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ORIGINAL ARTICLE

The efficacy and safety of thalidomide for treating metastatic breast cancer: a systematic review

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Abstract

Objective This systematic review was conducted to investigate the efficacy and safety of thalidomide in metastatic breast cancer (MBC).

Methods Based on pre-defined inclusion and exclusion criteria, data were independently collected from different databases by three investigators. Overall, three studies were included.

Results The included studies indicated that no patient achieved a partial or complete response from different thalidomide dose levels. Thalidomide was well-tolerated at doses of 100 mg, 200 mg, and 400 mg. In all three studies, common side effects included constipation, somnolence, fatigue, peripheral neuropathy, and dry mouth. Circulating angiogenic factors were not significantly correlated with disease progression.

Conclusion The available evidence indicates that single-agent thalidomide has little or no activity in patients with MBC.

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Key words: thalidomide; metastatic breast cancer (MBC); vascular endothelial growth factor (VEGF); tumor necrosis factor-α (TNF-α)

In the late 1950s, thalidomide was synthesized as a non-addictive, non-barbiturate sedative by a German pharmaceutical company. Later, it was discovered that thalidomide was an effective antiemetic and was used to control the symptoms of nausea and vomiting in pregnant women. In 1961, thalidomide was confirmed as the cause of the largest man-made medical disaster in history, with an estimated 10 000 children in 46 countries born with birth defects. Subsequently, thalidomide was withdrawn from the market in most countries. Over the next few decades, its immunomodulatory and antiangiogenic functions were revealed, resulting in novel therapeutic indications. In 1965, Jacob Sheskin serendipitously discovered that its immunomodulatory effects can be used to treat erythema nodosum leprosum (ENL) [1]. In 1994, Robert J. D'Amato [2] and colleagues discovered that orally administered thalidomide inhibits angiogenesis induced by basic fibroblast growth factor (bFGF) in a rabbit corneal micropocket assay. Based on these mechanisms, thalidomide was found to be highly effective in multiple myeloma treatment [3]. Currently, thalidomide is being evaluated for its efficacy in treating solid tumors, such as prostate cancer, glioblastoma, and neck squamous cell carcinoma [4].

Breast cancer is the most common cancer among females worldwide. With early tumor diagnosis, the five-year survival rate is up to 99%. Moreover, several patients remain disease-free throughout their lifetime [5]. However, breast cancer continues to cause more than 0.5 million deaths annually, with over 90% of deaths attributed to metastasis [6]. When cancer cells exit the primary site and spread to various organs, they must undergo several sequential steps. To achieve each step, cancer cells encounter multiple natural barriers, challenging the defined organization and established homeostasis of target organs. Abnormal tumor vessels demonstrate reduced perivascular cell (PVC) coverage, endothelial cell (EC) dissociation, and excess tumor vessel permeability, presenting opportunities for cells to metastasize [7]. In neoplasms, thalidomide exerts anti-inflammatory, anti-proliferative, and antiangiogenic activities [8]. A preclinical experiment utilizing the 4T1 breast cancer cell line has suggested that thalidomide reduces tumor volume and metastasis. The levels of two

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cytokines, vascular endothelial growth factor (VEGF) and tumor necrosis factor-α (TNF-α) decrease in thalidomide-treated tumor samples when compared with the control group [9]. Currently, thalidomide is tentatively used to treat some cancers, including breast cancer [10–12].

To date, no systematic review has investigated the efficacy and safety of thalidomide monotherapy for treating metastatic breast cancer (MBC). Consequently, we performed a systematic review to gain a perspective on thalidomide use for MBC treatment.

Materials and methods

Search strategy

PubMed, Biomedical Central, Google Scholar, and Cochrane databases were searched using combinations of the following terms: metastatic breast cancer/metastatic breast carcinoma, thalidomide. PubMed – metastatic breast cancer AND thalidomide (limited to English), metastatic breast carcinoma AND thalidomide (limited to English); Biomedical Central – metastatic breast cancer AND thalidomide; Google Scholar – metastatic breast cancer AND thalidomide; Cochrane – metastatic breast cancer AND thalidomide. The search was performed on November 3, 2015. To identify other potentially relevant studies, reference lists from the retrieved studies were searched manually where appropriate.

Selection

Studies were included in the systemic review if they used single-agent thalidomide to treat breast cancer. Studies were excluded if they focused on other stages of breast cancer or failed to analyze efficacy or toxicity.

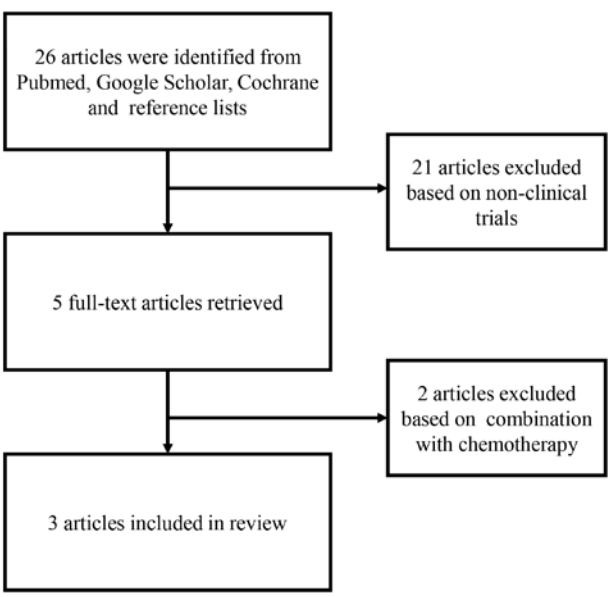

Fig. 1 Flow chart of literature identification and selection process

Data extraction

Data from eligible studies were extracted by two independent reviewers (S.Y.W. and Z.X.M.). Any disagreement was resolved by consulting a third reviewer (Y.J.). The following data were extracted from studies that met the eligibility criteria: author details, publication year, study design, therapeutic regimens, number of patients, patient age, objective response, stable disease, progressive disease, and toxicity response. VEGF, bFGF, and TNF-α levels in patient sera were collected.

Outcome measurement

The primary outcome was the objective response or stable disease with continued treatment until progression. Additionally, toxicity data were summarized. During treatment, serum concentrations of bFGF, TNF-α, and VEGF were measured.

Results

Study selection

In total, 26 articles were identified by searching databases (Fig. 1). After removing 21 non-clinical trials, the full-text of the remaining 5 studies were reviewed, and 2 studies were excluded as thalidomide was combined with chemotherapy. Finally, three studies met the pre-defined criteria and were included in this systematic review.

Study characteristics

The study characteristics and patient clinical data are shown in Table 1. Of the three studies, one was randomly designed, while the others were observational studies. In the study performed by Baidas *et al* [10], 28 patients were randomized based on two thalidomide doses. Overall, 14 patients received a low dose (200 mg/d), and 14 received high-dose (800 mg/d) therapy. Every 2 weeks, an escalation of 200 mg was permitted in the 800 mg/d arm, in patients with no toxicity up to a maximum of 1200 mg/d. In the study undertaken by Eisen *et al* [11], 12 patients with breast cancer were prescribed 100 mg oral thalidomide every night. In the study of Morabito *et al* [12], thalidomide was orally administered at a fixed daily dose of 400 mg for at least 8 weeks. In all three studies, treatment continued until evidence of disease progression or unacceptable toxicity was encountered, or in case the patient wished to discontinue treatment for any reason.

Survival

The prognosis is summarized in Table 2. Based on the investigated thalidomide doses, no patient achieved a partial or complete response. Baidas *et al* reported that

Table 1 Patient characteristics

Characteristic	100-mg daily dose level (*n* = 12)	200-mg daily dose level (*n* = 14)	400-mg daily dose level (*n* = 12)	800-mg daily dose level (*n* = 14)
Age (years)				
30–40	N/A	1	Median 53.5	3
41–50	N/A	7	Range 40–71	2
51–60	N/A	5		4
61–70	N/A	0		4
71–85	N/A	1		1
Prior chemotherapy regimens				
0 or1	N/A	2	N/A	2
2 or 3	N/A	12	9	12
≥ 4	N/A	N/A	3	N/A
High-dose chemotherapy with PBSC support	N/A	3	N/A	2
No. of hormonal therapy courses				
0 or 1	N/A	7	N/A	5
2–4	N/A	7	N/A	9
Site of disease				
Bone only	N/A	1	1	0
Lymph node only	N/A	3	N/A	1
Liver	N/A	1	Viscera (11)	1
Chest	N/A	1	N/A	0
Number of metastatic sites				
1	N/A		1	12
2	N/A	8 (2–4 sites)	4	N/A
3	N/A		6	N/A
≥ 4	N/A		1	N/A
Hormone				
Positive	N/A	N/A	8	N/A
Negative	N/A	N/A	4	N/A

Note: N/A: not applicable

Table 2 Efficacy of thalidomide for inducing remission

Study	Study design	No. of patients	Dose	Rx route	CR + PR	SD	PD
Baidas SM 2000 [10]	RCT	14	200-mg	Po	0	0	13/14
		14	800-mg	Po	0	0	13/14
Eisen T 2000 [11]	Observational study	12	100-mg	Po	0	0	12
Morabito A 2005 [12]	Observational study	12	400-mg	Po	0	0	12

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

two patients receiving the 200-mg dose demonstrated disease stability at 8 weeks [10]. The first patient presented a 43% reduction in hilar size and mediastinal lymphadenopathy (site of measurable disease) at 8 weeks. However, at 16 weeks, the disease had progressed, and the patient was excluded from further participation. This patient had previously received adjuvant chemotherapy with cyclophosphamide and doxorubicin, followed by paclitaxel, and then vinorelbine for metastatic disease. The second patient presented a relatively indolent chest-wall disease, progressing slowly with no treatment over the 20 months preceding thalidomide therapy. At the 8-week staging, the disease had stabilized, but the patient was excluded from further participation at week 11 due to grade 3 peripheral neuropathy. At the 200-mg dose level, one patient was removed from the study at week 2 owing to disease progression. At the 400-mg dose level, the time to disease progression did not exceed 10 weeks. At the 800-mg dose level, the time to progression was within 8 weeks. Morabito *et al* reported that the median time to progression was 8 weeks (range, 4–10 weeks) [12]. The median overall survival was 16 weeks (range, 8–54 weeks).

Table 3 Adverse events with thalidomide use

Adverse effect	100-mg daily dose level (*n* = 12)	200-mg daily dose level (*n* = 14)	400-mg daily dose level (*n* = 12)	800-mg daily dose level (*n* = 14)	% of total patients
Constipation	N/A	3 (21%)	7 (58.3%)	10 (71%)	20 (38.4%)
Somnolence	N/A	4 (29%)	7 (58.3%)	8 (57%)	19 (36.5%)
Fatigue	N/A	6 (43%)	N/A	6 (43%)	12 (23.0%)
Peripheral neuropathy	N/A	5 (36%)	N/A	4 (29%)	9 (17.3%)
Dizziness and instability	N/A	2 (14%)	N/A	4 (29%)	6 (11.5%)
Dry mouth	N/A	2 (14%)	N/A	6 (43%)	8 (15.3%)
Skin rash	N/A	1 (7%)	N/A	2 (14%)	3 (5.7%)
Nausea	N/A	0 (0%)	N/A	2 (14%)	2 (3.8%)
Anorexia	N/A	1 (7%)	N/A	1 (7%)	2 (3.8%)
Arrhythmia	N/A	1 (7%)	N/A	0 (0%)	1 (3.8%)
Neutropenia	N/A	1 (7%)	N/A	1 (7%)	2 (3.8%)
Headaches	N/A	1 (7%)	N/A	1 (7%)	2 (3.8%)
Hypotension	N/A	0 (0%)	N/A	1 (7%)	1 (1.9%)
Asthenia	N/A	N/A	4 (33.3%)	N/A	4 (7.6%)

Note: N/A: not applicable

Side effects

In the three studies, all patients were evaluated for toxic effects (Table 3). Thalidomide was well-tolerated at doses of 100 mg, 200 mg, and 400 mg. At the 800-mg dose level, the main side effect was dose-limiting toxicity that required dose reduction in seven patients. In all studies, the most common side effects were constipation and somnolence. In Eisen's study, the precise frequency of adverse events in patients with MBC could not be confirmed [11]. One patient receiving the 200 mg dose was removed because of grade 3 neurotoxicity (peripheral neuropathy). At the 400-mg dose, four patients experienced mild asthenia. Moreover, five serious adverse events were reported in Baidas' study [10]. Furthermore, two patients receiving the 200-mg dose, as well as one administering 800 mg, demonstrated disease progression. Two patients continued treatment with no similar episodes. Of these patients, one receiving the 200-mg dose developed dizziness and palpitations, and the other receiving the 800-mg dose experienced vomiting and headaches necessitating intravenous hydration.

Circulating angiogenic markers

In most patients, circulating angiogenic growth factor levels were detected at baseline. Baidas *et al* reported that baseline and altered TNF-α levels were significantly increased [10]. Additionally, bFGF and VEGF seemed random in a single patient who experienced a near-partial response; however, this patient experienced decreasing serial TNF-α levels from baseline to each time point. Following serial measurements, Eisen *et al* simultaneously observed that rising VEGF levels were associated with disease progression in 6 of 11 patients [11].

Discussion

In this systematic review, we analyzed the efficacy and safety of thalidomide in patients with progressive MBC. In total, 3 studies involving 52 patients were included. As a single agent, thalidomide demonstrated no efficacy in the different dose arms. At the 200-mg dose level, two patients demonstrated stable disease at 8 weeks; however, one patient's improvement was short-lived, and the other case experienced tumor stability at 8 weeks, probably due to the indolent disease history rather than thalidomide therapy.

Based on the negative results of these three studies, the non-hematologic toxicities were mild. Constipation, somnolence, fatigue, peripheral neuropathy, and dry mouth were common. At the 200-mg and 800-mg doses, apart from one patient with grade 3 neuropathy at 200 mg and seven patients with moderate somnolence at 800 mg, no other symptoms required dose modification. Based on observed results, the main side effect was somnolence (dose-limiting toxicity), necessitating dose reduction in the high-dose arm. Thalidomide was well-tolerated at doses of 100 mg and 400 mg. As an antiangiogenic agent, thalidomide can potentially modulate the tumor microenvironment and improve immunotherapy, depending on the optimal dose [13]. In mouse models, thalidomide, at a low concentration, stimulates vessel maturation and increases the cytotoxic agent delivery, increasing survival in the animals [14–16]. In the future, we need to explore the optimal doses of thalidomide combined with chemotherapy, radiotherapy, or immunotherapy. In patients with MBC, thalidomide may be considered a relatively safe agent.

In Colleoni and Eisen's study, baseline levels of

circulating angiogenic growth factors were determined in nearly all patients [11, 19]. No clear relationship was observed between the absolute level of VEGF and tumor response. Notably, the proportion of patients with elevated TNF-α levels was significantly greater, and these TNF-α levels decreased significantly following thalidomide therapy. This may be attributed to the progression of breast cancer. Eisen's study demonstrated increased VEGF levels in six patients with progressive disease [11]. Reportedly, thalidomide inhibits proinflammatory TNF-α production, as well as the effects of bFGF and VEGF on tumor growth in animal models [17–18]; however, TNF-α, VEGF, and bFGF levels may be of limited value in selecting patients for thalidomide therapy or monitoring their therapeutic response. In future studies, we plan to increase the number of samples and/or explore novel biomarkers that may be more reliable.

Here, we systematically reviewed the current literature to compare the efficacy and safety of single-dose thalidomide for MBC therapy. Notably, available evidence indicates no potential survival advantage from thalidomide monotherapy. In two phase II studies evaluating chemotherapy in combination with thalidomide, Colleoni *et al* have suggested that adding thalidomide failed to benefit patients with MBC [3, 19]. However, these results do not preclude the efficacy of thalidomide in other settings, such as in patients with other malignancies [20]. Moreover, they do not preclude the drug's possible activity when combined with other classically active agents, such as hormone therapy or immunomodulators. In conclusion, further well-designed and prospective studies need to be undertaken.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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