Original Investigation

Cutaneous Adverse Effects Associated With the Tyrosine-Kinase Inhibitor Cabozantinib

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IMPORTANCE Cabozantinib S-malate is a vascular endothelial growth factor receptor 2, c-MET, and RET multitargeted tyrosine kinase inhibitor that has antiangiogenic and antitumorigenic properties with potential efficacy for the treatment of several cancers. Cutaneous reactions, one of the most frequently observed adverse effects associated with tyrosine kinase inhibitors, can significantly affect patients' quality of life and drug adherence and represent a major therapeutic challenge to maximizing the efficacy of targeted cancer therapy.

OBJECTIVE To describe the frequency and spectrum of skin reactions in patients with urothelial carcinoma receiving cabozantinib as monotherapy.

DESIGN, SETTING, AND PARTICIPANTS A single-institution study at the Clinical Research Center at the National Institutes of Health included 41 consecutive adults with metastatic, progressive urothelial carcinoma enrolled in a National Cancer Institute open-label, nonrandomized, phase 2 clinical trial. Patients receiving cabozantinib were evaluated for the development of skin reactions at each treatment visit from October 2012 to June 2014 by the primary oncology team and referred for dermatologic evaluation as appropriate.

MAIN OUTCOMES AND MEASURES A detailed history, full-body physical examination, and clinical photographs of cutaneous lesions were obtained.

RESULTS Of 41 consecutive patients who received cabozantinib, 30 (73%) developed 1 or more cutaneous toxic effects. Adverse events included hand-foot skin reaction (22 [54%]), generalized pigment dilution and/or hair depigmentation (18 [44%]), xerosis (8 [20%]), scrotal erythema/ulceration (6 [15%]), and nail splinter hemorrhages (5 [12%]). Eighteen patients (44%) had 2 or more cutaneous adverse events. Reactions developed in 17 of 30 patients (57%) during the first month of cabozantinib treatment and in 24 of 30 (80%) by the second month. Of patients with skin toxic effects, dose reduction was required for symptom management in 9 of 30 patients (30%), and treatment discontinuation was required in 4 of 30 (13%).

CONCLUSIONS AND RELEVANCE Cabozantinib monotherapy is associated with 1 or more cutaneous adverse events in most patients. Early detection and prompt treatment may increase patients' adherence to tyrosine kinase inhibitor therapy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01688999
in tumor cells, signaling pathways that control fundamental cell processes, such as cell differentiation, proliferation, motility, and cell death and survival, are often dysregulated, leading to cell transformation and proliferation.1

Tyrosine kinases, when activated, phosphorylate signal transduction molecules that regulate cell transformation, proliferation, apoptosis, angiogenesis, invasion, and migration.2 Tyrosine kinase inhibitors (TKIs) have emerged as important antineoplastic therapies effective in a number of malignant neoplasms and provide better selectivity in tumor cell death compared with conventional chemotherapy. Such targeted therapies offer renewed hope for effective cancer therapy and reduced toxic effects of drugs.

Cabozantinib S-malate (Cometriq in the United States; Exelixis Inc) is a small-molecule, multitargeted inhibitor predominantly targeting receptor tyrosine kinase c-MET (hepatocyte growth factor receptor), tyrosine kinase RET, and vascular endothelial growth factor receptor (VEGFR) 2. Cabozantinib also inhibits VEGFRs 1 and 3, mast/stem cell growth factor (c-KIT), fms-like tyrosine kinase 3, tyrosine-protein kinase receptor, ROS, tyrosine kinase receptor A/B, and Axl. In 2012, cabozantinib was approved by the US Food and Drug Administration for treatment of progressive, metastatic, medullary thyroid cancer.

Clinical phase 1 and 2 trials3–4 of cabozantinib have been conducted in various malignant neoplasms including medullary thyroid, gastric, renal cell, pancreatic, and prostate cancer. A randomized, placebo-controlled, phase 2 study has been completed in patients with castrate-refractory prostate cancer, and phase 3 trials are ongoing in renal cell carcinoma, prostate cancer, and hepatocellular carcinoma.5–8 A phase 3 trial involving 330 patients with medullary thyroid cancer demonstrated improvement in median progression-free survival to 11.2 months vs 4 months with placebo.9 The drug is also currently under investigation for treatment of urothelial carcinoma since preclinical and correlative studies10 have demonstrated an important role for c-MET in the pathogenesis of that cancer. Serum c-MET levels have been reported10 to be elevated in patients with metastatic vs muscle-invasive disease, and urine-shed c-MET is elevated in patients with visceral metastasis compared with patients without visceral metastasis. Overexpression of c-MET in tumor cells has been shown11 to significantly correlate with poor survival.

The most commonly observed adverse events associated with cabozantinib from pooled single-agent studies12 include fatigue, diarrhea, decreased appetite, nausea, weight loss, and vomiting. Hand-foot skin reaction (HFSR), a major dose-limiting skin toxic effect of TKIs, has been reported with cabozantinib at a frequency of approximately 40%.12–13 Skin rash including HFSR, xerosis, pruritus, erythema, and pigmentary changes were also reported,12–13 but other skin manifestations have not been described. We describe the clinical spectrum of dermatologic adverse effects observed in a subset of patients with bladder cancer treated with cabozantinib as monotherapy in a phase 2 clinical trial conducted at the National Institutes of Health Clinical Center, Bethesda, Maryland.

### Methods

Patients with advanced/metastatic bladder cancer were enrolled in an institutional review board–approved open-label, nonrandomized, phase 2 clinical trial of cabozantinib at the National Cancer Institute, Bethesda, Maryland. Informed written consent was obtained from all patients; participants received reimbursement for travel expenses. The primary outcome of the trial was the response rate of cabozantinib in patients with progressive, metastatic urothelial cancer. The major inclusion criteria for patients entering this study included a histologically confirmed diagnosis of urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis; age 18 years or older; prior treatment with at least 1 cytotoxic regimen; Karnofsky performance scale score of 60% or more; and adequate organ function. Major exclusion criteria included prior treatment with cabozantinib, treatment with small-molecule inhibitors of VEGFR within 2 years of study enrollment, cytotoxic chemotherapy within 3 weeks before the first dose of the study treatment, recent radiotherapy or radionuclide therapy, or primary brain tumor or active brain metastases.

Cabozantinib was administered at a dosage of 60 mg/d by mouth in each 28-day cycle. At each treatment visit from October 2012 to June 2014, patients were examined and questioned about the development of skin reactions. Those with skin signs or symptoms were referred to the Dermatology Consultation Clinic, where a detailed dermatologic history was taken, full-body examination was performed, and photographs were obtained. Adverse events were determined using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.14

### Results

#### Patient Population

Patients ranged in age from 41 to 82 years, and treatment duration ranged from 2 weeks to 20 months. Of 41 consecutive patients who received treatment, 30 individuals (73%) developed skin toxic effects. Cutaneous adverse events included HFSR, xerosis, pigment dilution/hair depigmentation, scrotal erythema or ulceration, and nail splinter hemorrhages (Table 1). Eighteen patients (44%) had 2 or more cutaneous toxic effects; the prevalence and timing of the effects are reported in Table 2. Skin reactions were documented in 17 of 30 patients (57%) during the first cycle (28 days) of cabozantinib treatment. Seven additional patients (23%) had documented skin reactions in the second cycle (56 days). Dose reduction was required for symptom management in 9 of 30 patients (30%), and treatment discontinuation was required in 4 of 30 patients (13%). In general, symptoms persisted over time and improved with temporary withholding of cabozantinib or dose reductions but did not resolve until discontinuation of therapy. Supportive care measures ameliorated the symptoms associated with skin toxic effects.
Dermatologic Adverse Effects Associated With Cabozantinib

Of 41 patients treated with cabozantinib, 22 (54%) developed HFSR. The median onset of symptoms was 4.0 weeks (range, 1.9-23.6 weeks). The HFSR typically manifested as tender, callus-like hyperkeratosis on the soles or palms with surrounding erythema, edema, and occasional bullae formation, most often localized over pressure-bearing surfaces (Figure 1A and B). Visible signs were typically preceded by symptoms of dysesthesia and severe pain induced by pressure, which significantly interfered with daily activities. Among the 22 patients with HFSR, affected areas were limited to the palms in 5 individuals (23%), the soles in 9 patients (41%), and both palms and soles in 8 (36%). Erythema and desquamation on the distal fingertips and/or interdigital skin were also common, occurring in 7 patients (32%). The dorsal aspects of the hands and feet were spared in all patients. Patients manifested either grade 1 (11 [50%]) or grade 2 (11 [50%]) severity HFSR. Dose reduction was required for symptom management in 8 patients (36%), and treatment discontinuation was necessary in 4 (18%).

All patients were given prescriptions for prophylactic application of ammonium lactate, 12%, lotion to their palms and soles twice daily at baseline. Once symptoms developed, urea cream, 20%, was used twice daily on the palms and soles and clobetasol propionate, 0.5%, cream was applied daily to the affected areas. Patients were advised to avoid friction, excessive pressure, and extreme temperatures to the palms and soles. Soft gel shoe inserts, well-fitted shoes, and thick cotton socks were recommended for protection. One patient reported a worsening of foot calluses and pain following the use of a pumice stone. Another patient reported significant improvement in tenderness and callus formation on the feet with the daily use of an over-the-counter instrument (Emjoi Micro-Pedi; Nano) for skin debridement and exfoliation.

Other skin findings included pigment dilution and/or hair depigmentation, xerosis, scrotal erythema, and subungal splinter hemorrhages. Generalized pigment dilution and/or hair depigmentation developed in 18 patients (44%) (Figure 1C and D). Skin pigment dilution was observed in 17 patients (41%) and hair depigmentation was observed in 6 (15%). Pigment dilution was both diffuse and patchy in appearance. Pigment dilution was noted to be reversible in 1 patient (2%) after cabozantinib dose reduction. Hair depigmentation was visible on...
the scalp, eyelashes, eyebrows, and torso. The median time to documentation of pigment changes was 11.4 weeks. Anecdotally, several patients noted that they would develop sunburn more easily during treatment with cabozantinib. Of the 18 patients with pigment dilution and/or hair depigmentation, 7 patients were ethnically pigmented (4 [22%] African American, 1 [6%] of Indian descent, 1 [6%] of Italian descent, and 1 [6%] Mexican American); the remaining 11 patients (61%) were white.

Xerosis developed on the hands, feet, or torso in 8 (20%) patients. The median time to onset of xerosis was 5.1 weeks. Seven patients (88%) with xerosis had concomitant HFSR. Management included the use of emollients and creams with urea, which resulted in improvement of skin dryness.

Scrotal erythema developed in 6 patients (15%) at a median of 5.3 weeks after initiating treatment (Figure 2A). Three men (7%) developed scrotal erythema and edema of grade 1 or 2, and 1 (33%) of these patients also had involvement of the glans penis and inner thighs after 2 weeks of therapy. Three patients (7%) developed a grade 2 scrotal ulcer. These adverse effects were managed with treatment interruption of 7 to 14 days, an athletic supporter to reduce friction, and a barrier ointment or paste, such as zinc oxide and menthol (Calmoseptine; Calmoseptine Inc) ointment. In 4 of the 6 patients (67%), scrotal erythema and/or ulceration occurred during or after the first cycle (4 weeks of therapy), and treatment was withheld for 7 to 14 days owing to concurrent HFSR or diarrhea. Therapy was restarted with a dose reduction; however, all 4 patients had disease progression at the first restaging (8 weeks). No female genital symptoms were reported.

### Table 2. Prevalence and Timing of Skin Adverse Effects Associated With Cabozantinib

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Patients, No. (%)</th>
<th>Median Onset After Drug Initiation, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-foot skin reaction</td>
<td>22 (54)</td>
<td>4.0</td>
</tr>
<tr>
<td>Pigment dilution/hair graying</td>
<td>18 (44)</td>
<td>11.4</td>
</tr>
<tr>
<td>Xerosis</td>
<td>8 (20)</td>
<td>5.1</td>
</tr>
<tr>
<td>Scrotal ulcer/erythema/edema</td>
<td>6 (15)</td>
<td>5.3</td>
</tr>
<tr>
<td>Splinter hemorrhages</td>
<td>5 (12)</td>
<td>NA</td>
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</tbody>
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Abbreviation: NA, not available.
Subungual splinter hemorrhages were present in 5 patients (12%). As shown in Figure 2B, they appeared as longitudinal brown-to-black lines beneath the distal nail plate. Splinter hemorrhages were asymptomatic and did not require treatment.

Discussion

Hand-foot skin reaction, also referred to as palmar-plantar erythrodysesthesia and chemotherapy-associated acral erythema, is a frequently observed sequela of conventional chemotherapy agents and typically improves on treatment cessation. However, TKIs are typically prescribed for long-term treatment, and, as a result, HFSR has become a major management issue in the use of these therapies. Hand-foot skin reaction is the most common cutaneous toxic effect seen with the TKIs sorafenib tosylate and sunitinib malate, both of which inhibit VEGFR, platelet-derived growth factor receptor, c-KIT, and fms-like tyrosine kinase 3 (Table 3). The median onset of HFSR in our cohort (4 weeks) is comparable to the onset of HFSR associated with sorafenib (2-4 weeks) and sunitinib (4-12 weeks).

The clinical appearance and distribution of TKI-associated HFSR differ from those of chemotherapy-associated HFSR, which classically manifests as diffuse palmarplantar erythema that occasionally involves the dorsal aspects of the hands and feet as well as intertriginous areas. Tyrosine kinase inhibitor-associated HFSR is characterized by bilateral, painful, localized calluslike hyperkeratosis with surrounding edema and erythema primarily affecting palmarplantar surfaces. Symptoms usually begin with dysesthesia and erythema that is worsened by mechanical or thermal stress, followed by increasing pain and callus-like thickening in the erythematos areas. Bullae, extensive desquamation, and ulceration can occur in severe cases. Histologic examination demonstrates acanthosis with kerati-

Table 3. Cutaneous Adverse Effects of Targeted Therapies and Associated Kinase Inhibition

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Cabozantinib</th>
<th>Sorafenib</th>
<th>Sunitinib</th>
<th>Imatinib</th>
<th>Erlotinib, Gefitinib, Cetuximab</th>
<th>Vemurafenib, Dabrafenib</th>
<th>Trametinib, Selumetinib</th>
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<tbody>
<tr>
<td>Kinase inhibition</td>
<td>VEGFR2, c-MET, RET, c-KIT, FLT3, Tie-2</td>
<td>VEGFR2/3, PDGFR, RAF (A,B,C), FLT3</td>
<td>VEGFR2, PDGFR, c-KIT, FLT3</td>
<td>Bcr-abl, PDGFR, c-KIT</td>
<td>EGFR</td>
<td>BRAF</td>
<td>MEK</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hair or skin depigmentation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Xerosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Scrotal erythema or ulceration</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Nail splinter hemorrhage</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Paronychia</td>
<td></td>
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<td></td>
<td></td>
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<td>+</td>
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</tr>
<tr>
<td>Periorbital edema</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Facial erythema</td>
<td>+</td>
<td></td>
<td></td>
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<td>+</td>
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<td>+</td>
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</tbody>
</table>

Abbreviations: c-KIT, mast/stem cell growth factor; EGFR, epidermal growth factor receptor; FLT3, fms-like tyrosine kinase 3; MEK, mitogen-activated protein/extracellular signal-regulated kinase; PDGFR, platelet-derived growth factor receptor; Tie-2, tyrosine-protein kinase receptor; VEGFR, vascular endothelial growth factor receptor.

* Modeled after Robert et al. The plus sign indicates that the adverse effect has been reported; blank cells indicate that there has been no report.
nococyte vacuolization, hyperkeratosis, parakeratosis, inflammatory infiltrates, and telangiectasia.22-23 Lesions are most prominent on the pressure points of the palms and soles but may affect the lateral sides of the hands and feet, the web spaces between digits, and periungual skin if these areas are exposed to mechanical stress.23-25

The pathogenesis of HFSR is not fully understood. Various hypotheses have been proposed, including toxic drug concentrations in association with acral sweat glands, capillary microtrauma at sites under mechanical stress leading to leakage of the drug into the surrounding tissue, and breakdown products from the drug accumulating in certain areas of the skin.22 A role for mechanical stress is supported by the finding that TKI-associated HFSR often occurs on pressure-bearing plantar surfaces. It is speculated that the antiangiogenic effect of VEGFR blockade in the vascular endothelium may impair vascular repair, leading to elevated levels of the drug in the tissue. Unlike sunitinib and sorafenib, cabozantinib also inhibits the tyrosine-protein kinase 2 (Tie-2) receptor, a pathway implicated in vascular remodeling.24 Inhibition of this receptor, therefore, may also contribute to the development and persistence of cabozantinib-induced HFSR. Hand-foot skin reaction has been associated25,26 with a favorable clinical outcome in patients who receive sorafenib treatment. Studies are needed to investigate the role of HFSR as a biomarker of clinical outcome in patients who receive cabozantinib.

Current therapeutic recommendations for HFSR are primarily based on case reports and series owing to a lack of clinical trial data. Dose modification or drug discontinuation usually leads to rapid improvement of painful lesions but at the potential expense of cancer response. Patients should be advised to avoid mechanical trauma to the skin (heavy weight lifting, long walks, or intense exercise), friction (tightly fitted shoes, gloves, or clothing), and extreme hot or cold temperatures.27 The use of thick cotton socks, gel shoe inserts, and orthotics are recommended to lessen and redistribute pressure across the plantar surfaces.27 Paraging hyperkeratotic lesions can be beneficial for symptom relief but should be performed with caution to avoid infection. Topical salicylic acid, 2% to 5%, or urea ointments, 10% to 50%, may be used for hyperkeratosis and moisturizing. Topical corticosteroids (eg, clobetasol) may be of some benefit for erythematous and inflammatory lesions. Limited data exist on the use of systemic therapies, such as vitamin E and pyridoxine (vitamin B6).28-33

Hair and/or generalized skin depigmentation were observed in 18 patients (44%) at a median of 11.4 weeks after cabozantinib initiation. Patients receiving long-term cabozantinib therapy, therefore, may develop increased photosensitivity and should be advised of this risk and appropriate UV-protective measures. Hair and skin depigmentation is also observed in association with sunitinib and imatinib,34 particularly in heavily pigmented skin, and is reversible within a few weeks of discontinuing therapy. Patients who receive sunitinib in a cyclic manner develop alternating horizontal bands of depigmented and normal hair resulting in a characteristic striped appearance.39 Cabozantinib, imatinib, and sunitinib inhibit c-KIT, which regulates the development, migration, and survival of melanocytes.40-42

Xerosis was also noted in our series in 8 patients (20%) and is a well-recognized phenomenon in association with sorafenib (10%-20%) and sunitinib (16%).43,44 In our cohort, xerosis primarily affected the distal extremities, and all patients with xerosis also developed HFSR. Acral involvement resulted in painful fissures and affected some patients’ ability to grasp objects. Frequent application of emollients with urea, 5% to 10%, usually results in improvement of xerosis.

Scrotal xerosis was observed in 6 of 24 (25%) of the male patients in our series, including ulceration in 3 (50%) of these men, with a median onset of 5.3 weeks. Although this manifestation has not been previously described in association with cabozantinib, scrotal symptoms have been reported45-47 in 3 case reports and 1 case series in association with sunitinib or sorafenib. In a series of 40 patients with renal cell carcinoma treated with sunitinib, 5 (12.5%) manifested scrotal xerosis and desquamation.47 Scrotal symptoms in previously reported45-47 patients developed within the first 3 weeks of treatment and were reversible after a 1- to 2-week treatment-free period. Iacovelli et al48 reported a female patient who developed vulvar pain and pruritus during the second cycle of sunitinib, with resolution of the symptoms after 7 days of drug interruption. Scrotal xerosis developed concurrently with HFSR following 2 weeks of sorafenib therapy in a patient recently reported by Guerra et al.49 The inguinal area and scrotal skin are well supplied with vasculature50 and are prone to friction and trauma. It is speculated that inhibition of VEGF and hypoxia-inducible factor 1-a may play a role in this adverse effect.45-47 Painful scrotal xerosis can also be seen in the setting of traditional chemotherapeutic drugs, which, together with erythematous involvement of the hands, feet, and other intertriginous areas, constitute a spectrum of chemotherapy-associated cutaneous toxic effects termed toxic xerosis of chemotherapy.51 Three patients in our cohort reported both scrotal symptoms and HFSR, but the lack of involvement of the inguinal creases and other intertriginous areas suggests a slightly altered presentation compared with classic toxic xerosis of chemotherapy. It is also possible that commonly seen pelvic lymphadenopathy leading to scrotal, pelvic, or lower extremity edema may have contributed to the relatively high incidence of scrotal symptoms in the present study. Scrotal xerosis/ulceration in our cohort was managed with treatment interruption and supportive approaches. Physicians should be aware that this adverse effect may be underrecognized and be alert that patients may be hesitant to mention genital or perianal symptoms.

Subungual splinter hemorrhages were observed in 5 patients (12%) in our cohort and are frequently seen with TKIs that block VEGFR function, particularly sunitinib and sorafenib. These hemorrhages appear as single or multiple linear red or black streaks under the nails, similar to splinter hemorrhages that have been classically described in patients with infective endocarditis.52 The mechanism is thought to be related to the antiangiogenic effect of TKIs; specifically, the ability to repair
traumatized nail-bed capillaries that sustain frequent micro-injuries at finger extremities may be prevented by VEGFR blockade.20 Previous authors20,53 have suggested that nail beds could offer a simple way to monitor the antiangiogenic effects of drugs that target VEGFR.

Conclusions

The development of novel molecularly targeted drugs, such as TKIs, represents a major milestone in cancer treatment. These potent drugs, however, are associated with numerous adverse effects, many of which are cutaneous and can affect patients’ quality of life and impede their adherence to long-term treatment. It is crucial for dermatologists to be familiar with skin reactions associated with these medications since early detection and prompt treatment may increase adherence to this potentially effective intervention. Management of the symptoms requires a multidisciplinary approach between the dermatology and oncology services, and controlled trials are needed to assess the benefit of treatment options, particularly for disabling complications such as HFSR.

REFERENCES