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Retrospective Study

Risk of second primary malignancies in a population-based study of adult patients with essential thrombocythemia

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Abstract

AIM: To determine the risk of second primary malignancy (SPM) and survival of patients with essential thrombocythemia (ET).

METHODS: We identified all patients with ET diagnosed during 2001 to 2011 from the Surveillance, Epidemiology and End Results (SEER) 18 database. Actuarial and relative survival methods were used to calculate the survival statistics. We utilized the SEER 13 database to calculate SPM. We used multiple primary standardized incidence ratio (SIR) session of the SEER*Stat software (version 8.1.5) to calculate SIR and excess risk of SPM for ET patients.

RESULTS: Age standardized five-year cause-specific survival was greater for patients < 50 years *vs* those ≥ 50 years (99.4% *vs* 93.5%, *P* < 0.01). Five-year cause-

specific survival was lower for men *vs* women (70.2% *vs* 79.7%). A total of 201 patients (2.46%) developed SPM at a median age of 75 years. SPMs occurred at an observed/expected (O/E) ratio of 1.26 (95%CI: 1.09-1.45, $P = 0.002$) with an absolute excess risk (AER) of 37.44 per 10000 population. A significantly higher risk was noted for leukemia (O/E 3.78; 95%CI: 2.20-6.05, $P < 0.001$; AER 11.28/10000).

CONCLUSION: ET patients have an excellent cause-specific five-year survival but are at an increased risk of SPM, particularly leukemia, which may contribute to excess deaths.

Key words: Essential thrombocythemia; Second primary malignancy; Survival

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Core tip: Second primary malignancy (SPM) contributes to worse survival in essential thrombocythemia (ET). We utilized the Surveillance, Epidemiology and End Results database to analyze the risk of SPM in ET patients diagnosed during 2001-2011. Two hundred and one patients (2.46%) developed SPM at a median age of 75 years. SPMs occurred at an observed/expected (O/E) ratio of 1.26 (95%CI: 1.09-1.45, $P = 0.002$) with an absolute excess risk of 37.44 per 10000 population. A significantly higher risk was noted for leukemia (O/E 3.78; 95%CI: 2.20-6.05, $P < 0.001$). An increased risk of SPM, particularly leukemia, may contribute to excess deaths in ET.

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INTRODUCTION

Essential thrombocythemia (ET) is a subtype of myeloproliferative disorder, which lacks BCR-ABL fusion transcript^[1,2]. In United States, the estimated annual incidence is approximately 2.5 cases per 100000 population, whereas the prevalence is estimated to be approximately 24 cases per 100000 population^[3,4]. Patients with ET generally have an excellent survival. A large study has shown a median survival of 20 years for the entire cohort of patients with ET and a median survival of 33 years for those < 60 years. Nonetheless, the life expectancy of patients with ET is inferior to sex- and age-matched population^[5]. Another study has also demonstrated a median survival of approximately 19 years but the survival was worse than the general population, particularly after the first

decade^[6]. Risk factors associated with inferior survival include advanced age at diagnosis, leukocytosis and thrombosis; the mutational status of janus kinase 2 (JAK2) and calreticulin (CALR) genes may not definitely influence survival^[7-9]. The thrombohemorrhagic events and second primary malignancy (SPM) are among the frequent causes of death in ET^[10-12]. ET may progress to other myeloid malignancies such as myelofibrosis, myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)^[2,12]. The probability of transformation to leukemia is 1%-5% during the first decade but increases significantly in the subsequent decades^[2,6]. Additionally, patients with ET may also develop lymphoid malignancies such as non-Hodgkin's lymphoma (NHL) and solid organ malignancies^[13,14]. The treatment with cytotoxic chemotherapy decreases the incidence of thrombohemorrhagic events but may increase the risk of hematological SPM^[2]. The risk of SPM may be high in patients exposed to alkylating agents and radioactive phosphorus, more so when used in high doses^[2,12,15,16]. A study from Italy has demonstrated that the use of alkylating agents such as melphalan may be associated with a higher risk of developing second hematologic malignancies but not non-hematological malignancies^[17]. Prior studies assessing the risk of SPM in ET utilized data mainly from outside the United States. Although the risk of MDS/AML in ET has been studied, the risk of other malignancies is not well determined in United States population-based studies. This United States population-based database analysis aimed to determine the probability of SPM and survival in patients with ET^[18]. The influence of age at diagnosis and disease duration on the probability of SPM was also analyzed.

MATERIALS AND METHODS

We utilized Surveillance, Epidemiology and End Results (SEER) database to extract data on all ET patients diagnosed and treated between 1973 and 2011. The SEER is a program of the National Cancer Institute (NCI) that provides cancer data from population-based cancer registries and covers 28% of the total United States population. The database covers data from 25% of all White population, 26% of African Americans, 38% of Hispanics, 50% of Asians, 44% of American Indians and Alaska Natives and 67% of Hawaiian/Pacific Islanders^[19]. Patients with ET were identified using International Classification of Diseases for oncology, 3rd edition (ICD)-O-3 code 9962/3 from the SEER 18 registry. Prior studies have used a similar approach in identifying patients with ET from the SEER database^[20,21]. Cases with unknown age or survival time and those diagnosed at autopsy and by death certificate only were excluded. SEER started reporting data on chronic myeloproliferative disorders including ET from 2001; as a result our analysis was restricted to cases diagnosed after 2001 only^[21]. Actuarial and relative survival methods were used to calculate the survival statistics. We computed

Table 1 Characteristics of patients with essential thrombocythemia

Characteristics	n (%)
Age	
< 50 yr	1600 (19.7)
50-70 yr	2958 (36.5)
> 70 yr	3558 (43.8)
Sex	
Male	3195 (39.4)
Female	4921 (60.6)
Race	
White	6332 (78)
African American	971 (12)
Other ¹	576 (7.1)
Unknown	237 (2.9)
Marital status	
Single/unmarried	1152 (14.2)
Married	3815 (47)
Divorced/separated/widowed	2125 (26.2)
Unknown	1024 (12.6)
Year at diagnosis	
2001-2005	3035 (37.3)
2006-2010	4251 (52.4)
2011-present	840 (10.3)

¹Other race indicates Asian, Hispanic, Native North American and other racial groups.

age-standardized cause-specific survival using the cause-specific death classification available from the SEER registry. Cause-specific survival is a net survival measure that computes survival from cancer related causes of death in the absence of other causes of death. A prior study from SEER registry has shown that cause-specific survival rates may be a reliable alternative to relative survival methods when suitable life tables are not available^[22]. Relative survival rate, which measures net cancer survival controlling for differences in mortality for causes other than cancer, was defined as the ratio of observed survival of a group of cancer patients to the expected survival of a comparable cohort of cancer free patients. Expected survival was computed using the Ederer II method. All calculations were age standardized to the International Cancer Survival Standard for age 15+ years^[23].

For the calculation of SPM, we utilized the SEER 13 registry using patients with ET diagnosed between 2001-2010. Using Warren and Gates criteria as modified by NCI^[24], SPM was defined as a metachronous malignancy developing at least six months after the diagnosis of ET. A similar approach for the definition of SPM has been used in prior SEER based studies^[25,26]. We used multiple primary standardized incidence ratio (SIR) session of the SEER*Stat software (version 8.1.5) to calculate SIR and absolute excess risk (AER) of SPM for ET patients. SIR is obtained by dividing the observed number of second malignancies by the expected number of cases that would occur in a reference population without the index malignancy. Confidence intervals (at 95%) and *P*-values were calculated using Poisson exact methods for the ratio of observed to expected events.

AER was defined as the excess (observed-expected) number of second cancers in patients with index ET, per 1000 person years at risk. For patients who developed more than one malignancies after the primary disease, all of the subsequent malignancies were counted in the numerator for the calculation of SIR. The strata for SPMs were defined as a priori, and we included at least ten observed occurrences in each stratum.

Statistical analysis was done using SEERstat version 8.1.5 (National Cancer Institute, Bethesda, Maryland) and STATA (Stata-Corp, College-Station, Texas). Differences between survival rates of two groups were analyzed using the *Z* test for comparison of population proportions. All *P*-values were two sided and the level of significance was chose at 0.05. Institutional review board waiver was obtained from the University of Nebraska Medical Center Institutional Review Board prior to conducting this study.

RESULTS

A total of 8152 cases were identified from the SEER 18 registry, out of which 36 cases met the exclusion criteria (23 had unknown survival and 13 cases diagnosed prior to 2001). The remaining 8116 cases included 39.4% males (*n* = 3195) and 60.6% (*n* = 4921) females, and had a median age at diagnosis of 68 years (range < 1-107) (Table 1). Only 17 patients were less than 18 years old (0.7% of total). Ethnicity included 78% Whites, 12% African Americans, 7% others (American Indian/Alaska Native or Asian/Pacific Islander) and 3% unknown. The median year at diagnosis was 2007 (range 2001-2011).

The overall 1-year and 5-year age-standardized cause-specific survival of the study cohort was 99.1% and 94.9% respectively. The 5-year cause-specific survival was significantly different for patients below 50 years vs those 50 years and above (99.4% vs 93.5%; *P* < 0.01; Figure 1A) as well as for men vs women (93.1% vs 96.0%; *P* < 0.01; Figure 1B) (Table 2). Similarly, the age-standardized 1-year and 5-year relative survival rates were 96.6% and 88.4% respectively.

At a median follow-up of 3 years (range, 6-129 mo), 201 patients (2.46%) out of 2913 patients with ET developed SPM. The median age at diagnosis was 75 years (range, 39-94 years). None of the patients less than 18 years old developed SPM. SPMs occurred at an SIR of 1.26 (95%CI: 1.09-1.45; *P* = 0.002) with an AER of 37.44 per 10000 population. The risk for developing leukemia (SIR 3.78; 95%CI: 2.20-6.05, *P* < 0.001; AER 11.28/10000), particularly AML (SIR 7.74; 95%CI: 3.71-14.24, *P* < 0.001; AER 7.86/10000), and kidney cancer (SIR 2.40; 95%CI: 1.15-4.42, *P* = 0.01; AER 5.27/10000) was high (Table 3).

The risk of SPM was higher after 24 mo of diagnosis of ET (Table 4). Before 24 mo, the risk of development of leukemia (O/E 3.88, CI: 1.42-8.44, *P* < 0.05), particularly AML (O/E 9.02, CI: 2.46-23.09, *P* < 0.05) was noted to be higher than expected. After a follow-up

Table 2 Age standardized cause-specific survival rates of the study population

Survival at defined time period	Entire cohort	Male	Female	Patients < 50 yr	Patients ≥ 50 yr
12 mo	99.10%	98.80%	99.30%	99.90%	98.90%
24 mo	98.30%	97.80%	98.70%	99.80%	97.90%
36 mo	97.20%	96.20%	97.90%	99.70%	96.50%
48 mo	96.10%	94.80%	96.90%	99.70%	95.00%
60 mo	94.90%	93.10%	96.00%	99.40%	93.50%

The percentage indicates cause-specific survival of specified population at defined time period.

Table 3 Risk of second primary malignancies among the study population

SPM	Observed	SIR	95%CI	AER	P-value
All sites	201	1.26	1.09-1.45	37.44	0.002
Solid	162	1.15	0.98-1.35	19.43	0.074
Colorectal	12	0.66	0.34-1.15	-5.62	0.916
Lung/bronchus	31	1.31	0.89-1.86	6.67	0.133
Breast	24	1.06	0.68-1.58	1.29	0.743
Prostate	24	1.11	0.71-1.65	2.14	0.594
Kidney	10	2.40	1.15-4.42	5.27	0.014
Lymphoma	12	1.59	0.82-2.78	4.02	0.127
Leukemia	17	3.78	2.20-6.05	11.28	< 0.001
AML	10	7.74	3.71-14.24	7.86	< 0.001

AER: Absolute excess risk; SIR: Standardized incidence ratio; SPM: Second primary malignancies.

of 24 mo, the risk of SPM in general (O/E 1.31, 95%CI: 1.1-1.55, $P = 0.002$), kidney cancer (O/E 3.27, 95%CI: 1.5-6.21, $P = 0.003$), and leukemia (O/E 3.72, 95%CI: 1.86-6.66, $P < 0.001$), particularly AML (O/E 7.08, 95%CI: 2.6-15.4, $P < 0.001$) was determined to be higher.

The risk of AML was noted to be higher among all age groups (Table 5). The risk of SPM in general (O/E 1.78), solid tumors (O/E 1.75), and AML (O/E 12.7) were noted to be higher among patients 18-60 years old. Among patients ≥ 60 years old, the risk of kidney cancer (O/E 2.42) and leukemia (O/E 3.78), particularly AML (O/E 7.06) was higher.

DISCUSSION

Our study demonstrates excellent age-standardized cause-specific five-year survival with 99.4% of patients below 50 years of age and 93.5% of patients above 50 years of age alive at 5 years. The five-year overall survival was significantly lower in patients over 50 years of age as well as in males as compared to females.

A Mayo clinic study demonstrated significantly higher OS in patients younger than 60 years vs those 60 years or older (32 years vs 19 years, $P < 0.001$). While OS was similar to general population in the first decade of disease [risk ratio (RR), 0.72; 95%CI: 0.50-0.99], OS was significantly worse after the first decade (RR, 2.21; 95%CI: 1.74-2.76, at 20 years and RR, 3.37; 95%CI: 1.84-5.65, at 30 years). This is consistent with fact that the incidence of SPM such as leukemia

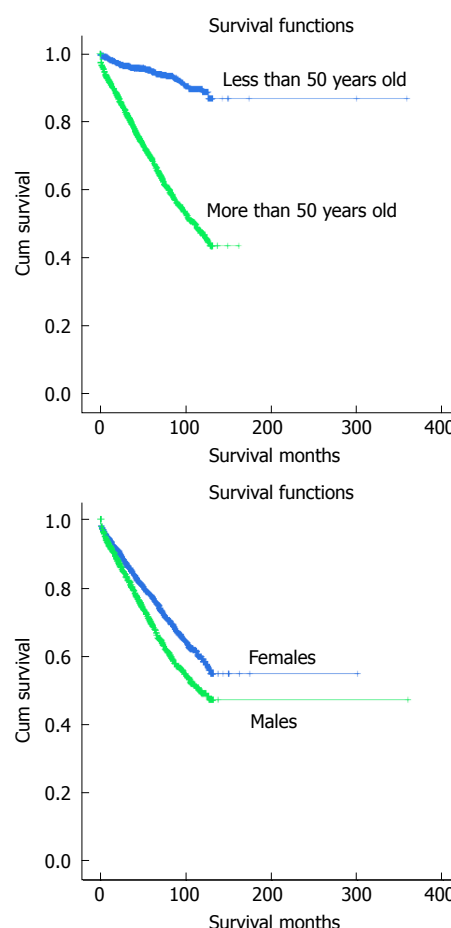


Figure 1 Cumulative survival (Kaplan-Meier estimates) of patients with essential thrombocythemia based on age (A) and gender (B). The log rank test was statistically significant with a P -value of < 0.01 .

and myelofibrosis is higher after the first decade^[6,10,27]. A number of factors may determine the OS of these patients. The prognostic factors associated with the poor outcomes are age at diagnosis of ≥ 60 years, leukocyte count more than $15 \times 10^9/L$, a history of thrombosis, diabetes, hypertension and tobacco smoking^[6].

In our study, a significantly elevated risk was noted for the development of AML and kidney cancer and especially after 24 mo of diagnosis of ET. Such increased risk has been noted in other studies also. In a retrospective population-based Danish cohort study, patients with ET, compared to those without, had a higher risk for developing hematological and solid malignancies with the SIR of 5 (95%CI: 3.6-6.9) and 1.2 (95%CI:

Table 4 Risk of second primary malignancies based on the follow-up duration

SPM	Overall SIR (95%CI)	SIR at 6-23 mo follow-up (95%CI)	SIR at > 24 mo follow-up (95%CI)
All sites	1.26 (1.09-1.45) ¹	1.16 (0.9-1.49)	1.31 (1.1-1.55) ¹
Solid malignancies	1.15 (0.98-1.35)	1.09 (0.82-1.43)	1.18 (0.97-1.43)
Colorectal	0.66 (0.34-1.15)	0.47 (0.10-1.38)	0.76 (0.35-1.44)
Lung/bronchus	1.31 (0.89-1.86)	1.48 (0.76-2.58)	1.23 (0.74-1.92)
Breast	1.06 (0.68-1.58)	0.91 (0.37-1.88)	1.14 (0.66-1.82)
Prostate	1.11 (0.71-1.65)	1.03 (0.45-2.03)	1.15 (0.66-1.87)
Kidney	2.40 (1.15-4.42) ¹	0.71 (0.02-3.95)	3.27 (1.5-6.21) ¹
Hematologic malignancies	2.36 (1.63-3.29) ¹	2.03 (0.97-3.73)	2.53 (1.62-3.76) ¹
Lymphoma	1.59 (0.82-2.78)	1.56 (0.42-3.99)	1.61 (0.69-3.17)
Leukemia	3.78 (2.2-6.05) ¹	3.88 (1.42-8.44) ¹	3.72 (1.86-6.66) ¹
AML	7.74 (3.71-14.24) ¹	9.02 (2.46-23.09) ¹	7.08 (2.6-15.4) ¹

¹Indicates a statistically significant value. AML: Acute myeloid leukemia; SIR: Standardized incidence ratio; SPM: Second primary malignancies.

Table 5 Risk of secondary primary malignancies based on age at the time of diagnosis of essential thrombocythemia

SPM	Overall SIR (95%CI)	SIR for age group, 18-60 yr (95%CI)	SIR for age group, > 60 yr (95%CI)
All sites	1.26 (1.09-1.45) ¹	1.78 (1.31-2.36) ¹	1.15 (0.98-1.35)
Solid tumors	1.15 (0.98-1.35)	1.75 (1.27-2.35) ¹	1.03 (0.85-1.23)
Colorectal	0.66 (0.34-1.15)	1.33 (0.27-3.88)	0.56 (0.26-1.07)
Lungs/bronchus	1.31 (0.89-1.86)	2.36 (0.86-5.13)	1.19 (0.77-1.75)
Breast	1.06 (0.68-1.58)	1.08 (0.40-2.35)	1.06 (0.63-1.67)
Prostate	1.11 (0.71-1.65)	1.91 (0.82-3.76)	0.92 (0.52-1.49)
Kidney	2.40 (1.15-4.42) ¹	2.32 (0.28-8.37)	2.42 (1.05-4.78) ¹
Lymphoma	1.59 (0.82-2.78)	1.72 (0.21-6.23)	1.57 (0.75-2.88)
Leukemia	3.78 (2.2-6.05) ¹	3.74 (0.45-13.51)	3.78 (2.12-6.24) ¹
AML	7.74 (3.71-14.24) ¹	12.73 (1.54-45.98) ¹	7.06 (3.05-13.90) ¹

¹Indicates a statistically significant value. AML: Acute myeloid leukemia; SIR: Standardized incidence ratio; SPM: Second primary malignancies.

1.0-1.4) respectively^[13]. Another retrospective study from Italy ($n = 331$) showed cumulative incidence of SPM of 13% from the time of diagnosis of ET^[17]. The study determined a particularly higher incidence of AML^[17]. The risk of developing AML in ET depends on multiple factors such as old age, decreased hemoglobin and increased platelet count $\geq 1000 \times 10^9/L$ ^[28]. Additionally, the risk increases with longer follow-up, with one study demonstrating a relatively low probability of developing leukemia in the first decade (1.4%) but significantly increased risk in the second (8.1%) and third decades (24.0%)^[6]. The probability of occurrence of AML may also increase with the use of leukemogenic therapy such as radioactive phosphorus (P^{32}) and alkylators such as chlorambucil^[2,7,29,30]. Although the presence of JAK2V617F mutation and cytogenetic abnormalities may not increase the probability of developing leukemia^[2], the probability is increased in the presence of 2 or more somatic mutations^[31].

In our study, the risk of SPM varied based on the age at diagnosis of ET and the follow-up duration. The risk of developing leukemia especially AML was increased after 6 mo of diagnosis of ET and persisted beyond 24 mo of follow-up, consistent with prior studies^[6]. Although patients < 60 years had a higher risk of overall SPM, the increased risk of kidney cancer and leukemia was noted in those above 60 years. Prior studies have shown that

the risk of SPM differed based on the age of patients. In Passamonti study, age > 65 years was determined to be a risk factor for developing SPM including leukemia^[32]. A Danish study demonstrated that the probability of non-hematologic and hematologic malignancies was higher in younger patients (20-49 years vs 50-69 and > 70 years)^[13]. Such conflicting results may be accounted by the differences in the characteristics of patients and other risk factors for SPM in different studies.

Potential limitations of this research are its retrospective study design, possibility of coding errors in the SEER database and inability to obtain data on potential impact of other factors such as therapy or other risk factors for SPM such as smoking. Detection bias is another potential shortcoming of the study, since many asymptomatic malignancies may be over diagnosed because of closer follow-up of patients following the diagnosis of ET. The strength of this study includes real world data from a relatively large number of ET patients. Our study demonstrated that patients with ET have an excellent five-year survival. Besides bleeding and thrombotic events, patients diagnosed with ET are also at risk of developing SPM. The risk of leukemia, particularly AML, can affect patients of all age groups and persists over time. Clinical trials on early detection of SPM may be considered in patients with ET. Additionally, patients with ET should be encouraged to undergo age and sex-

appropriate cancer screening tests.

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COMMENTS

Background

Patients with essential thrombocythemia (ET) have an excellent cause-specific five-year survival but are at an increased risk of second primary malignancy (SPM), particularly leukemia, which may contribute to excess deaths.

Research frontiers

A few United States studies have evaluated the risk of myelodysplastic syndrome/acute myeloid leukemia (AML) in ET but not the risk of other hematological or solid-organ malignancies.

Innovations and breakthroughs

This large Surveillance, Epidemiology and End Results database-based study confirmed an increased risk of SPM in patients with ET. A significantly higher risk was noted for leukemia. An increased risk of SPM, particularly leukemia, may contribute to excess deaths in ET. The risk of developing leukemia especially AML was increased after 6 mo of diagnosis of ET and persisted beyond 24 mo of follow-up, consistent with prior studies. Prior studies have shown conflicting results on the impact of age on the risk of SPM. In this study, the risk of overall SPM was higher in patients younger than the age of 60 years, however, the increased risk of kidney cancer and leukemia was noted in those above 60 years. The risk of leukemia, particularly AML, can affect patients of all age groups and persists over time.

Applications

The knowledge of an increased risk of SPM in patients with ET has implications in patient education, planning of preventive cancer screening strategies and may serve as a foundation for future research targeted at understanding the tumorigenesis in these patients.

Terminology

SPM: A metachronous malignancy developing at least six months after the diagnosis of ET; Relative survival rate: Ratio of observed survival of a group of cancer patients to the expected survival of a comparable cohort of cancer free patients. It measures net cancer survival controlling for differences in mortality for causes other than cancer; Cause-specific survival: A net survival measure that computes survival from cancer-related causes of death in the absence of other causes of death; Standardized incidence ratio: Ratio obtained by dividing the observed number of second malignancies by the expected number of cases in a reference population without the index malignancy; Absolute excess risk: Excess (observed-expected) number of second cancers in patients with ET, per 1000 person years at risk.

Peer-review

The paper is about an interesting topic. It is well written and the methods are sound. The conclusions are consistent with the results.

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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-angiogenetic 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 of relevant studies, including relevant review articles^[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	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 fluvastatin; 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 fluvastatin^[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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