

Sorafenib in breast cancer treatment: A systematic review and overview of clinical trials

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Abstract

AIM: To evaluate the current role of sorafenib, an oral multikinase inhibitor in the treatment of breast cancer.

METHODS: An extensive search of the literature until March 2016 was carried out in Medline and clinicaltrials.gov, by using the search terms "sorafenib" and "breast cancer". Papers found were checked for further relevant publications. Overall, 21 relevant studies were found, 18 in advanced breast cancer (16 in stage IV and two in stages III-IV) and three in early breast cancer.

RESULTS: Among studies in advanced breast cancer, there were two trials with sorafenib as monotherapy, four trials of sorafenib in combination with taxanes, two in combination with capecitabine, one with gemcitabine and/or capecitabine, one with vinorelbine, one with bevacizumab, one with pemetrexed and one with ixabepilone, three trials of sorafenib in combination with endocrine therapy and two trials in women with brain metastases undergoing whole brain radiotherapy. In addition, there was one trial of sorafenib added to standard chemotherapy in the adjuvant setting, and two trials in the neoadjuvant setting. In general, sorafenib was well tolerated in breast cancer patients, though its dosage had to be adjusted in some trials, and discontinuation rates were high, particularly for the combination of sorafenib with anastrozole. Sorafenib monotherapy and combinations with taxanes, bevacizumab and ixabepilone showed inadequate efficacy, while efficacy results from combinations with gemcitabine and/or capecitabine and possibly tamoxifen were more promising.

CONCLUSION: At present, sorafenib should not be

used for the treatment of breast cancer outside of clinical trials and more clinical data are needed in order to support its standard use in breast cancer therapy.

Key words: Breast cancer; Sorafenib; Kinase inhibitors; BRAF; Mitogen-activated protein kinase

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Core tip: In this systematic review of the literature, the role of sorafenib in the treatment of breast cancer has been evaluated. Regarding toxicity, sorafenib was generally well tolerated in breast cancer patients, while in terms of efficacy the most promising results came from clinical trials evaluating sorafenib in combination with gemcitabine and/or capecitabine and possibly tamoxifen. Efficacy was inadequate with sorafenib monotherapy and combinations with taxanes, bevacizumab and ixabepilone.

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INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death among women worldwide. It is estimated that each year breast cancer will be diagnosed in 1.7 million women and cause 520000 deaths around the world. Furthermore, it is estimated that breast cancer alone accounts for 25% of all cancer cases and 15% of all cancer deaths among females^[1]. Despite the widespread use of breast cancer screening, leading to detection at early stages^[2] and despite ongoing progress in adjuvant treatment strategies^[3], still many women will develop metastatic disease and eventually die from breast cancer. Hence, new treatment modalities are needed, especially in order to treat breast cancer metastases.

Sorafenib (Nexavar[®], Bayer and Onyx Pharmaceuticals) is a small molecule, which acts as an inhibitor of various tyrosine kinases, including BRAF, C-RAF, vascular endothelial growth factor receptor and platelet-derived growth factor receptor, RET, c-KIT and FMS-like tyrosine kinase-3^[4-6]. Sorafenib is administered orally, and it is approved for the treatment of advanced renal cell carcinoma, advanced hepatocellular carcinoma, and advanced thyroid cancer^[6-8]. Its possible mechanisms of anti-tumor action include inhibition of tumor growth and tumor progression, inhibition of metastasis and angiogenesis, as well as down-regulation of mechanisms that protect tumors from apoptosis^[6-8]. The clinical application of sorafenib, especially in the treatment of renal cancer, is based on its activity on angiogenesis

inhibition, and parallels other anti-angiogenic agents^[9]. Since targeting angiogenesis has been also a valid approach in the treatment of advanced breast cancer, the role of sorafenib, was investigated for this indication as well^[10]. The aim of the present study was to evaluate the current role of sorafenib in the treatment of breast cancer, especially its efficacy and safety profile, based on available evidence from clinical trials.

MATERIALS AND METHODS

An extensive search of the literature was carried out in the bibliographic database Medline for articles ever published until March 2016, by using the search terms "sorafenib" and "breast cancer" in the field "Title". No other limits or filters were used, including no limits for language and year of publication. A further search was conducted in clinicaltrials.gov, a public database of registered clinical trials, by using the same key-words, *i.e.*, "sorafenib" and "breast cancer".

Inclusion criteria included published and ongoing clinical trials evaluating the efficacy and toxicity of sorafenib in early and advanced breast cancer. Exclusion criteria included the following study characteristics: Case reports, animal and *in vitro* studies, clinical trials with inconclusive information and clinical trials in various cancer types besides breast cancer.

At first, the titles of studies were screened and irrelevant publications were excluded. Evaluation of the abstract of the remaining studies followed. Finally, the content of the main text of identified studies was evaluated. The lists of references^[11-13], were searched in order to identify possibly additional articles meeting the inclusion criteria. A meta-analysis was not possible due to extensive differences between studies.

RESULTS

Thirty-six papers were found by the Medline search and 30 clinical trials by the clinicaltrials.gov search. After screening the titles, abstracts and/or the full-texts of these studies, 21 relevant trials were identified; most of these studies involved patients with metastatic (16 studies) and/or advanced breast cancer (stages III-IV; two studies), while three studies involved patients with breast cancer stages I -III. An overview of these clinical trials is presented in Table 1.

Among studies in metastatic and/or advanced breast cancer, there were two trials with sorafenib as monotherapy^[13-15], three trials of sorafenib in combination with paclitaxel^[16,17], one trial of sorafenib in combination with docetaxel and/or letrozole^[18], two trials of sorafenib in combination with capecitabine^[19,20] and one with gemcitabine and/or capecitabine^[21]. In stage IV disease there was also one trial of sorafenib in combination with vinorelbine^[22], one with bevacizumab^[23], one with pemetrexed^[17] and one with ixabepilone^[24].

Regarding endocrine therapy in metastatic breast

Table 1 Overview of clinical trials evaluating sorafenib in breast cancer treatment

Ref.	Regimen	Study design	Number of patients	Disease stage	Toxicity	Clinical efficacy
Moreno-Aspitia <i>et al</i> ^[14]	Sorafenib as monotherapy	Phase II; 1 arm	23	Stage IV	Manageable	Low
Bianchi <i>et al</i> ^[15]	Sorafenib as monotherapy	Phase II; 1 arm	54	Stage IV	Manageable	Low
Gradishar <i>et al</i> ^[16]	Sorafenib + paclitaxel	RCT (<i>vs</i> placebo)	237	Stage IV	Manageable	Better TTP
NCT00622466 (ongoing) ^[17]	Sorafenib + paclitaxel	RCT (<i>vs</i> placebo)	41	Stage IV	NA	NA
NCT00499525 (ongoing) ^[17]	Sorafenib + paclitaxel	RCT (<i>vs</i> placebo)	180	Stages III-IV	NA	NA
Mariani <i>et al</i> ^[18]	Sorafenib + docetaxel and/or letrozole	RCT (<i>vs</i> placebo)	218	Stage IV	Manageable	Not better
Baselga <i>et al</i> ^[19]	Sorafenib + capecitabine	RCT (<i>vs</i> placebo)	229	Stage IV	High	Better PFS
Baselga <i>et al</i> ^[20] (ongoing)	Sorafenib + capecitabine	RCT (<i>vs</i> placebo)	519	Stage IV	NA	NA
Schwartzberg <i>et al</i> ^[21]	Sorafenib + gemcitabine and/or capecitabine	RCT (<i>vs</i> placebo)	160	Stages III-IV	Manageable	Better PFS
Luu <i>et al</i> ^[22]	Sorafenib + vinorelbine	Phase I/ II; 1 arm	11/35	Stage IV	Manageable	Low
Mina <i>et al</i> ^[23]	Sorafenib + bevacizumab	Phase II; 1 arm	18	Stage IV	Substantial	Low
NCT02624700 (ongoing) ^[17]	Sorafenib + pemetrexed	Phase II; 1 arm	35	Stage IV	NA	NA
Yardley <i>et al</i> ^[24]	Sorafenib + ixabepilone	Phase I/ II; 1 arm	10/76	Stage IV	High	Low
Isaacs <i>et al</i> ^[25]	Sorafenib + anastrozole	Phase I/ II; 1 arm	35	Stage IV	High	Benefit 23%
Massarweh <i>et al</i> ^[26]	Sorafenib + endocrine therapy ¹	Phase II; 1 arm	11	Stage IV	Manageable	Promising ⁴
NCT00634634 (ongoing) ^[17]	Sorafenib + letrozole	Phase I/ II; 1 arm	54	Stage IV	NA	NA
NCT01724606 (ongoing) ^[17]	Sorafenib + WBRT ²	Phase I	24	Stage IV	NA	NA
NCT01621906 (ongoing) ^[17]	Sorafenib + WBRT (18F-FLT-PET <i>vs</i> MRI)	Diagnostic	20	Stage IV	NA	NA
Spigel <i>et al</i> ^[27]	Sorafenib + AC-T ²	One arm	45	Stages I-III	Limited	NA
Loibl <i>et al</i> ^[28]	Sorafenib + EC-T ³	Phase II	36	Stages II -III	Manageable	pCR 27.7%
Bazzola <i>et al</i> ^[29]	Sorafenib + letrozole + cyclophosphamide ³	One arm	13	Stages II -III	Tolerable	Clinical /no pCR

¹Tamoxifen or anastrozole or letrozole or exemestane or fluevestrant; ²Adjuvant; ³Neoadjuvant; ⁴With tamoxifen. WBRT: Whole brain radiotherapy; NA: Not available; pCR: Pathological complete response; PET: Positron emission tomography; MRI: Magnetic resonance imaging.

cancer, there were three trials evaluating sorafenib in combination with endocrine therapy: One in combination with anastrozole^[25], one in combination with tamoxifen or anastrozole or letrozole or exemestane or fluevestrant^[26] and one in combination with letrozole^[17]. Finally, two trials were found, involving patients with brain metastases undergoing whole brain radiotherapy^[17].

In breast cancer stages I -III, there was one trial of sorafenib added to standard AC-T chemotherapy in the adjuvant setting^[27], and two trials in the neoadjuvant setting in stages II -III, one in combination with standard EC-T chemotherapy^[28] and one in combination with letrozole and cyclophosphamide^[29].

DISCUSSION

Sorafenib, a multiple tyrosine kinase inhibitor, is an orally administered small molecule, which has been evaluated in numerous clinical trials in breast cancer patients. The present study aimed to clarify the current role of sorafenib in breast cancer treatment.

Most clinical trials identified in our study involved patients with advanced and/or metastatic breast cancer. Sorafenib as a single agent was administered in two phase II clinical trials involving 23^[14] and 54 patients^[15] with stage IV breast cancer; in both studies, toxicity was clinically manageable, whereas efficacy was limited, precluding future application of sorafenib monotherapy in breast cancer.

In a multi-national, randomized, placebo-controlled trial, involving 237 patients with metastatic breast cancer, sorafenib was added to paclitaxel^[16]; toxicity was

manageable with dose reduction; time to progression and overall response were significantly improved; however progression-free survival and overall survival did not differ significantly. Results from two ongoing randomized, placebo-controlled trials (NCT00622466 and NCT00499525^[17]) evaluating the same combination are awaited. In another randomized, placebo-controlled trial, published only in abstract form, involving 218 patients with metastatic breast cancer, sorafenib was added to docetaxel and/or letrozole^[18]; though toxicity was manageable, no improvement in terms of efficacy was found.

Baselga *et al*^[19] reported the results of a phase II B trial, involving 229 patients with HER-2-negative metastatic breast cancer; patients were randomly assigned to first- or second-line capecitabine in combination with sorafenib or placebo; though the addition of sorafenib to capecitabine significantly improved progression free survival, there was no significant improvement for overall survival and overall response, and the dose of sorafenib (400 mg twice daily) resulted in unacceptable toxicity for many patients. These findings led to the initiation of RESILIENCE^[20], an ongoing multi-national, randomized, placebo-controlled, phase III confirmatory trial in HER-2-negative, stage IV, breast cancer patients, comparing capecitabine plus a reduced initial sorafenib dose and possible dose-escalation with capecitabine plus placebo; enrollment began in November 2010 with a target of approximately 519 patients. In a similar study, published by Schwartzberg *et al*^[21], 160 HER-2-negative patients with locally advanced or metastatic breast cancer whose disease progressed during or after bevacizumab were randomized to chemotherapy plus sorafenib or chemotherapy plus placebo; initially,

chemotherapy was gemcitabine, but later, capecitabine was allowed as an alternative; the addition of sorafenib provided a statistically significant progression-free survival benefit, with manageable toxicities but frequent dose reductions.

Combinations of sorafenib with other agents in metastatic breast cancer have shown less promising results. In particular, the combination of sorafenib with vinorelbine in a phase I and II study with 11 and 35 patients with metastatic breast cancer, respectively, showed manageable toxicity but low efficacy; the authors concluded that this combination may be of interest if specific biomarkers guiding patient selection can be identified^[22]. The combination of sorafenib with bevacizumab in a phase II, one arm study, involving 18 patients had substantial toxicity and minimal efficacy^[23]. Likewise, in a Phase I and II study with 10 and 76 patients with metastatic breast cancer, respectively, the combination of ixabepilone and sorafenib was poorly tolerated and the activity of the combination was similar to the activity previously reported with single-agent ixabepilone or taxanes^[24]. Results from an ongoing study (NCT02624700)^[17] in stage IV breast cancer evaluating the combination of sorafenib with pemetrexed are awaited.

Regarding sorafenib in combination with endocrine therapy in hormone receptor positive metastatic breast cancer, results from two trials have been reported^[25,26]. In a phase I/II trial, involving 35 patients who had disease recurrence or progression while on aromatase inhibitors, the combination of sorafenib with anastrozole was associated with an encouraging clinical benefit rate of 23%, suggesting that sorafenib may be able to restore sensitivity to hormone therapy; however, this combination was associated with significant toxicity^[25]. In a pilot phase II study, involving 11 patients, sorafenib was added to endocrine therapy, to tamoxifen in 7 cases, and in one case each to anastrozole, letrozole, exemestane and fulvestrant; toxicity was manageable with promising results in terms of efficacy, since most patients developed stable disease^[26]. Results from an ongoing study (NCT00634634) evaluating the combination of sorafenib with letrozole are awaited^[17].

A special issue in metastatic breast cancer is the administration of sorafenib to patients with brain metastases, undergoing whole brain radiotherapy (WBRT). In an ongoing phase I clinical trial (NCT01724606)^[17], the safety and efficacy of this combination is under evaluation. Another ongoing study (NCT01621906)^[17] from the same center compares 18F-FLT-PET with MRI as imaging methods in the evaluation of response to treatment with sorafenib and WBRT.

Finally, the addition of sorafenib to chemotherapy in the adjuvant and neoadjuvant setting has been evaluated in three clinical trials^[27-29]. In a pilot, one arm study^[27], 45 patients with node-positive or high-risk early-stage breast cancer (stages I - III) received adjuvant doxorubicin and cyclophosphamide followed by paclitaxel and sorafenib; though sorafenib was generally associated with limited

severe toxicity, many patients discontinued sorafenib early; the authors concluded that additional studies of sorafenib in breast cancer in the neoadjuvant and triple-negative settings are warranted. In SOFIA^[28], a phase II, single arm clinical trial, 36 HER-2-negative patients with stage II - III disease received neoadjuvant EC (epirubicin plus cyclophosphamide) in 3-weekly cycles followed or preceded by 12 wk of paclitaxel; sorafenib was added to EC or paclitaxel or the whole chemotherapy regimen; the authors concluded that the addition of sorafenib to this regimen is feasible if the starting dose is 200 mg, escalated every 3 wk based on patients' individual toxicities. In another single-arm study in the neoadjuvant setting^[29], 13 estrogen receptor-positive, postmenopausal, breast cancer patients with stage II - III disease received for 6 mo the combination of letrozole, metronomic cyclophosphamide and sorafenib; the combination was well tolerated, and although no pathological complete response was found, still clinical response rates were promising.

In conclusion, sorafenib is generally well tolerated in breast cancer patients with either metastatic disease or at earlier stages. However, in some clinical trials sorafenib discontinuation rates were high or sorafenib dosage had to be adjusted, due to unacceptable toxicity. To date, sorafenib as a single agent and combinations of sorafenib with taxanes, bevacizumab and ixabepilone have shown inadequate efficacy. More promising efficacy results came from clinical trials with sorafenib in combination with gemcitabine and/or capecitabine and possibly tamoxifen. At present, sorafenib should not be routinely administered for the treatment of breast cancer outside of clinical trials. More evidence from ongoing and future clinical trials should clarify the possible role of sorafenib in the treatment of breast cancer patients.

COMMENTS

Background

Sorafenib is a small molecule, acting as an inhibitor of various tyrosine kinases; it is approved for the treatment of advanced renal cell carcinoma, advanced hepatocellular carcinoma, and advanced thyroid cancer. Its possible mechanisms of action include inhibition of tumor growth, progression, metastasis and angiogenesis and down-regulation of mechanisms protecting tumors from apoptosis. The clinical application of sorafenib, especially in renal cancer, is based on its anti-angiogenesis activity. Since targeting angiogenesis has been also a valid approach in the treatment of advanced breast cancer, the role of sorafenib, was investigated for this indication as well. The aim of the present study was to evaluate the current role of sorafenib in the treatment of breast cancer, based on available evidence from clinical trials.

Research frontiers

Sorafenib is being evaluated in combination with various chemotherapeutic and/or endocrine agents, especially in the treatment of advanced breast cancer. The current hotspot of research is the clinical application of sorafenib in breast cancer therapy in combination with various agents, in order to improve treatment efficacy with an acceptable toxicity profile.

Innovations and breakthroughs

In this systematic review of the literature, the role of sorafenib in the treatment of breast cancer was evaluated. Overall, 21 relevant studies were identified, 18 in advanced breast cancer (16 in stage IV and two in stages III-IV) and three

in early breast cancer. In advanced breast cancer, there were two trials with sorafenib as monotherapy, four trials of sorafenib in combination with taxanes, two with capecitabine, one with gemcitabine and/or capecitabine, one with vinorelbine, one with bevacizumab, one with pemetrexed, one with ixabepilone, three trials with endocrine therapy and two trials in women with brain metastases undergoing whole brain radiotherapy. In early breast cancer, there was one trial of sorafenib added to standard chemotherapy in the adjuvant setting, and two trials in the neoadjuvant setting. In terms of efficacy, sorafenib monotherapy and combinations with taxanes, bevacizumab and ixabepilone showed inadequate efficacy, while results from combinations with gemcitabine and/or capecitabine and possibly tamoxifen were more promising. In terms of toxicity, sorafenib was well tolerated in breast cancer patients, though its dosage had to be adjusted in some trials, and discontinuation rates were high, particularly for the combination of sorafenib with anastrozole.

Applications

At present, sorafenib should not be used for the treatment of breast cancer outside of clinical trials; more clinical data are needed in order to support its standard use in breast cancer therapy.

Terminology

Sorafenib (Nexavar®, Bayer and Onyx Pharmaceuticals): A small molecule, administered orally. Sorafenib is approved for the treatment of the following types of cancer: Advanced renal cell carcinoma, advanced hepatocellular carcinoma, and advanced thyroid cancer. Sorafenib chemical mechanism of action: Inhibition of various tyrosine kinases, including BRAF, C-RAF, vascular endothelial growth factor receptor and platelet-derived growth factor receptor, RET, c-KIT and FMS-like tyrosine kinase-3. Sorafenib biological mechanism of action: Inhibition of tumor growth, progression, metastasis and angiogenesis and down-regulation of mechanisms protecting tumors from apoptosis. Rationale for clinical application of sorafenib: Mainly its activity on angiogenesis inhibition, especially in advanced renal cancer. Tumor angiogenesis: Formation of new blood vessels by malignant tumors.

Peer-review

This is an excellent and well designed article.

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