A review of the mechanism of action and clinical applications of sorafenib in advanced osteosarcoma

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Abstract

Objective: To summarise the contemporary literature regarding sorafenib and its effectiveness as a novel treatment in advanced osteosarcoma.

Background: Modern treatment has seen the cure rate of osteosarcoma increase to 65%. However, in patients who do not achieve remission, prognosis is poor, as there are no effective, consensual second line therapies. Sorafenib has emerged as a potentially viable drug to be used in this context.

Method: A literature review was conducted evaluating articles pertaining to osteosarcoma and sorafenib. Clinical studies were prioritised, but preclinical data was also evaluated to elaborate on mechanisms and potential targets for the future. Limitations of the review and data were explored.

Conclusion: In isolation, sorafenib was shown to only provide brief clinical benefit due to various described mechanisms. However, when combined with other drugs that addressed its weaknesses or other aspects of the pathogenesis of osteosarcoma, it proved to be effective in reducing disease progression in a variety of advanced cases. Further investigation into the use of sorafenib in combination therapy is needed. Specifically, the combination of sorafenib with denosumab has displayed potential to be an effective future treatment for osteosarcoma.

1. Introduction

Osteosarcoma is the most common bone tumour in children, adolescents and young adults [1,2]. Risk factors for osteosarcoma are outlined in Table 1. It is most common between the ages of 10–19, and the incidence rate for the condition ranges between one and five cases per one million people [1,3–6]. It has a variable prognosis, and the main factors affecting disease course have been highlighted in Table 2. Current treatment for osteosarcoma has achieved a universal cure rate of 65% [7]. When diagnosed, patients commence induction chemotherapy [8,9]. The tumour is surgically resected and analysed, and if 90% or more of the tumour is necrosed, the chemotherapy regime is continued to eliminate micrometastasis [1,10]. However, there is no standardised treatment for osteosarcoma that has failed to respond to the first chemotherapy regime [11]. Thus, researchers have attempted to identify potential drugs to fulfil this role. One such drug is sorafenib, which is sold under the trade name “Nexavar” [9]. This literature review evaluates the mechanism of action and efficacy of sorafenib in the treatment of osteosarcoma refractory to chemotherapy.

2. Methodology

The terms “sorafenib OR Nexavar” and “osteosarcoma” were used to search the PUBMED database. The initial search was conducted during March 2016, and was repeated in April 2016. The searches were repeated and the original paper was reviewed in January 2017 to account for new evidence. Both preclinical and clinical data sources were evaluated. The oldest article discussing osteosarcoma and sorafenib was from 2009 [24].

3. Discussion

3.1. Preclinical data: osteosarcoma pathogenesis and sorafenib mechanism of action

Osteosarcoma is a multifactorial disease with a range of genes and mutations contributing to the pathogenesis [25]. The mitogen activated protein kinase/extracellular regulated kinase (MAPK/ERK) pathway is involved in tumour cell proliferation and metastasis [24]. Sorafenib is an inhibitor of a variety of tyrosine kinase receptors and is used to treat chemotherapeutic tumours of the thyroid, liver and kidney [26–29]. It is...
more refractory osteosarcoma progression can be temporarily inhibited by a direct inhibitor of this MAPK/ERK pathway, and acts by binding to sorafenib [40]. Of these patients, three achieved disease survival at 4 months. However, only 29% had stable disease at 6 months: the benefit of sorafenib was small, and possible explanations were investigated.

3.3. Preclinical data: use of sorafenib in conjunction with other pharmacotherapies

Consulting data from an acute myelogenous leukaemia study, the Italian Sarcoma Group hypothesised that sorafenib was being countered by an interaction with mammalian target of rapamycin complex 2 (mTORC 2) [41,42]. mTORC1 and mTORC2 are protein complexes that stimulate the MAPK/ERK pathway downstream from the primary targets of sorafenib, promoting disease progression and metastatic potential [43]. Sorafenib was shown to inhibit mTORC1, but stimulate mTORC2 [24,44]. Thus, despite inhibiting the MAPK/ERK pathway upstream, sorafenib was also stimulating it downstream, resulting in disease progression by upregulating the expression and activity of mTORC2 [24,44]. Sorafenib was subsequently combined with everolimus, a drug that disassembles mTORC 2 and minimises the stimulatory effect of this protein. [41,42]. In vivo and in vitro investigation demonstrated that the combination of the drugs significantly reduced tumour growth, angiogenesis and metastasis [41]. Additionally, immunohistochemistry identified a significant reduction in the activity of mTORC1 and 2 [41].

Preclinical trials have explored the relevance of Receptor Activator of Nuclear Factor κ B (RANK) [10]. RANK is stimulated by RANKL secreted by osteoblasts, which causes differentiation of osteoclasts and stimulates bone resorption. This has also been shown to cause increase in cell mobility in osteosarcoma models [10]. Additionally, overexpression of RANK and RANKL is associated with increased rates of metastasis and poorer outcomes for patients [45]. Denosumab is a monoclonal antibody against RANKL, preventing it from stimulating RANK [46]. Preclinically, it has demonstrated the ability to reduce proliferation and motility of osteosarcoma cells [47]. Thus, given the reported effectiveness of both everolimus and denosumab, studies were conducted to explore the combination of sorafenib and these two drugs.

3.4. Clinical efficacy of sorafenib in combination with other drugs

The Italian Sarcoma Group conducted another phase II clinical trial [9]. It was non randomised, as researchers selectively nominated patients with unresectable tumours refractory to both chemotherapy and radiotherapy. This trial tested sorafenib in combination with everolimus, the aforementioned mTORC 2 disassembler [41]. 38 patients were enrolled in the trial, and 17 (45%) of these were progression free at 6 months. 37% of patients were alive after twelve months, but only 5% were alive after 24 months [9]. The goal of the trial was to achieve 50% of patients with progression free survival at 6 months to justify a phase III trial. Thus, sorafenib and everolimus failed to achieve the target. Despite this, the benchmark for an experimental treatment of sarcoma to be considered feasible is 20% of subjects having progression free survival at 6 months [48]. The combination exceeded this threshold and was greater than sorafenib used in isolation and should thus still be considered for future investigation. Further preclinical trials should also be undertaken to identify more agents with which to combine this therapy in order to increase the duration of the response and possibly achieve curative action.

In 2015 a case was published involving a patient who had been given two regimes of chemotherapy, radiotherapy and tumour curttage, but was still experiencing progression in their spinal osteosarcoma [11]. Biopsy showed that the tumour was over-expressing RANK, and the osteoid matrix contained a large amount of RANKL. Thus, the patient was started on sorafenib and denosumab (monoclonal antibodies against RANKL). Despite osteosarcoma being consistently documented as a tumour incurable with pharmacotherapy alone, within eight months, positron emission tomography identified a complete direct inhibitor of this MAPK/ERK pathway, and acts by binding to rapidly accelerated fibrosarcoma protein kinase (RAF), stem cell growth factor receptor (c-kit), fibroblast-like growth factor receptor (FGFR) and platelet derived growth factor receptor (PDGFR) [30–34]. These actions prevent the activation of the MAPK/ERK pathway, mitigating cell growth and proliferation and depleting the tumour’s cell population [30]. Furthermore, sorafenib has been shown to inhibit a variety of other proteins associated with osteosarcoma. [24,35–37]. 63% of osteosarcoma cell lines have upregulated VEGFR and it is associated with angiogenesis and metastasis [37]. Sorafenib also promotes apoptosis in a variety of cancer types by downregulating anti-apoptotic protein MCL-1 [38]. 84% of osteosarcoma cell lines evaluated in a laboratory were found to have elevated expression of MCL-1, making it an important drug target to promote tumour cell death [24].

Table 1
Risk factors for osteosarcoma [3,6,12–16].

| Other diseases as risk factors | Other risk factors |
|-------------------------------|-------------------|
| Previous osteomyelitis        | Hispanic and African heritage |
| Paget’s bone disease (elderly populations) | Tall stature/large growth spurs |
| Hereditary Multiple Osteochondromas | Previous localised radiation treatment |
| Familial gene mutations, including: | Being aged between 10 and 19, or older than 65 |
| – RB1 (Retinoblastoma) |  |
| – RELQ4 (Rothmund-Thomson) |  |
| – BLM (Bloom) |  |
| – WRN (Werener) |  |
| – p53 (Li-Fraumeni Syndrome) |  |
| – Diamond-Blackfan Anemia | Being female (in elderly populations) |
| | Being male (in young populations) |

Table 2
Factors affecting osteosarcoma prognosis [1,3,4,12,17–23].

| Factors supporting a positive outcome for the patient | Factors supporting a negative outcome for the patient |
|-------------------------------------------------------|-----------------------------------------------------|
| > 90% necrosis in response to neoadjuvant (induction) chemotherapy | < 90% necrosis in response to neoadjuvant chemotherapy |
| Wide surgical margin upon resection | Age > 40 years |
| Early diagnosis | Tumour located in the axial skeleton |
| Diagnosis before 12 years of age | Metastases at diagnosis |
| | Osteoblastic subtype |
| | Unresectable tumour |
| | Pathological fractures |
| | High serum concentration of vascular endothelial growth factor (VEGF) |

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metabolic remission [11,49]. Eighteen months afterwards, no remission was detectable. This is the only clinical example reported to date pairing sorafenib with denosumab or any agent against RANK in osteosarcoma, with the only ongoing clinical trial still being conducted [50]. Therefore, it remains to be seen whether denosumab can reproduce these effects on a larger scale given its history of controversial evidence.

Combination therapy with sorafenib has also seen negative results in the reported literature. One clinic used molecular profiling to sequence the genes and identify prevalent proteins in two cases of osteosarcoma [50]. One of these patients was identified to be best suited to treatment with sorafenib. It was combined with the mTORC inhibitor temsirolimus and bevacizumab (monoclonal antibodies against VEGF A, inhibiting angiogenesis). Despite this, the cancer progressed, and the patient was palliated. However, this case does not necessarily disprove the effectiveness of sorafenib. Firstly, the mTORC inhibitor used was not everolimus: there is no evidence for combining sorafenib with temsirolimus [9,41]. Additionally, osteosarcoma is a heterogenous tumour with a variety of different cell populations [9]. In this case, the tumour was not surgically resected, and so could not be histologically examined in its entirety; only a small population of cells were examined. Thus, whilst sorafenib may have been the optimum treatment for the cells within the biopsy, the large majority of the tumour may have actually been non-responsive to the drug. Alternatively, sorafenib may have rapidly selected out those cells sensitive to the therapy, causing the cell population non-responsive to it to thrive and proliferate, thus increasing tumour bulk. Ultimately, sorafenib did not achieve a positive clinical outcome in this study despite being paired with an mTORC inhibitor. Although the reasoning in this case was flawed, it must be considered when evaluating its effectiveness as a novel osteosarcoma treatment [51].

4. Limitations of the review

Sorafenib is a relatively new drug. More so, the combination of sorafenib with other drugs for osteosarcoma is a treatment modality that has existed in the literature for a mere 12 months. Thus, large scale data and relationships are not yet available. More clinical data is required to properly evaluate the efficacy of sorafenib and sorafenib combination therapy as a second line treatment for osteosarcoma. In particular, denosumab and sorafenib is a combination that demands further evaluation. Additionally, both phase II trials were conducted by the Italian Sarcoma Group. All other clinical evidence evaluated was on a far smaller scale. Thus, to ensure validity of the data, sorafenib must undergo further clinical trials conducted by other research institutions. Finally, all future clinical trials should focus on sorafenib in the context of combination therapy, as this review has foregrounded evidence suggesting that it is ineffective in isolation [39,40].

5. Conclusion

Sorafenib works by inhibiting a variety of proteins. The majority of these are tyrosine kinase receptors, and the primary mechanism is inhibition of the MAPK/ERK pathway. Laboratory studies demonstrated the biological plausibility of sorafenib in treating osteosarcoma by measuring its success in various in vitro and in vivo studies. However, subsequent clinical trials revealed sorafenib was only effective for a short duration, achieving minimal clinical benefit in the target patient groups. Subsequently, further preclinical trials focused on combining sorafenib with other drugs to overcome resistances against it to augment the duration of its therapeutic effect. Specifically, sorafenib was combined with everolimus, an mTORC inhibitor in on trial, and denosumab, a population of monoclonal antibodies against RANKL, in another. Both hypotheses proved to be true, and they were thus applied clinically. The trial with everolimus was on a much larger scale than that with denosumab. However, in both cases, sorafenib proved to be a far more effective treatment when combined with adjunct pharma-cotherapy. Thus, more trials are recommended with different drug combinations to further evaluate the usefulness of sorafenib in the context of advanced osteosarcoma. Additionally, given the evidence highlighted in this review, sorafenib should not be used in isolation, as this was not associated with a strong clinical outcome. It should be combined with other drugs that will subvert its weaknesses and address more broadly the pathophysiological processes of osteosarcoma. In particular, the combination with denosumab was effective despite being an isolated case, and the combination should be assessed on a larger scale.

References

[1] M.S. Isakoff, S.S. Bielack, P. Meltzer, R. Gorlick, Osteosarcoma: current treatment and a collaborative pathway to success, J. Clin. Oncol. 33 (27) (2015) 3029–3035. http://jco.ascopubs.org/content/early/2015/08/21/JCO.2014.59.4995.short
[2] J.P. He, Y. Hao, X.L. Wang, X.J. Yang, J.F. Shao, F.J. Guo, et al., Review of the molecular pathogenesis of osteosarcoma, Asian Pac. J. Cancer Prev. 15 (15) (2014) 5967–5976. http://www.ncbi.nlm.nih.gov/pubmed/25124559.
[3] E. Weed, C. De Santis, A. Robbins, B. Kohler, A. Jemal, Childhood and adolescent cancer statistics, 2014, CA Cancer J. Clin. 64 (4) (2014), pp. 83–103. http://onlineibrary.wiley.com/doi/10.3322/caac.21219/abstract
[4] K. Berner, T.B. Johannesen, A. Berner, H.K. Haugland, B. Bjerkehagen, P.J. Bohler, et al., De novo trends on incidence and survival in a nationwide and unselected cohort of patients with skeletal osteosarcoma, Acta Oncol. 54 (1) (2015) 25–33. http://www.ncbi.nlm.nih.gov/pubmed/24957555.
[5] M. Sampo, M. Koivikko, M. Taskinen, P. Kallio, A. Kivioja, M. Tarkkanen, et al., Incidence, epidemiology and treatment results of osteosarcoma in Finland – a nationwide population-based study, Acta Oncol. 50 (8) (2011) 1206–1214. http://www.ncbi.nlm.nih.gov/pubmed/22023116.
[6] S.A. Savage, L. Mirabello, Using epidemiology and genomics to understand osteosarcoma etiology, Sarcoma 2011 (2011) 548151. http://www.hindawi.com/journals/sarcoma/2011/548151/.
[7] M.M. Haglindm, H.J. Coenen, H. Gelderblom, R.R. Markklinm, H.I. Vos, E.S. de Bont, et al., A first step toward personalized medicine in osteosarcoma: pharmacogenetics as predictive marker of outcome after chemotherapy-based treatment, Clin. Cancer Res. 21 (15) (2015) 3436–3441. http://www.ncbi.nlm.nih.gov/pubmed/25829401.
[8] X. Xiao, W. Wang, H. Zhang, P. Gao, B. Fan, C. Huang, et al., Individualized chemotheraphy for osteosarcoma and identification of gene mutations in osteosarcoma, Tumour Biol. 36 (4) (2015) 2427–2435. http://www.ncbi.nlm.nih.gov/pubmed/25431261.
[9] G. Grigiani, E. Palmerini, V. Ferrari, L. D’Ambrosio, R. Bertulli, S.D. Asafetm, et al., Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial, Lancet Oncol. 16 (1) (2015) 98–107. http://www.thelancet.com/journals/lanonc/article/PII:S1470-2045(14)71470-6/abstract
[10] S. Salah, R. Abradm, I. Sultan, S. Yaser, A. Shehadeh, Osteosarcoma with metastasis at initial diagnosis: current outcomes and prognostic factors in the context of a comprehensive cancer center, Mol. Clin. Oncol. 2 (5) (2014) 811–816. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4106754/
[11] R. Calthomas, C. Rothermundt, B. Bode, B. Fuchs, R. von Moos, M. Schwitter, RANK ligand blockade with denosumab in combination with sorafenib in chemorefractory osteosarcoma: a possible step forward? Oncology 88 (4) (2015) 257–260. http://www.ncbi.nlm.nih.gov/pubmed/25531914.
[12] G. Agarwal, H.S. Kochar, P.K. Julla, S. Bahadur, Osteosarcoma as a second malignant disease in a case of bilateral retinoblastoma, Indian J. Otolaryngol. Head. Neck Surg. 63 (Suppl 1) (2011) 115–117. http://www.ncbi.nlm.nih.gov/pubmed/22754660.
[13] S. Iwata, T. Ishii, A. Kawai, T. Hiruma, T. Yonomoto, H. Kamoda, et al., Prognostic factors in elderly osteosarcoma patients: a multi-institutional retrospective study of 86 cases, Ann. Surg. Oncol. 21 (1) (2014) 263–268. http://www.ncbi.nlm.nih.gov/pubmed/23975321.
[14] T. Vellertti, N. Xie, Y. Wang, H. Huang, Q. Yang, X. Chen, et al., P53 functional abnormality in mesenchymal stem cells promotes osteosarcoma development, Cell Death Dis. 7 (6) (2016) e2015. http://www.nature.com/cddes/journal/v7/n6/full/cddes201567a.html
[15] S.A. Savage, L. Mirabello, Using epidemiology and genomics to understand osteosarcoma etiology, Sarcoma 2011 (2011) 548151. http://www.hindawi.com/journals/sarcoma/2011/548151/.
[16] T.B. Bertrand, A. Cruz, J. Binnie, D. Cheong, G.D. Letson, Do surgical margins affect local recurrence and survival in extremity, nonmetastatic, high-grade osteosarcoma? Clin. Orthop. Relat. Res. 474 (3) (2016) 677–683. http://www.ncbi.nlm.nih.gov/pubmed/26013185.
[17] G.M. O’Kane, K.A. Cadoos, E.M. Walsh, R. Emerson, P. Dervan, C. O’Kane, et al., Perioperative chemotherapy in the treatment of osteosarcoma: a 26-year single institution review, Clin. Sarcoma Res. 5 (2015) 17. http://www.ncbi.nlm.nih.gov/pubmed/25430158.
[18] K. Berner, T.B. Johannessen, A. Berner, H.K. Haugland, B. Bjerkehagen, P.J. Bohler, et al., Time-trends on incidence and survival in a nationwide and unselected cohort...
of patients with skeletal osteosarcoma, Acta Oncol. 54 (1) (2015) 25–33.

M.M. Haglindt, M.J. Goen, H. Gohderblom, R.R. Makkinje, H.I. Voo, E.S. de Bont, et al., A first step toward personalized medicine in osteosarcoma: pharmacogenetics as predictive marker of outcome after chemotherapy-based treatment, Clin. Cancer Res. 21 (15) (2015) 3436–3441.

S.K. Denduluri, Z. Wang, Z. Yan, J. Wang, Q. Wei, M.K. Mohammed, et al., Molecular pathogenesis and therapeutic strategies of human osteosarcoma, J. Biomed. Res. (2015) 30.

S. Isewa, T. Yonemoto, T. Iizasa, Y. Niihe, H. Kamoeda, T. Iishi, Oligo-recurrence of osteosarcoma patients: treatment strategies for pulmonary metastases, Ann. Surg. Oncol. 22 (Suppl 3) (2015) 1332–1338.

T.A. Marko, B.J. Diemser, L.G. Spector, Prevalence of metastasis at diagnosis of osteosarcoma: an international comparison, Pediatr. Blood Cancer (2016).

M. Kaya, T. Wada, S. Nagoya, M. Sasaki, T. Matsunuma, T. Yamashita, The level of vascular endothelial growth factor as a predictor of a poor prognosis in osteosarcoma, J. Bone Jt. Surg. Br. 91 (6) (2009) 784–788.

Y. Pignochino, G. Grignani, G. Cavalloni, M. Motta, M. Tapporo, S. Bruno, et al., Sorafenib blocks tumour growth, angiogenesis and metastatic potential in preclinical models of osteosarcoma through a mechanism potentially involving the inhibition of ERK1/2, MCL-1 and ezrin pathways, Mol. Cancer (2009) 118.

M.L. Broadhead, J.C. Clark, D.E. Myers, C.R. Dass, P.F. Chong, The molecular pathogenesis of osteosarcoma: a review, Sarcoma 2011 (2011) 959248.

Q. Yang, S. Zhang, M. Kang, R. Dong, J. Zhao, Synergistic growth inhibition by sorafenib and cisplatin in human osteosarcoma cells, Oncol. Rep. 33 (5) (2015) 2537–2544.

V. Gupta-Abramson, A.B. Troxel, A. Nelloro, K. Puttaswamy, M. Reddinger, K. Ransone, J.S. Mandel, K.T. Flaherty, L.A. Loewe, P.J. O’Dwyer, M.S. Bross, Phase II trial of sorafenib in advanced thyroid cancer, J. Clin. Oncol. 26 (2008) 4714–4719.

J.M. Llovet, S. Ricci, V. Mazzaferro, P. Hilgard, E. Gane, J.F. Blanc, et al., Sorafenib blocks tumour growth, angiogenesis and metastatic potential in preclinical models of osteosarcoma through a mechanism potentially involving the inhibition of ERK1/2, MCL-1 and ezrin pathways, Mol. Cancer (2009) 118.

S.M. Wilhelm, C. Carter, L. Tang, D. Wilkie, A. McNabola, H. Rong, et al., BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis, Cancer Res. 64 (19) (2004) 7099–7109.

D.L. Lacey, W.J. Boyle, W.S. Simonet, P.J. Kostenuik, W.C. Dougall, J.K. Sullivan, et al., Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the role of RANKL in osteosarcoma, J. Exp. Med. (2010) 207:639–649.

A.G. Beristain, S.R. Narala, M.A. Di Grappa, R. Khokha, Homotypic RANK signaling participates in the inhibition of osteosarcoma MG63 cells with sorafenib treatment, Cell Oncol. 23 (2) (2012) 508–519.

Z. Bago-Horvath, K. Schmid, F. Rosler, K. Nagy-Bojariszky, P. Funovics, et al., Personalized comprehensive molecular profiling of high-risk osteosarcoma: implications and limitations for precision medicine, Oncotarget 6 (38) (2015) 40642–40654.