Search for Evidence-Based Approaches for the Prevention and Palliation of Hand–Foot Skin Reaction (HFSR) Caused by the Multikinase Inhibitors (MKIs)

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ABSTRACT

Background. The anticancer multikinase inhibitors (MKIs) are associated with cutaneous adverse events, including hand–foot skin reaction (HFSR), a condition affecting 20%–40% of patients. Symptoms are usually mild, but can evolve into a painful condition that limits function and impacts quality of life (QoL), resulting in shortened cancer treatment duration or intensity. The goal of this study was to systematically review the literature on the prevention and palliation of MKI-associated HFSR, to identify areas for further clinical study, and to provide a foundation for evidence-based guidelines for HFSR management.

Methods. Systematic searches of the National Library of Medicine’s PubMed database, Cochrane Reviews, BIOSIS, CancerLit, and the American Society of Clinical Oncology website were conducted using search terms for cutaneous toxicities associated with chemotherapeutic agents. Articles were categorized (C) based on type of agent and cutaneous reaction as: C1 (MKI and HFSR); C2 (MKI and other cutaneous toxicity); C3 (other antineoplastic agents and HFSR); and C4, other.

Results. Of the 2,069 abstracts screened, 350 (17%) met the criteria for C1–C4, with 56 (16%) coded as C1 with details of HFSR histology, pathogenesis, clinical outcome, QoL impact, and/or prevention and treatment approaches in MKI-treated patients. No randomized, controlled trials (RCTs) on prevention/palliation of HFSR were identified. Anecdotal evidence or expert opinion advocated protective measures, preventive and therapeutic skin care, systemic analgesics for pain, vitamin B6, and MKI dose modification.

Conclusion. No articles containing evidence from RCTs on preventive/palliative approaches to MKI-assoc-
associated HFSR have been published. Systematic study of optimal treatment strategies for HFSR is needed to ad-


INTRODUCTION
Chemotherapeutic agents such as capecitabine and doxorubicin have long been noted for their potential to cause skin toxicities that affect the hands and feet, varying in occurrence and severity by type of agent and dosing schedule [1–5]. Novel targeted therapies have recently demonstrated efficacy against several tumor types; however, use of several of the multikinase inhibitors (MKIs), such as sorafenib or sunitinib, has also led to the cutaneous toxicity known as hand–foot skin reaction (HFSR) in 20%–40% of treated patients [1, 2, 5]. The appearance of MKI-associated HFSR differs from the hand–foot skin toxicities (i.e., hand–foot syndrome [HFS]) seen with older chemotherapeutic agents [6, 7]. It usually presents as a mild-to-moderate cutaneous reaction [5, 8], is not age limited [3], and may evolve into a painful condition that limits daily functioning and affects quality of life (QoL) [1, 2, 4, 5]. The HFSR symptom burden experienced by the patient may eventually cause the oncologist to limit or reduce MKI treatment duration or intensity, or to end treatment. Signs and symptoms of HFSR may include pain, swelling, numbness, tingling, redness of the skin of the hands or feet, and flat blisters or hyperkeratotic lesions [9–12]. As the hyperkeratotic areas thicken, scaly lesions resembling skin calluses surmount the erythematous patches. In high-grade, fully developed lesions, large tense blisters can develop [12].

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v3.0) grading system for dermatologic toxicities [13], the most widely used method of grading for HFSR [3, 5], is shown in Table 1. The grading system used in the sorafenib U.S. prescribing information, which is more descriptive and specific to HFSR symptoms reported with sorafenib, also is shown [14]. Grade 1 HFSR is characterized by numbness, dysesthesia, paresthesia, tingling, painless swelling, and erythema or discomfort of the hands or feet that does not disrupt the patient’s normal activities. Characteristics of grade 2 HFSR include painful erythema and swelling of the hands or feet and/or discomfort affecting the patient’s normal activities. Grade 3 HFSR is characterized by moist desquamation, ulceration, blistering, or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

Prompt identification and management of HFSR may be essential to facilitate the continuation of MKI therapy [15–17]. The primary objective of this literature review study was to determine the extent of evidence-based treatment for MKI-associated HFSR available in the peer-reviewed literature. A systematic and intensive review revealed that no evidence-based treatment algorithms exist for the effective prevention and treatment of cutaneous toxicities from MKIs [15]. Several experience-based practices are consistently seen and reported in the literature; these practices were presented in a recent publication summarizing the proceedings of an expert panel [5].

METHODS
Searches of the peer-reviewed literature were conducted via the National Library of Medicine’s PubMed database, the Cochrane Database of Systematic Reviews, and the BIOSIS and CancerLit databases listed in the archives through August 31, 2008. Literature search terms were broad based to capture skin toxicities associated with chemotherapy and were not specific to a certain agent or treatment approach. The searches used variations and synonyms of the key word “hand–foot syndrome” including hand–foot skin reaction, acral erythema, palmar–plantar erythrodysesthesia, acral erythema, acral erythrodysesthesia, Burgdorf reaction, and toxic erythema of the palms and soles, among other variations of the terms already stated. Medical subject heading (MeSH) searches were conducted using the terms skin disease, hand injuries–chemically induced, and erythema and were combined with MeSH terms, including antineoplastic agents and protein kinase inhibitors. The names of specific agents entered into the MeSH search included: sorafenib, sunitinib, gefitinib, erlotinib, temsirolimus, capecitabine, gemcitabine, 5-fluorouracil, tegafur, emitefur, vinorelbine, liposome-encapsulated or continuous-infusion doxorubicin, floxuridine, cytarabine, methotrexate, palifermin, docetaxel, cisplatin, clofarbine, cyclophosphamide, daunorubicin, etoposide, fluorouracil, hydroxyurea, 6-mercaptopurine, paclitaxel, 6-thioguanine, and troxacitabine [18]. Additional searches focused on the toxicity of anticancer agents, patient management, and general cutaneous reactions to kinase inhibitors. When retrieval results exceeded 1,000 records, queries were limited to recent English-language clinical studies, meta-analyses, reviews, or practice guidelines. Additional articles that were similar or related to those already found were either brought to our
attention by expert panel members for further scrutiny or appeared in abstracts presented at recent American Society of Clinical Oncology congresses. Included for review in this study were all citations categorized (C) as C1 (pertaining to MKI-associated HFSR) and containing details on histology, pathogenesis, incidence, QoL, impact, treatment, or prevention. This literature was distinguished from related published material categorized as: C2 (citations that focused on MKI-associated skin reactions other than HFSR such as acneiform eruptions or skin rash histology, pathogenesis, incidence, treatment, or prevention); C3 (citations that focused on antineoplastic agents other than MKIs, such as capecitabine, doxorubicin, etc.); or C4 (citations that did not focus on clinical details of pathophysiology or treatment of HFSR/HFS but on other issues related to HFSR such as complications, study design issues, health care policy, or patient needs). Copies of articles were obtained and reviewed for all retained citations reporting clinical results of patient treatment approaches regardless of: (a) sample size or study design, (b) whether they were reviews of the scientific literature on HFSR treatment or outcomes, and (c) whether they were case studies. Excluded from further review were C1 articles that solely presented attitudes or opinions regarding HFSR without reference to any of the above inclusion criteria. Each citation was judged independently by two reviewers. Any discrepancies that arose regarding inclusion were resolved either by clarification followed by unanimous agreement or after review of the full article in question. Finally, we considered “evidence” as data or information that originated from objective tests of efficacy in clinical or case studies published in the scientific literature rather than from anecdotal observations.

**RESULTS**

In total, 2,069 abstracts were identified. All were screened for consistency with the search objectives. Abstracts covering the wrong condition or topics unrelated to antineoplastic therapy were eliminated. A total of 350 abstracts (16%) met the criteria for inclusion in C1–C4 (Fig. 1) and were stored in a reference database. Fifty-six (16%) were in-
Prevention Approaches for MKI-Associated HFSR

Evidence and reports on prevention and palliation of HFSR relevant to developing evidence-based clinical practice guidelines are shown in Table 2. Recommendations for the prevention and treatment of MKI-associated HFSR in the examined literature were based on: practices implemented during clinical trials of MKI agents, post-marketing practices, approaches derived from personal clinical experiences of the authors, and strategies used for chemotherapy-induced HFS (non-MKI agents) but applied to HFSR resulting from MKI therapy. The range of treatment goals and prophylactic recommendations identified included: (a) controlling the presence of plantar hyperkeratosis, a putative risk factor for HFSR, by prophylactic removal of the hyperkeratotic areas followed by application of a moisturizing cream; (b) pedicures; and (c) the cushioning of callused areas by means of soft or padded shoes [19, 20]. Among other approaches were the prophylactic use of exfoliating products applied to the calluses [17] and administration of prophylactic pyridoxine (vitamin B₆). The role of these recommendations in preventing chemotherapy-induced HFS remains under debate [21–23].

Recommendations on Patient Education Prior to Initiation of Drug Therapy

Because most MKIs are self-administered oral medications, effective patient education about HFSR prior to commencement of therapy and guidance on skin care and protection is another strategy for prevention [4]. Oncology providers are encouraged to listen to patients’ concerns, offer options to enhance patient comfort, and identify treatment issues early [17]. No studies were found that tested the efficacy of patient education approaches for HFSR (e.g., printed material, video or photographic aides, or other media) [15, 24] on the likelihood of developing HFSR, or the severity of symptoms.

Treatment/Palliation Approaches for Management of Symptoms of MKI-Associated HFSR

Grade 1

Clinical goals for grade 1 HFSR (Table 3) as cited in the literature included instituting supportive measures, con-
continuation of MKI treatment, control of hyperkeratotic areas, maintaining the moisture of the skin, and continuing patient education on skin care and protection. Specific approaches employed to achieve these goals included the use of keratolytics such as 40% urea and/or salicylic acid to aid in the natural exfoliation of the callused areas followed by cushioning of the affected regions with gel inserts or the use of soft shoes. Frequent application of emollients and creams may be important to maintain moisture of the skin and to prevent cracks or breaks in dermal integrity. A dermatologic referral of patients with unique skin presentations or those who fail to respond to HFSR treatment, combined with active collaboration among dermatologists, podiatrists, oncologists, and oncology nurses, was recommended. Unfortunately, none of the C1 publications covering recommendations for grade 1 MKI-associated HFSR presented scientifically collected evidence on the benefits of adherence to these general treatment strategies. All of the recommendations were based on the personal experience of the authors or case studies.

### Grade 2

No recommendations are cited in the literature for management approaches specific to grade 2 MKI-associated HFSR involving compounds or procedures for skin care or symp-

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**Table 2. Recommendations for prophylactic management of hand-foot skin reaction**

<table>
<thead>
<tr>
<th>Clinical goals/objectives</th>
<th>Recommendations</th>
<th>Source</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen for pre-existing plantar hyperkeratosis</td>
<td>Suitable podiatry care</td>
<td>Personal experience or recommendation of the authors</td>
<td>[8, 10, 11, 19]</td>
</tr>
<tr>
<td>Prophylactic removal of the hyperkeratotic areas</td>
<td>Manicure or pedicure before and during treatment to remove hyperkeratosis</td>
<td>Personal experience or recommendation of the authors</td>
<td>[7–11, 19]</td>
</tr>
<tr>
<td>Prophylactic skin care</td>
<td>● Emollients</td>
<td>Personal experience or recommendation of the authors</td>
<td>[7, 11, 15, 17, 20, 25, 38, 45]</td>
</tr>
<tr>
<td>Protection of pressure-sensitive areas of the hands and feet</td>
<td>Wear well-fitting, soft shoes (e.g., sandals), foam-type absorbing soles, and shock absorbers to relieve painful pressure points</td>
<td>Personal experience or recommendation of the authors</td>
<td>[3, 10, 19, 20]</td>
</tr>
<tr>
<td>Prophylactic systemic treatments</td>
<td>Preventive administration of pyridoxine (doses of 50–150 mg/day)</td>
<td>Work of Vukelja et al. [46] in a patient with 5-FU–induced PPE; cited by others</td>
<td>[3, 16, 46, 47]</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoids&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Opinion of the author</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclooxygenase-2 inhibitors&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Work of Lin et al. [47] with capcitabine and celecoxib; cited by others</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Route of administration is not identified; no evidence of successful use.

<sup>b</sup>Effective as a systemic approach for prophylaxis of chemotherapy-associated hand–foot syndrome (5-FU, capecitabine, tegafur, emitefur, vinorelbine, doxorubicin, irinotecan, cytarabine, floxuridine), as well as sorafenib.

Abbreviations: 5-FU, 5-fluorouracil; PPE, palmar–plantar erythrodysesthesia.
Clinical goals for grade 2 HFSR included controlling hyperkeratosis, cushioning callused areas, moisturizing the skin, controlling symptoms, and relieving discomfort. The specific treatment approaches cited for grade 1 HFSR also applied to grade 2 HFSR (Table 4). The major approach used to control grade 2 HFSR is described in the reviewed literature as dose adjustment of MKIs. Recommendations for dosage or regimen adjustments for sorafenib were based on the proceedings from the expert panel [5] and were based on whether this was the first occurrence of grade 2 HFSR or a second, third, or fourth occurrence (Table 4).

### Table 3. Recommendations for management of grade 1 hand–foot skin reaction (HFSR)

<table>
<thead>
<tr>
<th>Clinical goals/objectives</th>
<th>Recommendations</th>
<th>Source</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatology referral and management</td>
<td>Early and appropriate dermatologic management</td>
<td>Personal experience of the authors</td>
<td>[3, 36, 45]</td>
</tr>
<tr>
<td></td>
<td>Active collaboration between dermatologists and medical oncologists or urologists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local control of symptoms at first signs of paresthesias</td>
<td>Over-the-counter products help patients maintain a sense of control over their treatment plan</td>
<td>Personal experience of the author</td>
<td>[4]</td>
</tr>
<tr>
<td>Control hyperkeratosis through products that aid in natural exfoliation</td>
<td>Decrease thickness of hyperkeratotic areas with keratolytics, such as 40% urea and/or salicylic acid Nonprescription emollient Twice-daily application of the products appears adequate</td>
<td>Personal experience of the authors</td>
<td>[4, 7, 8, 11, 14, 19, 37, 38, 48]</td>
</tr>
<tr>
<td>Highly inflammatory lesions</td>
<td>Dermocorticoids are unproven</td>
<td>Cited work of others</td>
<td>[15, 19]</td>
</tr>
<tr>
<td>Cushioning the callused areas to relieve discomfort</td>
<td>Footwear: gel inserts may provide some relief; loose-fitting shoes or slippers Analgesics: low- to moderate-dose analgesics; applying sunburn-relief spray to affected areas when needed Local/regional cooling, cold compresses: cold compresses/ice packs for pain relief; cooling battery or cooling hand and foot baths to relieve the symptoms Foot soaks: soaking feet in magnesium sulfate to soften calluses and reduce pain upon pressure</td>
<td>Personal experience of the author</td>
<td>[3, 4, 7, 8, 11, 34, 36, 49, 50]</td>
</tr>
<tr>
<td>Local application of occlusive emollients to maintain moisture and treat dry skin</td>
<td>Frequent application of highly occlusive emollients Emollient and urea-based creams may provide comfort and softening of the lesions Diligent application of creams and lotions especially to palms and soles Keep affected areas soft and pliable to prevent cracks or breaks in skin integrity</td>
<td>Personal experience of the authors</td>
<td>[11, 36]</td>
</tr>
<tr>
<td>Dose adjustment for grade 1 HFSR seen with sorafenib</td>
<td>Continue treatment with sorafenib and consider topical therapy for symptomatic relief</td>
<td>Expert panel</td>
<td>[5]</td>
</tr>
</tbody>
</table>

### Grade 3

Clinical goals for grade 3 HFSR included symptom reduction and prevention of further progression [3, 25–27]. Specific supportive measures included topical therapies such as cortisone creams and topical antibiotics. Systemic strategies to reduce symptoms and prevent further progression included pyridoxine in doses of 50–150 mg/day [3, 25–27]. The efficacy of corticosteroids has not been established. The cornerstone of the treatment recommendations is interruption of MKI treatment for a minimum of 7 days until toxicity has resolved to grade 0 or 1 (Table 5) and a decrease by one dose level (sorafenib, 400 mg daily or 400 mg every
other day) when resuming treatment. Specific recommendations for resumption of treatment and for a second or third occurrence of grade 3 HFSR can be found in Table 5 [5]. Overall, there are limited evidence-based data to guide selection of the most effective and specific measures on the management of MKI-associated grade 3 HFSR. The literature search identified a single uncontrolled HFSR treatment study of 12 patients predominantly with grade 3 toxicity [26], and reported improvement in skin toxicity with treatments including single-agent 40% urea cream, 0.1% tazarotene cream, and 5% fluorouracil cream. The recommendations and treatment approaches listed in Table 5 are based solely on clinical experience, case studies, or uncontrolled trial designs. In a case study of three patients on a sunitinib treatment regimen, the occurrence of adverse effects diminished during the rest period within the treatment cycle [28] and/or upon dose reduction of sunitinib [29].

Clinical reports of grade 3 HFSR treatment [4, 19] have observed that toxicity may resolve within a few days by employing approaches such as dose interruption/reduction and systemic or local supportive measures, after which treatment with MKIs can be resumed. In a dermatologic subanalysis of the Treatment Approaches in Renal Cancer Global Evaluation Trial [30], grade 3 HFSR resulted in 50% dose reductions in two of the 43 renal cell carcinoma (RCC) patients receiving sorafenib, and toxicity resolved in 3–4 weeks without long-term sequelae [31]. Upon restoration of full-dose sorafenib, HFSR recurred in only one of those patients. No sorafenib-induced nevi modifications were observed; however, since this study, several nevi eruptions have occurred in patients treated with sorafenib [32, 33]. In a single case study of a patient with RCC who presented with HFSR after treatment with sorafenib, discontinuation of treatment for 14 days combined with topical treatment and mild analgesics for pain led to resolution of the HFSR [34]. After the HFSR had resolved, sorafenib was

Table 4. Recommendations for management of grade 2 hand–foot skin reaction (HFSR)

<table>
<thead>
<tr>
<th>Clinical goals/objectives</th>
<th>Recommendations</th>
<th>Source</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General goals for controlling hyperkeratosis, cushioning callused areas, moisturizing the skin, controlling the symptoms, relieving discomfort</td>
<td>See recommendations for grade 1 HFSR (Table 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose adjustment for grade 2 HFSR seen with sorafenib</td>
<td>On the first occurrence of grade 2 HFSR, promptly institute supportive measures such as topical therapy for symptomatic relief and consider a dose decrease of sorafenib to 400 mg daily for a minimum of 7 days and up to 28 days. If toxicity resolves to grade 0 or 1 after dose reduction, increase to registration dose: sorafenib, 400 mg twice daily. If toxicity does not resolve to grade 0 or 1 despite dose reduction, interrupt MKI treatment for a minimum of 7 days and until toxicity has resolved to grade 0 or 1. When resuming treatment after dose interruption, begin at reduced dose: sorafenib, 400 mg daily. If toxicity is maintained at grade 0 or 1 at reduced dose for a minimum of 7 days, increase to registration dose. On the second or third occurrence of grade 2 HFSR, follow steps for first occurrence; upon resuming MKI treatment, decrease dose by one dose level (sorafenib, 400 mg daily or 400 mg every other day); decision whether to re-escalate dose should be based on clinical judgment and patient preference. On the fourth occurrence of grade 2 HFSR, the decision whether to discontinue MKI treatment should be based on clinical judgment and patient preference.</td>
<td>Expert panel</td>
<td>[5]</td>
</tr>
</tbody>
</table>

Abbreviation: MKI, multikinase inhibitor.
Table 5. Recommendations for management of grade 3 hand–foot skin reaction (HFSR)

<table>
<thead>
<tr>
<th>Clinical goals/objectives</th>
<th>Recommendations</th>
<th>Source</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local topical strategies to reduce symptoms and prevent further progression</td>
<td>Treatment of blisters and erosions with a wet disinfectant Emollient and urea-based creams may provide comfort and softening of the lesions Diligent application of creams and lotions especially to palms and soles For severe forms of HFSR, the combination of a cortisone cream and topical antibiotic such as fluconazole or gentamicin is recommended Efficacy of dimethylsulfoxide has not been substantiated</td>
<td>Personal experience or recommendation of the authors Uncontrolled observational study</td>
<td>[3, 7, 20, 51, 26]</td>
</tr>
<tr>
<td>Systemic strategies to reduce symptoms and prevent further progression</td>
<td>Pyridoxine may be beneficial (doses of 50–150 mg/day) Mechanism of action is still unknown Only in a few exceptional cases is systemic administration of corticosteroids or antihistamines indicated to complement therapy Efficacy of corticosteroids has not been established</td>
<td>Work of Vukelja et al. [46] in a patient with 5-FU–induced PPE; cited by others Personal experience or recommendation of the authors</td>
<td>[3, 15, 20, 46]</td>
</tr>
<tr>
<td>Dose adjustment recommendations for grade 3 HFSR seen with sorafenib</td>
<td>On the first occurrence of grade 3 HFSR, institute supportive measures such as topical therapy for symptomatic relief and interrupt MKI treatment for a minimum of 7 days and until toxicity has resolved to grade 0 or 1 When resuming treatment after dose interruption, decrease by one dose level (sorafenib, 400 mg daily or 400 mg every other day) If toxicity is maintained at grade 0 or 1 at reduced dose for a minimum of 7 days, increase by one dose level (sorafenib, 400 mg twice daily or 400 mg daily) On the second occurrence of grade 3 HFSR, follow steps for first occurrence; upon resuming MKI treatment, decrease dose by one dose level (sorafenib, 400 mg daily or 400 mg every other day); decision whether to re-escalate dose should be based on clinical judgment and patient preference On the third occurrence of grade 3 HFSR, the decision whether to discontinue MKI therapy should be based on clinical judgment and patient preference</td>
<td>Expert panel</td>
<td>[5]</td>
</tr>
</tbody>
</table>

Abbreviation: 5-FU, 5-fluorouracil; MKI, multikinase inhibitor; PPE, palmar–plantar erythrodysesthesia.
resumed at a 50% dose reduction without any further incidence of toxicity.

The range and variety of skin care products that have been cited in the literature as having treatment potential for the management of HFSR are listed in Table 6.

**DISCUSSION**

No evidence-based treatment algorithms exist for cutaneous toxicities of the MKIs in the dermatologic or oncologic literature [17, 35]. Our systematic review of the published literature through August 31, 2008, revealed that current recommendations on the clinical approaches to HFSR prevention and treatment are largely anecdotal, derived from case reports, based on practices implemented during clinical trials to optimize MKI treatment duration, culled from postmarketing practices, or extrapolated from approaches used for chemotherapy-induced HFS (e.g., capecitabine, 5-fluorouracil [5-FU], doxorubicin) rather than specifically from MKIs. The literature on treatment of HFS stemming from the use of chemotherapeutic agents and the current recommendations may or may not be appropriate in treating the side effects of newer agents [36]. Thus far, there is no evidence-based rationale to advocate for any of the preventive measures for chemotherapy-induced HFS for prophylaxis of MKI-associated HFSR [25, 36]. Therefore, it will be important to understand the similarities and differences between the pathogenesis, histology, clinical course, and complications of dermatologic reactions (HFS) induced by traditional agents, such as capecitabine and 5-FU, and those induced by MKIs (HFSR) to develop appropriate, rationally developed interventions [36].

Among the C1 articles reviewed, none were randomized, controlled trials designed to test HFSR management approaches. In addition, none of the ancillary, prospective, observational, or case–control studies described in the literature had been designed to test the efficacy of distinct treatment approaches in the management of HFSR on either clinical or patient-reported outcomes. The phase I–III studies that have thus far established MKIs, such as sorafenib, as effective therapeutic agents for metastatic cancers have not included the systematic study of HFSR management approaches [30, 39, 40]. Thus, a major conclusion from our study points to the need for additional research to test and compare the various recommendations for prevention and treatment of HFSR and to further elucidate the most efficacious methods for treating the side effects observed with newer targeted therapies [36]. Specifically, research is needed on: (a) appropriate patient education on prophylaxis for HFSR and its effects on patient outcomes; (b) how often

| Table 6. Skin care products for use in hand–foot skin reactions (HFSR) (adapted from [17, 36]) |
|-----------------------------------------------|---------------------------------------------------------------|
| **Skin care products for acral erythema/xerosis** | **Product information** |
| Cetaphil® (Galderma Laboratories, Ft. Worth, TX) | Nondeodorant, fragrance-free products |
| Aveeno® (Johnson & Johnson, New Brunswick, NJ) | Nondeodorant, fragrance-free products |
| Udderly Smooth® (Redex Industries, Salem, OH), Gold Bond® (Chattem, Chattanooga, TN) | Thicker products with more intense moisturizing properties than basic lotions; anti-itch formulations are available |
| Norwegian Formula: Smoothing Relief Anti-Itch Moisturizer by Neutrogena® (Neutrogena, Los Angeles, CA) | Contains dimethicone 1%, camphor 0.1%, and lidocaine |
| Norwegian Formula: Foot Cream by Neutrogena® | Contains cetearyl alcohol, dimethicone, menthol, and urea |
| Bag Balm® (Dairy Association Co., Lyndonville, VT) | May provide “cooling” effect from eucalyptus |
| Eucerin® (Beiersdorf AG, Hamburg, Germany) Cream | Best used at night due to greasy formulation |
| Eucerin® Dry Skin Therapy | Contains urea and alpha hydroxy acid |
| Aquaphor® (Beiersdorf AG, Hamburg, Germany) Healing Ointment | Petrolatum 41% |
| Kerasal® (Alterna LLC, Whippany, NJ) | Salicylic acid 5% exfoliates and softens skin; urea 10% moisturizes skin |
| Blue Lizard® (Crown Laboratories, Johnson City, TN) | UV A and B sunblock, water resistant |
the patient should be seen by an oncologist or dermatologist after beginning treatment with MKIs; (c) how to accurately diagnose HFSR in its mild forms and recognize subsequent dermatologic complications; (d) how to effectively treat and remove the calluses on hands and feet without leading to increased HFSSR damage and symptom burden; (e) providing guidance to both patients and providers on the best types of gel inserts, cushions, and soft footwear; (f) identifying the treatment strategies that are most effective at each grade of toxicity or severity; and (g) testing the effectiveness of specific emollients and keratolytic creams for preemptive or reactive treatment of MKI-associated HFSR.

Efficacy studies on novel mechanism-based prophylactic or palliative therapy are needed to provide the data that may ultimately lead to the development of better tolerance of novel antineoplastic or targeted therapies with reduced dermatologic side effects [41]. A major pitfall of conducting such trials is the risk of ascribing an improvement to the palliative agent, when that improvement may represent the natural history of the dermatologic reaction or poor compliance with the inciting agent (MKI) [41]. Because dose reductions can postpone or undermine optimal anticancer treatment efficacy, the prevention and minimization of dermatologic adverse events through prompt recognition and management is an important goal. Treatment options will need to be adapted according to the availability of agents, reimbursement patterns, and national and international treatment guidelines [15].

Another important need is a better understanding of the psychological and social implications that dermatologic reactions have on patients receiving cancer treatment. Brief toxicity screens serve as poor substitutes for the measurement of patient well-being. None of the studies or reports in the reviewed literature included a detailed assessment of QoL and patient symptom burden. Tools for the assessment of patient response to preventive and palliative measures, whether newly developed or adapted, are required to advance research on HFSR outcomes; such tools are essential for clinicians to gain an understanding of the full burden that HFSR imposes on daily life and whether the condition is moderated by patient characteristics, location of HFSR, and other comorbidities. In this regard, the dermatology literature shows that several questionnaires are available for patients to complete on a regular basis and thus provide information about their condition to aid investigators in understanding whether the dermatologic symptoms are worsening or improving and their impact on the patient’s QoL [42, 43]; however, none of the available measurement tools were developed to specifically assess HFSR. Detailed questionnaires for patient completion should be used in conjunction with accepted criteria, such as the NCI-CTCAE v3.0 [13, 41].

In order to apply a systematic approach to future research and development of evidence-based solutions for HFSR, it is essential to develop an evidence base for HFSR prevention and management goals and endpoints from rigorous study designs comparing clinical treatment alternatives or patient management strategies recommended in the scientific literature [44]. With regard to treatment goals, it was noted in our review that there is general consensus that hyperkeratosis is a risk factor for MKI-associated HFSR, and that these areas should be removed prophylactically before and during treatment, cushioned for orthopedic redistribution, and covered with emollient and/or keratolytic creams to moisturize and aid in natural exfoliation, respectively. However, the literature does not contain details on how to remove the hyperkeratosis or how to cushion these areas. Nor is there consensus on which specific agents to use, strength of the agent, dosage, duration or frequency, and supportive care practices. Thus, prospective studies, preferably randomized, double-blind, controlled designs of adequate size to detect meaningful effects, are needed to identify optimal treatment approaches developed though clinical experience to control the risk for HFSR, and to benefit patients. In addition to guideline evidence on effective treatments, prospective studies with health services research designs will be informative to identify optimal initiation of treatment: prophylaxis versus reactive treatment (waiting until symptoms arise and treating them reactively) as well as other elements of clinical practice that support clinical management of HFSR. Some of these considerations include identifying effective care processes such as the scheduling of visits with an oncologist for HFSR screening and monitoring, how to best deliver effective patient education, and the value of referrals for specialist care. For patients with extensive hyperkeratosis prior to initiating MKI treatment, comparisons of “standard” optimal care by an oncology team versus an approach supplemented by specialist care from dermatologic or podiatric consults (e.g., to remove hyperkeratosis and advise on cushioning of pressure areas and proper footwear) merit study for effects on the development or progression of HFSR. For patients with mild disability related to skin toxicity, studies are needed to weigh the benefit of traditional therapeutic approaches such as referrals to allied health for evaluation for adaptive equipment and assistance with independent living in prolonging treatment and reducing disability. Finally, HFSR outcomes should not only include consensus ratings on grade or severity, but also ratings from the patient’s perspective on tolerability and health-related QoL. With the advancements noted above, clinicians will have a scientific
basis for selecting and delivering the most effective therapy to prevent and manage HFSR.

**SUMMARY AND CONCLUSIONS**

It is important to identify effective, safe, and tolerable treatment options for prevention and palliation of cutaneous reactions to chemotherapy agents. Common themes for prophylaxis and grade 1 HFSR were consistently repeated throughout the peer-reviewed literature, focusing on the importance of controlling the hyperkeratosis and removing the calluses, cushioning of the hands and feet, and the use of creams to aid in the natural exfoliation and moisturization of the skin. Management of more severe cases of HFSR was discussed with a focus on dose modification and drug rechallenge, optimizing drug delivery. These observations are consistent with the best practice recommendations from the recently published expert panel [5]. Good clinical practice, as currently implemented, would involve following the recommendations of the expert panel. In regard to the published literature on HFSR associated with MKIs, although a number of treatments have been applied to prevent and treat HFSR, evidence establishing their efficacy using scientifically and clinically sound methods is missing.

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