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Clinical Presentation and Management of Hand–Foot Skin Reaction Associated with Sorafenib in Combination with Cytotoxic Chemotherapy: Experience in Breast Cancer

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ABSTRACT

Current combination therapies for advanced breast cancer provide a modest survival benefit but with greater toxicity than with monotherapies. New combinations are needed that improve the efficacy of current treatments and have acceptable tolerability profiles. Recent clinical trials have assessed the efficacy and safety of the multikinase inhibitor sorafenib in combination with common treatments for advanced breast cancer. Sorafenib has both antiangiogenic and antiproliferative activities and is indicated for patients with unresectable hepatocellular and advanced renal cell carcinoma. Generally, sorafenib is associated with manageable, non–life-threatening adverse events. One of the more common adverse events seen with sorafenib is hand–foot skin reaction, a dermatologic toxicity usually localized to the pressure points of the palms and soles. Although hand–foot skin reaction is reversible and not life threatening, it can have a significant impact on a patient's quality of life and may necessitate dose modification. Moreover, sorafenib is being evaluated in combination with breast cancer treatments that are associated with a similar dermatologic toxicity (e.g., capecitabine-induced hand–foot syndrome). This review looks at the use of sorafenib in combination with selected chemotherapies in patients with advanced breast cancer and considers the incidence, prevention, and management of hand–foot skin reaction. ***The Oncologist*** 2011;16:1508–1519

INTRODUCTION

Survival outcomes for patients with metastatic breast cancer (MBC) over recent decades have steadily improved with the introduction of new therapeutic agents [1, 2]. Combinations of cytotoxic agents have also provided modest advances in survival outcomes and disease control compared with single-agent regimens, but with greater toxicity. However, combination regimens have not shown a survival benefit compared with the sequential use of agents [3–7].

Targeted therapies have become practical candidates for use in combination therapies. Generally, targeted therapies have better hematopoietic and nonspecific toxicity profiles than chemotherapy [8, 9]. In phase III trials, bevacizumab, an antiangiogenic monoclonal antibody, provided a progression-free survival (PFS) benefit in human epidermal growth factor (HER)-2$^-$ MBC patients when added to standard chemotherapies (e.g., paclitaxel, docetaxel, capecitabine) [10–13]. Treatment was tolerable, but bevacizumab did not produce a longer overall survival (OS) time.

Recent studies support a potential role for sorafenib in the treatment of HER-2$^-$ MBC patients. Sorafenib is a multikinase inhibitor approved for hepatocellular and renal cell carcinoma. It has a multifaceted mechanism of action, with both antiproliferative and antiangiogenic activities. Investigational

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studies of sorafenib monotherapy demonstrated modest activity in heavily pretreated patients with MBC [14, 15]. Subsequently, a program of four double-blinded, randomized, placebo-controlled, phase IIb clinical trials—Trials to Investigate the Efficacy of Sorafenib (TIES)—was initiated to assess sorafenib in combination regimens for HER-2$^-$ advanced breast cancer. Efficacy and safety data have been reported for three of these studies. Compared with the control arm (placebo plus chemotherapy), the addition of sorafenib to capecitabine provided a PFS benefit [16, 17], a PFS trend favored the addition of sorafenib to paclitaxel as first-line therapy [18, 19], and the addition of sorafenib to gemcitabine or capecitabine resulted in a longer PFS interval in patients previously treated with bevacizumab [20]. Generally, these regimens were tolerable, with manageable toxicity and no unexpected safety issues. The most common high-grade toxicity with combination therapy was palmar–plantar erythrodysesthesia, commonly known as hand–foot skin reaction (HFSR) when associated with sorafenib and other multikinase inhibitors and hand–foot syndrome (HFS) when associated with chemotherapy agents.

Although other toxicities were observed in the TIES studies, including other mucocutaneous events, the incidence and severity of HFSR with these combination regimens warrants consideration [16–20]. The incidence of HFSR in the TIES studies was notably higher than those reported in studies of single-agent sorafenib in patients with MBC [14, 15] and other tumor types [21–23]. Although HFSR is not life threatening (per the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 or 4.0, the most severe HFSR is grade 3 [24, 25]) and is reversible, sorafenib-induced HFSR can significantly impact quality of life (QoL) and may necessitate dose modifications or treatment discontinuation [26–28]. Furthermore, sorafenib treatment is continuous, so even grade 1 or 2 toxicities can impact QoL if not properly managed over the long term. Clinicians should closely monitor patients receiving sorafenib for HFSR and be aware of prevention and management strategies that may reduce its incidence, duration, and severity.

This review provides an overview of sorafenib-based combinations in MBC patients with reference to its safety profile, focusing on HFSR and its management strategies.

Sorafenib in Solid Tumors

In general, sorafenib has a favorable safety profile. Side effects are manageable and rarely life threatening [21–23]. Three pivotal phase III, placebo-controlled monotherapy trials were conducted in patients with advanced renal cell carcinoma (the Treatment Approaches in Renal Cancer Global Evaluation Trial [TARGET] [22]) and with hepatocellular carcinoma (the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol [SHARP] trial [23] and the Asia-Pacific trial [21]). Sorafenib provided a PFS benefit in the TARGET trial over placebo (median PFS interval, 5.5 months versus 2.8 months; hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.35–0.55; $p < .01$) and a survival benefit in both the SHARP trial (median survival time, 10.7 months versus 7.9 months; HR, 0.69; 95% CI, 0.55–0.87; $p < .001$) and the Asia-Pacific trial (median survival time, 6.5 months versus 4.2 months; HR, 0.68; 95% CI, 0.50–0.93; $p = .14$) [21]. During these studies, sorafenib was shown to have an acceptable safety profile, with most events of grade 1 or 2 severity being gastrointestinal, constitutional, or dermatologic in nature. Grade 3 or 4 events associated with sorafenib included hypertension, diarrhea, weight loss, hypophosphatemia, thrombocytopenia, and HFSR [21–23].

Generally, HFSR was manageable, with some patients requiring dose modifications. The incidence of HFSR (any grade) in the sorafenib arms of these studies was in the range of 21%–45%, compared with 3%–7% in the placebo arms [21–23]. Grade 3 HFSR was infrequent in the sorafenib arms (6%–10.7%) but the rate was greater than in the placebo arms (0% to <1%). In the SHARP study, HFSR-related dose reductions occurred in 5% of patients in the sorafenib arm [23], and 1.3% discontinued sorafenib as a result of HFSR (data on file). HFSR-related dose reductions occurred in 11.4% of patients receiving sorafenib in the Asia-Pacific study [21].

A meta-analysis of sorafenib monotherapy for solid tumors reported HFSR rates in the range of 9%–61.9%, with a summary incidence of 33.8% (95% CI, 24.5%–44.7%) for HFSR of any grade and 8.9% (95% CI, 7.3%–10.7%) for grade 3 [29]. Sorafenib use in renal cancer patients was associated with a greater risk for HFSR of any grade than in other solid tumors (relative risk [RR], 1.52; 95% CI, 1.32–1.75), but this difference was not observed for grade 3 HFSR (RR, 0.98; 95%, CI 0.76–1.26). Overall, the risk for HFSR was 6.6 times greater with sorafenib than with placebo or interferon controls ($p < .001$).

HFSR has also been described in studies assessing sorafenib in combination regimens. A placebo-controlled phase III trial in advanced melanoma patients showed a 7% rate of grade 3 HFSR for patients treated with sorafenib in combination with second-line carboplatin plus paclitaxel (a rate comparable with that of sorafenib monotherapy) and a 0% rate for those given placebo plus carboplatin and paclitaxel [30]. On the other hand, a retrospective analysis of three trials in patients with solid tumors showed a higher HFSR rate for patients treated with the combination of sorafenib plus bevacizumab than for those treated with sorafenib alone [31]. Although bevacizumab is not associated with HFSR/HFS, the rates of any grade HFSR were 79% for sorafenib plus bevacizumab and 52% for sorafenib monotherapy, and the rates for grade 2 or 3 were 57% and 30%, respectively.

Clinical Features and Pathophysiology of HFSR

As the development of sorafenib in combination with cytotoxic therapies continues, it will be important for clinicians to understand the clinical features of HFSR and distinguish between sorafenib-associated HFSR and chemotherapy-associated HFS (Table 1 and Fig. 1) in order to modify the dose of the specific causative agent(s) and maintain dose intensity.

A dermatologic substudy of the TARGET trial ($n = 85$) described the incidence and severity of HFSR in greater detail

Table 1. Grading and clinical features of HFSR

	NCI-CTCAE version 3.0 [24]	NCI-CTCAE version 4.0 [25]	Sorafenib PI [65]	Symptoms [68]
Grade 1	Minimal skin changes or dermatitis (e.g., erythema) without pain	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema, or discomfort of the hands/feet that does not disrupt normal ADL	Numbness, unpleasant sensations when touching ordinary things, a burning or prickly feeling, tingling, painless swelling, redness or discomfort of hands/feet; symptoms do not affect ADL
Grade 2	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Painful erythema and swelling of the hands/feet and/or affecting the patient's normal activities	One or more of the following: painful redness, swelling, skin thickening of the hands/feet; symptoms create discomfort but do not affect ADL
Grade 3[a]	Ulcerative dermatitis or skin changes with pain interfering with function	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL	Moist desquamation, ulceration, blistering, or severe pain of the hands/feet or severe discomfort that causes the patient to be unable to work or perform ADL	One or more of the following: scaling or shedding of the skin, open sores, blistering, skin thickening, severe pain of the hands/feet, severe discomfort; unable to work or perform ADL

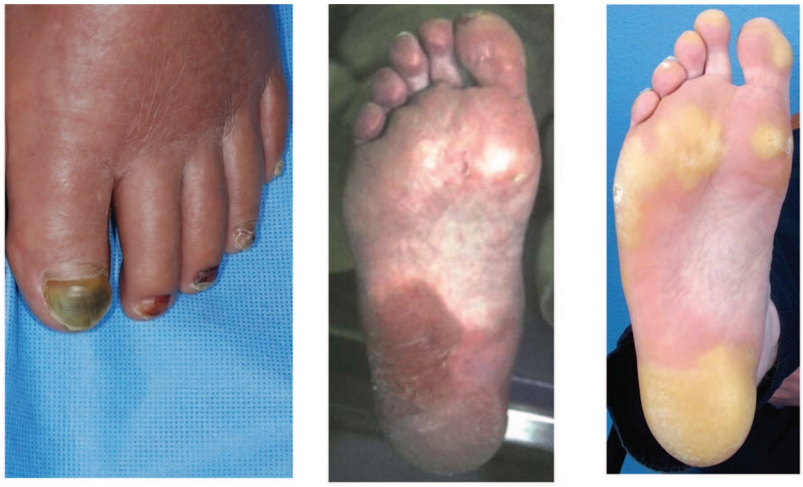
[a]Most severe grade.
Abbreviations: ADL, activities of daily living; HFSR, hand–foot skin reaction; NCI-CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events.
Modified from Anderson et al. 2009 [63], with permission.

[26]. HFSR was the most common cutaneous toxicity in the sorafenib arm (60% for any grade and 5% for grade 3) with no HFSR events in the placebo arm. Symptoms of HFSR included paresthesia, tingling, burning or painful sensations on the palms and/or soles, and a decreased tolerance for touching hot objects. These symptoms usually occurred before cutaneous lesions emerged and negatively affected walking in 35% of patients. Symmetric acral erythematous and edematous lesions were associated with desquamation and fissures, usually developing on the palms and soles but could involve the lateral sides of the fingers and toes. Hyperkeratosis was reported in 54% of patients with HFSR, usually as yellowish, painful plaques on pressure areas of the sole, sometimes encompassed by an erythematous/edematous halo [26]. Hyperkeratosis usually develops after blister formation and is a defining feature of HFSR compared with HFS (Fig. 1).

The incidence and severity of HFSR appear to be dose dependent. A pooled safety analysis of sorafenib in patients with advanced solid tumors showed that HFSR was infrequent for doses <300 mg twice daily (BID), but the incidence and severity increased for doses of 300–600 mg BID, with dose-limiting toxicity at 600 mg BID [32]. The rate of grade 3 HFSR was 3% in the cohort receiving the standard 400-mg BID dose ($n = 37$), whereas the rate was 31% in the 600-mg BID dose cohort ($n = 39$). The rate in the 800-mg BID cohort was 8%, but the sample size was small ($n = 13$). The continuous regimen might also increase drug concentrations, prolong exposure, and lead to accumulation in the skin [26]. Biopsies in patients with HFSR showed keratinocyte necrosis that correlated with time of drug initiation, as well as vessel ectasia and eccrine gland cystic degeneration [27].

The exact mechanism by which HFSR develops during sorafenib use is unknown [33]. The key may lie in the multiplicity of the drug's targeting mechanism because drugs inhibiting single pathways (e.g., vascular endothelial growth factor [VEGF] with bevacizumab) are not associated with HFSR [33]. In preclinical studies, sorafenib decreased both tumor cell proliferation and angiogenesis by inhibiting multiple signaling pathways. Proliferation was inhibited in some cell lines by sorafenib blockade of RAF-1 of the RAF/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK), or RAF/MEK/ERK, signaling pathway, as well as inhibition of the tyrosine kinases Flt-3 and c-KIT [34]. Upstream, sorafenib interfered with signaling via VEGF receptors (VEGFRs), platelet-derived growth factor receptor (PDGFR)-β and serine/threonine kinases in the RAF/MEK/ERK pathway, thus decreasing abnormal blood vessel proliferation.

It has been theorized that HFSR may occur because keratinocytes in the epidermis synthesize PDGF-α and PDGF-β, which activate PDGFRs located on dermal fibroblasts, capillaries, and eccrine glands [33]. Dermal eccrine glands also express c-KIT and PDGFR, targets of sorafenib. The higher incidence of HFSR when sorafenib is combined with bevacizumab [31] suggests that blockade of both the VEGF and PDGF pathways may hinder vascular repair, thereby triggering HFSR in areas that undergo repeated high-pressure insult, such as palms and soles.



Drug Class	Taxanes	Anthracyclines/ Antimetabolites	Multikinase Inhibitors
Lesion type	Erythematous maculopapules	Edema, erythema and, fissuring	Blisters with erythematous halo, followed by hyperkeratosis
Schedule specific	No	Yes	No
Location in hands	Dorsal	Ventral, diffuse palmar	Ventral, digit tips, over IP joints, thenar and hypothenar
Location in feet	Dorsal: Achilles tendon, malleoli	Ventral: diffuse soles	Ventral: heels, forefoot
Nail changes	Onycholysis	Hyperkeratosis	Subungual hemorrhages

Figure 1. Differentiation of HFSR and HFS [26, 27, 33, 53, 58, 59, 69].

Abbreviations: HFS, hand–foot syndrome; HFSR, hand–foot skin reaction; IP, interphalangeal.

Modified with permission from (i) Childress J, Lokich J. Cutaneous hand and foot toxicity associated with cancer chemotherapy. Am J Clin Oncol 2003;26:435–436, with permission. (ii) Photographs reprinted from Autier J, Escudier B, Wechsler J et al. Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. Arch Dermatol 2008;144:886–892 (multikinase inhibitors). Copyright © 2008 American Medical Association. All rights reserved. (iii) Lassere Y, Hoff P. Management of hand-foot syndrome in patients treated with capecitabine (Xeloda). Eur J Oncol Nurs 2004;8(suppl 1):S31–S40 (anthracyclines/antimetabolites), with permission, and photograph courtesy of Mario Lacouture, M.D. (taxane).

Sorafenib in MBC

Phase II investigations in MBC patients demonstrated moderate activity with sorafenib as monotherapy [14, 15]. In a study of 54 patients with MBC who had received prior MBC therapy (78% with three or more regimens), treatment with sorafenib (400 mg BID) resulted in a partial response in one patient (2%) and 20 patients achieved stable disease (37%) [14]. The most common grade 3 treatment-related adverse events (AEs) were rash/desquamation (6%), fatigue (4%), and HFSR (4%). These response data prompted further investigation of sorafenib in MBC patients, but as part of combination regimens.

Initial studies in patients with solid tumors demonstrated the feasibility and safety of combining sorafenib with cytotoxic agents [35]. Promising anticancer activity was observed in some tumor types, including MBC. In general, the combination treatments were tolerable, although dose-limiting toxicities, including HFSR, were reported. This was not unexpected, because a number of chemotherapies are associated with HFS [36–41].

A phase I/II study in MBC patients evaluated sorafenib in combination with anastrozole (1 mg daily) to overcome aromatase inhibitor (AI) resistance [42]. The study included 35 postmenopausal patients with hormone-positive MBC and disease recurrence or progression during AI treatment. The 400-mg BID sorafenib dose was selected as the phase II dose. One patient achieved a partial response and seven had stable disease for ≥24 weeks, resulting in a clinical benefit rate of 23%. The most common grade 3 or 4 AEs were HFSR (34%), fatigue (17%), rash (11%), emesis (11%), and hypertension (11%). Other grade 3 or 4 mucocutaneous events were infrequent (e.g., 3% for mucositis). The rate of dose reduction was 77% and the rate of discontinuation because of toxicity was 31%. The investigators concluded that future trials were warranted but with a lower sorafenib dose.

TIES

The TIES program was initiated to evaluate a potential role for sorafenib in combination with common chemotherapies for patients with HER-2$^-$ MBC and determine whether phase III trials were warranted. These four phase IIb, double-blinded, randomized, placebo-controlled trials aimed to assess sorafenib in combination with capecitabine, paclitaxel, gem-

Table 2. Dose modification schedule for HFSR/HFS during the SOLTI-0701 and NU07B1 trials

SOLTI-0701 [16]		NU07B1 [18]		2008 Consensus Panel [33]	
Initial dose: CAP, 1000 mg/m^2 BID[a] (14 days on, 7 days off); SOR/PL, 400 mg BID (continuous)		Initial dose: PAC, 90 mg/m^2 weekly (3 wks on, 1 wk off); SOR/PL, 400 mg BID (continuous)		Initial dose: SOR, 400 mg BID	
Grade 1	Continue at same dose	Grade 1	Continue at same dose	Grade 1	Continue at same dose
Grade 2 (first occurrence)	Interrupt until resolved to grade ≤1 and continue at same dose	Grade 2 (first occurrence)	Continue at same dose. If no improvement within 7 days, see below	Grade 2 (first occurrence)	Reduce dose to 400 mg daily for 7–28 days; if toxicity resolves to grade ≤1, then re-escalate dose to 400 mg BID; if no improvement, see below
Grade 2 (recurrent) or grade 3 (first occurrence/recurrent)	Interrupt until resolved to grade ≤1 and reduce by 1 dose level. Dose reduction steps:[b] (a) CAP, 750 mg/m^2 BID; (b) SOR/PL, 400 mg QD; (c) CAP, 500 mg/m^2 BID; (d) SOR/PL, 400 mg QOD; (e) Discontinue treatment with both study drugs	Grade 2 (no improvement within 7 days or second or third occurrence) or grade 3 (first or second occurrence)	Interrupt until resolved to grade ≤1 and reduce by one dose level. Dose reduction steps: (a) SOR/PL, 400 mg QD; (b) SOR/PL, 400 mg QOD	Grade 2 (no improvement within 28 days) or grade 3 (first occurrence)	Interrupt for ≥7 days until resolved to grade ≤1 and reduce by one dose level (400 mg QD/QOD); restart at reduced dose; if toxicity grade ≤1 for ≥7 days, re-escalate one dose level (400 mg BID/QD)
				Grade 2 (second or third occurrence) or grade 3 (second occurrence)	Interrupt until resolved to grade ≤1 and reduce by one dose level (400 mg QD/ QOD); restart at reduced dose; decision to re-escalate dose based on clinical judgment and patient preference
Grade 2 or 3 (persistent[c])	Discontinue both drugs	Grade 2 (fourth occurrence), grade 3 (3rd occurrence)	Discontinue SOR/PL	Grade 2 (fourth occurrence), grade 3 (third occurrence)	Decision to discontinue treatment based on clinical judgment and patient preference

In addition to dose modification, symptomatic treatment (e.g., topical therapy) was also recommended for any grade HFSR/HFS.
This is intended as a brief summary of the management guidance for HFSR/HFS from the study protocols of the SOLTI-0701 and NU07B1 trials and is not the complete protocol guidance.
[a]Dose could be titrated to 1,250 mg/m^2 as tolerated.
[b]Reduce dose at restart after each occurrence/recurrence is resolved.
[c]Lasting ≥21 days in duration.
Abbreviations: BID, twice daily; CAP, capecitabine; HFS, hand–foot syndrome; HFSR, hand–foot skin reaction; PAC, paclitaxel; PL, placebo; QD, once daily; QOD, once every other day.

citabine or capecitabine, and docetaxel and/or letrozole. The primary endpoint in each study was the PFS interval and the estimated sample size was 220 patients with locally advanced or metastatic disease. Three of the TIES studies have reported efficacy and safety data for the addition of sorafenib to capecitabine (the SOLTI-0701 study), paclitaxel (the NU07B1 study), and gemcitabine or paclitaxel (the AC01B07 study).

Sorafenib Plus Capecitabine

The SOLTI-0701 trial enrolled patients who had received no more than one prior metastatic treatment. Capecitabine, a prodrug of 5-fluorouracil, is indicated for MBC treatment either alone or with docetaxel [38–40]. Side effects associated with capecitabine include gastrointestinal events, fatigue, and HFS. Rates of HFS in breast cancer patients receiving capecitabine monotherapy have been in the range of 43%–63% for any grade and 11%–24% for grade 3 [39–41, 43–46]. In a phase II study of patients with MBC ($n = 126$) receiving capecitabine (1,250 mg/m^2 BID), the incidence of grade 3 HFS was 21%, with 17% of patients requiring dose reductions as a result of HFS [41].

In the SOLTI-0701 trial, patients were randomized to receive capecitabine (1,000 mg/m^2 BID, days 1–14 of a 21-day cycle) in combination with placebo or sorafenib (400 mg BID). The protocol outlined dosing algorithms to help manage persistent or high-grade AEs, including HFSR/HFS (Table 2). In total, 229 patients were randomized to treatment. The addition of sorafenib to capecitabine provided a significant PFS benefit over capecitabine monotherapy (median PFS time, 6.4 months versus 4.1 months; HR, 0.58; 95% CI, 0.41–0.81; one-sided

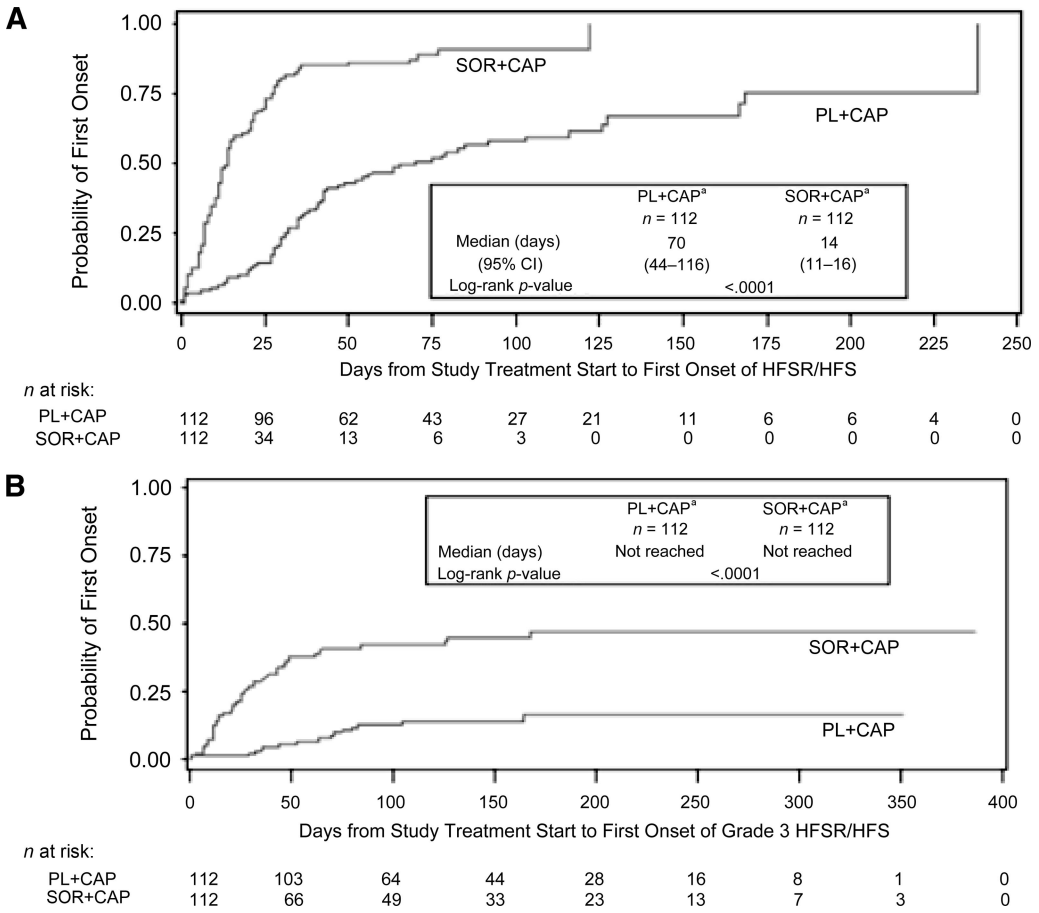


Figure 2. Time to first onset of HFSR/HFS by the Kaplan–Meier method during the SOLTI-0701 trial [47]. **(A):** Any grade event. **(B):** Grade 3 events.

[a]Safety population (patients who received any study drug[s]).

Abbreviations: CAP, capecitabine; HFS, hand–foot syndrome; HFSR, hand–foot skin reaction; PL, placebo; SOR, sorafenib.

$p = .0006$), supporting a phase III study of similar design [16, 17]. The overall response rates (ORRs) were 38.3% and 30.7% (one-sided $p = .12$), respectively, with median durations of response of 6.2 months and 4.1 months (one-sided $p = .048$), respectively. The OS duration did not differ statistically between treatment arms (median, 22.2 months versus 20.9 months, respectively; HR, 0.86; 95% CI, 0.61–1.23; one-sided $p = .21$). There was a nonsignificant trend in the OS time favoring sorafenib plus capecitabine over placebo plus capecitabine in the first-line subgroup (median, 22.8 months versus 18.6 months, respectively; HR, 0.67; 95% CI, 0.40–1.11; one-sided $p = .06$) that was not observed in the second-line subgroup (median, 19.0 months versus 23.4 months, respectively; HR, 1.08; 95% CI, 0.65–1.78; one-sided $p = .40$).

Overall, sorafenib plus capecitabine was tolerable with a manageable side-effect profile and no unexpected AEs [16, 17]. In the combination arm, the average duration of treatment was 33.8 weeks for sorafenib and 10.7 cycles for capecitabine. On average, the duration of treatment was shorter for placebo (22.5 weeks) plus capecitabine (7.4 cycles). Most AEs were grade ≤ 2. For AEs of any grade, rates were higher for sorafenib plus capecitabine than for placebo plus capecitabine: diarrhea (58% versus 30%), mucosal inflammation (33% versus 21%), rash (22% versus 8%), neutropenia (13% versus 4%), and HFSR/HFS (90% versus 66%). Generally, grade 3 or 4 AE rates were comparable between treatment arms, except for grade 3 HFSR/HFS (44% versus 14%). The incidences of grade 3 or 4 rash were 4% and 0%, respectively.

Dose modifications were common, but few patients discontinued treatment because of HFSR/HFS. In the combination arm, 53% of patients had their sorafenib dose reduced and 78% had their capecitabine dose reduced. In the control arm, the corresponding values for dose reductions were 14% for placebo and 33% for capecitabine. The rates of treatment discontinuation resulting from AEs were 20% in the combination arm and 9% in the control arm, with rates of 8% and 4%, respectively, specific to HFSR/HFS [16, 17].

The original SOLTI-0701 protocol required patient follow-up for compliance and safety every 3 weeks for the first 24 weeks of treatment. However, shortly after the start of the trial, HFSR/HFS was found to emerge within the first few months of treatment. Therefore, the protocol was amended to weekly follow-up visits for the first 6 weeks to closely monitor patients during the time of greatest risk. In a secondary analysis of the

SOLTI-0701 study [47], a Kaplan–Meier analysis of HFSR/HFS showed a shorter median time to onset with sorafenib plus capecitabine than with placebo plus capecitabine for any grade (median, 14 days versus 70 days; $p < .0001$) and for grade 3 (median not reached for either arm; $p < .0001$) (Fig. 2), with the highest incidence in the combination arm during cycle 1 for any grade (63%) and in cycle 2 for grade 3 (22%). The incidence of HFSR/HFS declined over the course of treatment, corresponding to an incremental reduction in the mean dose of study drugs, although a direct correlation could not be established.

Sorafenib Plus Paclitaxel

The NU07B1 study evaluated first-line therapy for advanced disease by comparing the combination of sorafenib plus paclitaxel with placebo plus paclitaxel in 237 patients [18]. Studies have demonstrated the clinical activity of paclitaxel in MBC patients and better survival outcomes than with other standard treatments [48–51]. Side effects associated with paclitaxel include neutropenia, leukopenia, alopecia, anemia, peripheral neuropathy, myalgia/arthralgia, nausea, and vomiting. Taxanes are not associated with HFS, although a syndrome characterized by periarticular thenar erythema with onycholysis (PATEO syndrome) with pain has been observed in up to 50% of patients receiving a taxane [52]. Because of the appearance of PATEO on the hands and feet, and its association with pain, it is frequently misdiagnosed as HFS [53]. Taxane-induced nail changes may be prevented with cold glove and sock therapy. In a study of 45 patients with solid tumors treated with docetaxel that compared the use of a frozen glove on one hand with no protection on the other, grade 1 or 2 onycholysis occurred in 11% and 51% of patients, respectively, and grade 1 or 2 skin toxicity occurred in 27% versus 59% of cases, respectively [52]. Similar benefits were observed with a frozen sock [54].

During the NU07B1 trial, paclitaxel was administered at a dose of 90 mg/m^2 per week (3 weeks on/1 week off) in combination with placebo or sorafenib (400 mg BID) [18, 19], with dosing algorithms to limit toxicity, including dermatologic events (Table 2). Assessment of the PFS intervals indicated a nonsignificant trend favoring sorafenib plus paclitaxel over placebo plus paclitaxel (median PFS time, 6.9 months versus 5.6 months; HR, 0.79; 95% CI, 0.56–1.11; one-sided $p = .09$), but this did not reach the predefined critical effect size. For secondary endpoints, sorafenib plus paclitaxel resulted in a greater median time to progression (8.1 months versus 5.6 months, respectively; one-sided $p = .017$), longer duration of response (5.6 months versus 3.7 months, respectively; one-sided $p = .008$), and higher ORR (67% versus 54%, respectively; one-sided $p = .023$). There was no significant difference between treatment arms in the OS times (median, 16.8 months versus 17.4 months, respectively; HR, 1.02; 95% CI, 0.72–1.46; one-sided $p = .45$) [18, 19].

Some AEs were more frequent in the combination arm than in the placebo arm [19]. The incidences of HFSR of any grade were 55% and 7%, respectively, and the incidences of grade 3 HFSR were 31% and 3%, respectively. Other AEs (any grade) that occurred more frequently in patients treated with sorafenib plus paclitaxel than for those given placebo plus paclitaxel included rash (19% versus 11%), stomatitis (17% versus 3%), diarrhea (37% versus 25%), and vomiting (29% versus 16%). The incidences of grade 3 or 4 AEs were generally comparable for sorafenib plus paclitaxel and placebo plus paclitaxel, with moderately higher rates for asthenia (7% versus 4%), neutropenia (13% versus 7%), anemia (11% versus 6%), and stomatitis (4% versus 0%). The incidences of grade 3 or 4 rash were 2% and 0%, respectively.

Patients receiving sorafenib plus paclitaxel required more dose modifications to manage toxicity than those receiving placebo plus paclitaxel. In the combination arm, sorafenib was interrupted for 55% of patients and reduced for 50%, with corresponding rates of 54% and 33% for paclitaxel. In the control group, the placebo dose was interrupted for 16% of patients and reduced for 9%, with corresponding values of 47% and 22% for paclitaxel [19]. Overall, 22% of patients in the sorafenib–paclitaxel arm and 6% of patients in the placebo–paclitaxel arm discontinued treatment as a result of AEs.

The incidence of grade 3 HFSR (31%) in the sorafenib arm during the NU07B1 trial appears higher than expected, given that paclitaxel is not associated with HFSR/HFS and that the rate of grade 3 HFSR for sorafenib, carboplatin, and paclitaxel in a melanoma study was 7% [30]. The higher incidence may be a result of greater awareness of sorafenib-induced HFSR during the NU07B1 trial than in previous studies or differences in the study populations. In a NU07B1 subgroup analysis, the rates of grade 3 HFSR in the sorafenib–paclitaxel arm were 34% for patients enrolled in centers in India and 21% for patients enrolled in centers outside India (U.S. or Brazil) [55]. Other studies have suggested differences in the incidence of HFSR by ethnicity, with Asian patients more frequently affected [56].

Sorafenib Plus Gemcitabine or Capecitabine

The AC01B07 trial enrolled 180 patients who had experienced disease progression during or after treatment with bevacizumab and randomized them to treatment with gemcitabine (1,000 mg/m^2 i.v., days 1 and 8 of a 21-day cycle) in combination with sorafenib (400 mg BID) or placebo [20]. After the start of the trial, the protocol was amended and capecitabine (1,000 mg/m^2 BID, days 1–14 of a 21-day cycle) was allowed as an alternative to gemcitabine at the treating physician's discretion. Most patients (83%) received gemcitabine. Gemcitabine is approved for use in MBC patients in combination with paclitaxel but is also used as monotherapy within sequential regimens [57]. The most common side effects associated with gemcitabine include nausea/vomiting, myelosuppression, renal and hepatic toxicities, fever, rash, and dyspnea.

Primary analysis of the AC01B07 trial demonstrated that the addition of sorafenib to chemotherapy provided a statistically significant longer PFS interval than with placebo (median, 3.4 months versus 2.7 months; HR, 0.65; 95% CI, 0.45–0.95; one-sided $p = .01$) and longer time to progression (median, 3.6 months versus 2.7 months; HR, 0.64; 95% CI, 0.44–0.93; one-sided $p = .009$). There was no statistical dif-

Table 3. Prevention and supportive care for HFSR related to sorafenib treatment [26, 33, 59–63]

Prevention/patient education
• Frequent communication, particularly in the first month of treatment initiation; patients should contact physician when signs or symptoms first appear
• Full-body skin exam for predisposing factors (hyperkeratosis, eczema, fungal disease, or malalignment) and, if indicated, pedicure by podiatrist or evaluation by orthotist
• Wear thick cotton gloves/socks to prevent injury and keep palms and soles dry, wear shoes with padded insoles to reduce pressure on feet
• Use mild soap to bathe (e.g., Aveeno® or Cetaphil®), pat skin dry (do not rub)
• Avoid excessive temperatures (hot water), excessive pressure, or friction to hands and feet (e.g., long walks or constrictive clothes/shoes/gloves)
Supportive care
Grade 1 (see also applicable grade 2 or 3 supportive care)
• Moisturizing creams (e.g., Udderly Smooth®, Aquaphor®, Eucerin®, Bag Balm®, Am-Lactin®, Lac-Hydrin®)
• Wear thick cotton gloves/socks at night for protection and to retain moisture
Grade 2 or 3 (in addition to applicable preventative strategies and grade 1 management)
• Treatment of blisters and erosions with topical antibiotics
• Topical corticosteroids (e.g., clobetasol 0.05%, fluocinonide 0.05%) for severe inflammation and painful erythematous areas (apply twice daily to affected areas only)
• Topical keratolytic agents (e.g., salicylic acid 6%, urea 20%–40%) for hyperkeratotic lesions (apply twice daily to affected areas only)
• Pain management with systemic medicine (e.g., nonsteroidal anti-inflammatory drugs, γ-aminobutyric acid agonists, narcotics) after assessment of bleeding risk and kidney function, and/or immersion of hands/feet in cool water

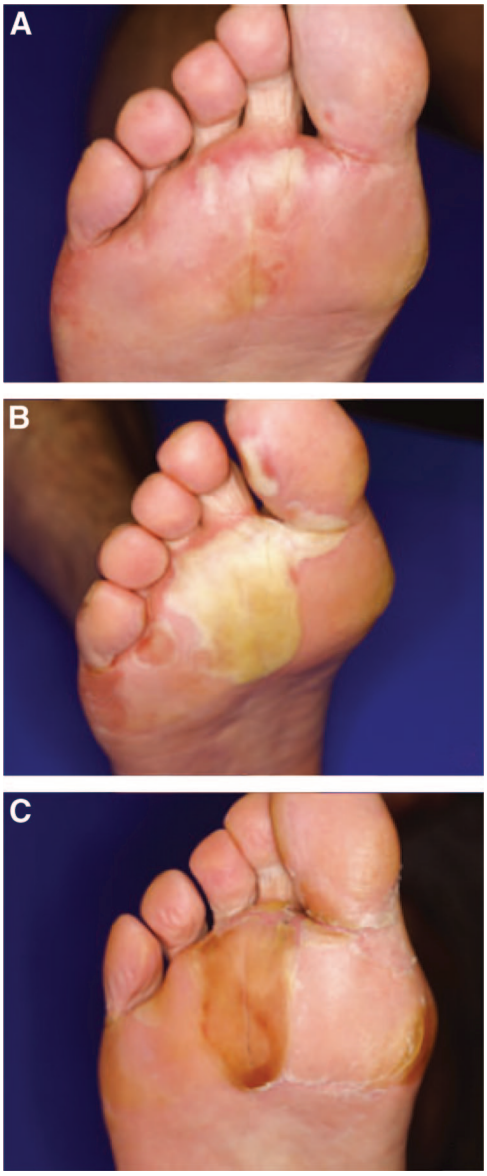


Figure 3. Time course of hand–foot skin reaction (HFSR) associated with sorafenib. **(A):** Early HFSR after 1 week of 400 mg sorafenib twice daily. **(B):** Progression of HFSR despite reduction to 400 mg daily and topical mometasone. **(C):** Sorafenib dosing interrupted, improvement in HFSR within 4 days. After 1 week of interruption, sorafenib was restarted at 400 mg daily without further complications. Reprinted from Degen A, Alter M, Schenck F et al. The hand-foot-syndrome associated with medical tumor therapy—classification and management. J Dtsch Dermatol Ges 2010;8:652–661, with permission.

ference between treatment arms for the ORR (19.8% versus 12.7%, respectively; one-sided $p = .12$). The addition of sorafenib was associated with higher rates of some grade 3 or 4 AEs, including HFSR/HFS (39% versus 5%), stomatitis (10% versus 0%), thrombocytopenia (10% versus 1%), fatigue (18% versus 9%), anemia (5% versus 0%), and rash (4% versus 0%). Updated safety data, including more detailed analyses of HFSR/HFS, and an analysis of OS outcomes are expected after the data mature.

Management Strategies for HFSR

The goals of prevention and management strategies for sorafenib-induced HFSR are to reduce the incidence, duration, and severity, minimize the impact on QoL, and maximize treatment potency and duration. Table 3 outlines prevention and management strategies that are also applicable to HFS [58].

Although preventive measures have not been assessed formally, a number of practical approaches are recommended [33, 59–63]. Patients should be aware of the signs and symptoms of HFSR and of prevention steps, and be advised to stay in

Table 4. Dose modification schedule and supportive care recommendations for HFSR/HFS for a phase III trial comparing capecitabine in combination with sorafenib or placebo for treatment of locally advanced or metastatic HER2-negative breast cancer (RESILIENCE)

	Dosing		
Toxicity grade	**Standard dose**	**Dose escalated**	**Supportive care**
Grade 0	Starting dose: SOR/PL,[a] 600 mg/day, 21-day cycle; CAP,[b] 2,000 mg/m^2 per day, 14 days of 21-day cycle	If standard dose is well tolerated SOR/PL,[a] 800 mg/day, 21-day cycle; CAP,[b] 2,500 mg/m^2 per day, 14 days of 21-day cycle	Frequent contact with patient; minimize vigorous activities that place stress on hands/feet (e.g., running) in first 4 wks; practical prevention strategies: pedicure by podiatrist for pre-existing hyperkeratosis; avoid hot water and clothing or activities that can cause friction on the skin; moisturizing cream applied sparingly; padded gloves and open shoes with padded soles should be worn to relieve pressure points
Grade 1	Continue at same dose	Continue at same dose	Continue prevention strategies; soak hands in cool water; apply petroleum jelly to moist skin; for hyperkeratotic lesions, exfoliate hands/feet and apply moisturizing exfoliant (urea- or salicylic acid-containing topical treatments) creams twice daily
Grade 2 or 3 (first occurrence/recurrent)	Interrupt until resolved to grade ≤1[c] Dose reduction steps:[d,e] (a) Reduce CAP to 1,500 mg/m^2 per day; (b) Reduce SOR/PL to 400 mg/day; (c) Reduce CAP to 1,000 mg/m^2 per day; (d) Reduce SOR/PL to 400 mg/QOD; (e) Discontinue both drugs	Interrupt until resolved to grade ≤1.[c] Dose reduction steps:[d,e] (a) Reduce capecitabine to 2,000 mg/m^2 per day; (b) Reduce SOR/PL to 600 mg/day; (c) Reduce CAP to 1,500 mg/m^2 per day; (d) Reduce SOR/PL to 400 mg/day; (e) Reduce CAP to 1,000 mg/m^2 per day; (f) Reduce SOR/PL to 400 mg QOD; (g) Discontinue both drugs	Continue prevention and management strategies; topical corticosteroids applied twice daily (for severe inflammation with painful erythema); analgesics for pain

This is intended as a brief summary of the management guidance for HFSR/HFS from the study protocol and is not the complete protocol guidance.
[a]SOR/PL tablets (200 mg per tablet) administered twice per day (e.g., one tablet in morning and two tablets in evening for 600-mg dose).
[b]CAP tablets administered twice per day (12 hours apart).
[c]Discontinue treatment if HFSR/HFS not resolved within 21 days.
[d]Reduce dose at restart after each occurrence/recurrence is resolved.
[e]Dose re-escalation after dose reduction for adverse events is not allowed for capecitabine but is allowed for sorafenib per protocol guidance.
Abbreviations: CAP, capecitabine; HFS, hand–foot syndrome; HFSR, hand–foot skin reaction; PL, placebo; SOR, sorafenib.

close contact with their physicians, particularly in the first 6 weeks of sorafenib treatment when HFSR usually emerges. Before sorafenib treatment begins, a qualified health care professional should conduct a baseline skin check for predisposing factors [33, 61, 63]. Hyperkeratotic areas or calluses should be removed via pedicure or manicure [33, 61, 63]. Feet and hands should be examined for areas under excessive friction or undue stress, and cushioning these areas is recommended [33, 63]. Although anecdotal evidence suggests that prophylactic pyridoxine (vitamin B_6) is beneficial for preventing HFSR [63], studies found pyridoxine to be ineffective for managing capecitabine-induced HFS [64].

If HFSR does occur, grade 1 can be managed with symptomatic interventions. Management strategies should be esca-

lated with increasing grades of severity (Fig. 3). If symptoms reach grade ≥2, the mainstay of management is dose modification, but supportive treatment should continue with other options considered. Severe inflammation and painful erythematous areas can be treated with topical corticosteroids [33]. Pain is the most significant HFSR symptom affecting QoL [28], therefore analgesia is of paramount importance. Once acute erythema improves, tender hyperkeratotic lesions may develop, which can be treated with topical keratolytics [33].

The U.S. prescribing information for sorafenib recommends dose modifications to manage treatment-related skin toxicity based on severity and occurrence (initial or subsequent) [65]. Elsewhere in the literature, experts have detailed similar dosing algorithms but with variations for dose interruption and reduction, as well as dose re-escalation as tolerated (Table 2) [33].

Although supportive care data are limited, formal studies are under way to improve the management of sorafenib-induced HFSR. A double-blinded, randomized, phase II study is assessing four different treatments for HFSR (urea 40% cream, fluocinonide 0.05% cream, tazarotene 0.1% cream, and bland emollient cream) in patients receiving sorafenib either alone or in combination with agents not associated with HFSR/HFS (ClinicalTrials.gov identifier, NCT00667589).

As demonstrated in the TIES studies, the management of HFSR in the MBC setting needs to be aggressive at all stages, particularly for sorafenib in combination with agents associated with HFS, such as capecitabine. Management strategies for capecitabine-induced HFS that have shown benefit in the uncontrolled setting include celecoxib [66] and high-potency topical steroids [58]. On the other hand, pyridoxine [64] and urea/lactic acid containing preparations [67] have not shown benefit.

In view of the SOLTI-0701 experience, a phase III trial comparing capecitabine in combination with sorafenib or placebo for treatment of locally advanced or metastatic HER2-negative breast cancer (RESILIENCE) has been initiated (ClinicalTrials.gov identifier, NCT01234337), with a similar design but with a number of important modifications. Patients will start treatment with sorafenib at a lower dose of 600 mg per day in combination with capecitabine at 2,000 mg/m^2 per day. The dosing algorithm of that study will allow dose escalation after the first cycle if fatigue and dermatologic and gastrointestinal toxicities are grade ≤1. Furthermore, the study protocol provides detailed measures for HFSR/HFS prevention and supportive care (Table 4).

Conclusions

Results from the TIES studies demonstrated clinical activity for sorafenib in HER-2$^-$ advanced breast cancer patients when combined with selected chemotherapies, compared with a placebo control. Sorafenib plus capecitabine provided a significant PFS benefit, supporting further study of this combination in the phase III setting (the SOLTI-0701 trial). A statistically significant longer PFS interval was also demonstrated when sorafenib was combined with gemcitabine or capecitabine in patients who had progressed during or after bevacizumab treatment (the AC01B07 trial), and sorafenib with first-line paclitaxel showed a trend of a longer PFS interval (the NU07B1 trial). The rate of grade 3 HFSR/HFS was high in the combination therapy arms of these studies. In the SOLTI-0701 trial, HFSR/HFS was both manageable and tolerable, but the high incidence necessitated modifications to the dosing schema and management strategies of the phase III RESILIENCE study.

As the potential role for sorafenib advances into novel therapeutic areas and as part of combination regimens, the management of HFSR will need to improve. Prevention strategies, proactive management, and, when necessary, dose modification should help patients maintain QoL as well as the clinical benefits of sorafenib treatment.

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