain a comprehensive understanding of the overall response rate, disease control rate, safety threshold, and therapeutic efficacy of axitinib in osteosarcoma treatment, future dedicated clinical trials focusing on osteosarcoma patients are imperative.

5.13. Pamufetinib

Pamufetinib (or TAS-115) is a tyrosine kinase inhibitor that targets PDGFR, VEGFR and MET. [122,123] An expansion cohort of a phase I study [124] aimed to assess the efficacy and safety of pamufetinib in treating osteosarcoma. While stable disease, reported at 50 %, was the best overall response, there were no complete or partial responses. Disease control rate was 40 %. Median progression-free survival was 3 months whereas the 4-month and 12-month progression-free rates were 42 % and 31 % respectively. Long-term disease control (>1 year) was achieved in three patients. Regarding the drug's safety profile, 85 % of patients had adverse drugs reactions of grade 3 or higher, but they were

considered manageable, and no drug-related deaths occurred. Finally, the authors found that pamufetinib is a promising treatment option for patients with advanced osteosarcoma.

A summary of the findings of the efficacy analysis of this systematic review is shown in Table 1.

6. Discussion

The objective of this review was to determine the most effective tyrosine kinase inhibitors for the treatment of mostly advanced osteosarcoma, as well as define the best strategies to use this class of drugs in combination with other treatments.

Numerous drugs have shown promising results; randomized phase III trials are therefore needed to establish the efficacy and safety of MTKIs that have shown promising results in the treatment of metastatic or relapsed OS. Cabozantinib achieved the highest 4-month progression-free survival as a monotherapy, and apatinib was associated with the highest rate of overall response as a monotherapy and in combination with chemotherapy, as well as the highest 4- and 6-month progression-free survival in association with etoposide and ifosfamide. Other MTKIs that have also yielded encouraging results include regorafenib, lenvatinib, and anlotinib. Exploring the effectiveness of other under-researched TKIs will be useful to determine the best treatment options.

Tyrosine kinase inhibitors have demonstrated activity in refractory OS patients; however, they do not consistently allow patients to achieve sufficient results alone. This reality warrants their usage combined with chemotherapy and/or other TKIs, which could be another option to reach better response rates and improve patient outcome.

Combining TKIs with chemotherapy has been shown to be a successful approach on numerous occasions, producing longer-lasting responses and reversing chemotherapy resistance.

One neglected parameter in these studies is variations in quality-of-life changes caused by treatment with tyrosine kinase inhibitors. Most trials label the toxicity profiles of the MTKIs they study as “acceptable”, despite dose reductions and treatment interruptions being frequently necessary [125]. Researchers could therefore benefit from inserting quality of life questionnaires into trials, so as to take patient perspectives into account. Identifying deteriorations in quality of life may allow for better patient compliance with treatment.

The modest outcomes in many studies may result from not selecting patients with biomarkers indicative of sensitivity to treatment. Grigani *et al.* found that pRPS6 (phosphorylated ribosome protein S6) and pERK1/2 are linked to more favorable outcomes in OS [94]. Furthermore, Italiano *et al.* demonstrated that VEGFA and soluble MET were also indicators of outcome [89]. Certain reports also described patients who achieved substantially improved results after receiving treatment consistent with a specific biomarker. More recent studies failed to identify biomarkers predictive of response. To establish stronger evidence, future larger-scale studies will have to identify biomarkers that will reliably predict sensitivity to MTKIs, enabling the selection of patients who will respond favorably [125].

It has been suggested that MTKIs that inhibit multiple RTKs simultaneously are more effective than kinase inhibitors with a narrower spectrum of inhibition. This finding can be explained by the diversity of RTKs expressed and/or amplified in OS. While this approach has demonstrated clinical activity and allowed for the improvement of patient outcomes, the potential use of combinations of selective TKIs on critical targets may allow for the avoidance of the unnecessary inhibition of unrelated pathways and thus relieve patients from enduring the toxicities related to treatment with “dirty” drugs [126]. This strategy will enhance patient quality of life and improve outcomes by reducing treatment-related deaths and treatment interruptions, which will permit continuing, long-lasting responses.

Table 1
Summary of our findings in this systematic review.

Reference	Type of study	Number of OS patients included	Treatment	Outcome
Xie et al, 2018	Clinical trial	37	Apatinib	Substantial improvement, of patient outcomes, heavy but manageable toxicity profile, disappointing duration of response
Xie et al, 2020	Clinical trial	43	Apatinib with camrelizumab	The benefits of bitherapy were insignificant.
Liao et al, 2020	Clinical trial	34	Apatinib	Patients benefitted from the treatment and tolerated apatinib well
Ye et al, 2022	Retrospective study	9	apatinib	Low dose apatinib reverses chemoresistance
[126]	Retrospective study	32	Apatinib or anlotinib	The efficacy and associated adverse events of both drugs varies based on the histological type of sarcoma with apatinib appearing to be more effective against osteosarcoma
Zheng et al, 2018	Retrospective study	10	Apatinib	Apatinib showed clinical activity and manageable safety
Liu et al, 2020	Retrospective study	105	Apatinib	Apatinib exhibited encouraging safety and efficacy
Tian et al, 2019	Retrospective study	27	Apatinib	Apatinib was effective and safe, no difference in outcome between patients treated with high or low-dose apatinib
Xie et al, 2021	Retrospective study	33	Apatinib with ifosfamide and etoposide	The combination showed great clinical promise.
Gong et al, 2022	Retrospective analysis	45	Apatinib plus chemotherapy	The combination resulted in more persistent responses compared to single agent apatinib
Yao et al, 2021	Meta-analysis	356	Apatinib	Apatinib is safe and effective, outcome is statistically

(*continued on next page*)

Table 1 (*continued*)

Reference	Type of study	Number of OS patients included	Treatment	Outcome
				correlated with dose
Xie et al, 2020	Sub-study of clinical trial	41	Apatinib	Adverse events are indicators of positive prognosis
Tian et al, 2021	Retrospective study	54	Apatinib	Pneumothorax is an indicator of positive prognosis
Davis et al, 2019	Clinical trial	42	Regorafenib	Regorafenib shows promising efficacy and safety
Duffaud et al, 2019	Clinical trial	43	Regorafenib	Regorafenib shows promising efficacy and safety
[95]	Retrospective study	31	Regorafenib or sorafenib or sorafenib plus everolimus	Regorafenib performed better than sorafenib monotherapy and sorafenib plus everolimus
Salto et al, 2021	Case report	1	Regorafenib	Regorafenib was identified as the cause of congestive heart failure
Pereira et al, 2021	Case report	1	Regorafenib	Regorafenib was identified as the cause of acute pancreatitis
Pierobon et al, 2020	Case report	3	Regorafenib	Regorafenib was identified as the cause of acute asymptomatic pneumothorax[a]
Gaspar et al, 2021	Clinical trial	64	Lenvatinib	Lenvatinib showed clinical activity and safety
Gaspar et al, 2021	Clinical trial	40	Lenvatinib with etoposide and ifosfamide	The tritherapy exhibited substantial improvement over single agent lenvatinib, while displaying a similar safety profile
[89]	Clinical trial	45	Cabozantinib	Cabozantinib showed clinical activity and had a manageable safety profile
[90]	Retrospective study	11	Cabozantinib	Cabozantinib showed clinical activity and had a manageable safety profile
Grigani et al, 2012	Clinical trial	35	Sorafenib	Sorafenib was considered safe and showed some activity
Grigani et al, 2015	Clinical trial	38	Sorafenib plus everolimus	Despite showing activity, the combination yielded disappointing outcomes compared to other TKIs
[97]	Retrospective study	29	Sorafenib or sunitinib or pazopanib or tensirolimus alone or with cyclophosphamide	Despite showing activity, the combination yielded disappointing outcomes compared to other TKIs
[98]	Retrospective study	7	Sorafenib with cyclophosphamide and bevacizumab	The combination was useful for maintenance or palliative care.
[110]	Clinical trial	46	Dasatinib	The dasatinib cohort did not exhibit statistically significant improvements over the placebo cohort
Baird et al, 2020	Clinical trial	37	Saracatinib	The saracatinib cohort did not show statistically significant improvements over the placebo cohort
[121]	Clinical trial	2	Axitinib	Future clinical trials focusing on osteosarcoma are needed
[81]	Clinical trial	29	Anlotinib	Anlotinib shows promising efficacy and safety
[84]	Retrospective study	32	Anlotinib withGemcitabine/ Docetaxel (GD)	The combination showed more efficacy with a manageable toxicity profile compared to GD alone
[85]	Retrospective study	13	Anlotinib plus chemotherapy or anlotinib alone	The combination did not show significant clinical benefit compared to anlotinib alone that showed promising efficacy and safety
[82]	Retrospective study	27	Anlotinib	Anlotinib shows promising efficacy with a tolerable safety profile against advanced bone sarcoma
Li et al, 2023	Retrospective study	16	Anlotinib	Anlotinib had a modest therapeutic effect with a manageable safety profile

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Table 1 (*continued*)

Reference	Type of study	Number of OS patients included	Treatment	Outcome
[118]	Clinical trial	4	Cediranib	Future clinical trials focusing on osteosarcoma are needed
[119]	Clinical trial	1	Cediranib	Future clinical trials focusing on osteosarcoma are needed
[115]	Clinical trial	12	Imatinib	Imatinib showed little to no activity and therefore provided disappointing results
[116]	Clinical trial	27	Imatinib	Imatinib showed very limited clinical benefit and therefore provided disappointing results
[100]	Clinical trial	12	Pazopanib	Pazopanib showed notable activity and was relatively well-tolerated
[101]	Clinical trial	28	Pazopanib plus topotecan	The combination did not achieve the predefined endpoints and had a bad toxicity profile
[102]	Retrospective study	8	Pazopanib	Pazopanib showed some activity and was well-tolerated in treating bone sarcomas
[103]	Retrospective study	6	Pazopanib	Pazopanib shows significant activity in bone sarcomas
[124]	Clinical trial	20	Pamufetinib	Pamufetinib shows promising efficacy and safety

[a] : Diagnosis made on a single patient.

7. Conclusion

In summary, tyrosine kinase inhibitors have shown potential as a therapeutic option for patients with osteosarcoma. We compared the outcomes of patients treated TKIs, including apatinib, regorafenib and cabozantinib, either administered alone or in combination with other systemic treatments. Pairing TKIs with chemotherapy proved to be an effective strategy. Identifying biomarkers predictive of response is imperative to enhance quality of life and extend survival. Large scale randomized controlled trial are needed to confirm the efficacy and safety profiles of these agents. Continued research is therefore critical to refine therapeutic approaches in order to improve outcomes and maintain quality of life to an acceptable standard.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

Fig. 2 was created using Biorender.com

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