Overview and Management of Dermatologic Events Associated with Targeted Therapies for Medullary Thyroid Cancer

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Background: Treatment options for patients with advanced or metastatic medullary thyroid cancer (MTC) have, in recent years, expanded with the approval of two tyrosine kinase inhibitors (TKIs): vandetanib and cabozantinib. Other agents, including TKIs, are under clinical investigation for MTC. Although patients treated with TKIs are at risk of developing dermatologic adverse events (AE), these untoward events may be mitigated through AE-driven algorithms.

Summary: AE-driven algorithms combine effective nonpharmaceutical and pharmaceutical treatment modalities implemented by a multidisciplinary effort that incorporates nursing interventions, patient education, and referrals to pain-management specialists, podiatrists, and dermatologists, as appropriate. Effective AE prevention and management reduce the need for dose interruptions and modifications, allowing patients the opportunity to derive the maximal benefit from TKI therapy, while maintaining quality of life.

Conclusions: Optimal use of targeted therapies in the treatment of MTC depends on careful patient selection, interdisciplinary communication, and patient education and encouragement to enhance compliance and safety, optimize consistent dosing, and maximize the use of effective therapies.

Introduction

THYROID CANCER IS THE MOST COMMON endocrine-related cancer (1) and is classified into three main histologic types: differentiated (papillary, follicular, and Hürthle), medullary, and anaplastic (undifferentiated) (2). The most common forms of thyroid cancer are papillary (80%) and follicular (11%); rarer types include medullary thyroid cancer (MTC) (4%) (2), Hürthle cell (3%), and anaplastic (2%) (3). While MTC is uncommon, it accounts for up to 14% of all thyroid cancer-related deaths (4). Approximately 70–75% of all MTC cases are sporadic and often present as a single unilateral tumor (5).

The five-year relative survival rate for patients with MTC by stage at diagnosis is 98% for stages I and II, 73% for stage III, and 40% for stage IV (3). Lower clinical stage and younger age (<40 years) at diagnosis are strong independent predictors for improved survival (4).

Patients with MTC are susceptible to the development of early metastatic disease. For example, 50–55% of patients with MTC develop local metastases to the lymph nodes, and 20% have metastatic disease to the lung, liver, or bone at diagnosis (6,7).

The main goals of treatment for patients with metastatic disease are optimizing survival and quality of life (QoL). Currently, there is no curative systemic therapy for patients with MTC, and treatment options for patients with recurrent or persistent disease are limited (2,8). Vandetanib is an oral small-molecule multitargeted tyrosine kinase inhibitor (TKI) of the product of the Rearranged during Transfection (*RET*) gene, vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor (EGFR) signaling pathways (9,10). Another small-molecule TKI, cabozantinib, also inhibits multiple tyrosine kinases, including RET, VEGFR2, as well as mesenchymal-epithelial transition factor (MET) (11,12). The U.S. Food and Drug Administration (FDA) approved vandetanib and cabozantinib for the treatment of advanced MTC in 2011 and 2012 respectively (12,13). Vandetanib also received marketing approval for MTC in Europe and Canada. Cabozantinib has recently been approved for treatment of MTC by the European Medicines Agency for this indication (14). Other TKIs are under clinical investigation for MTC (15), some of which are currently marketed for other indications. TKIs have varying profiles of potential pharmacologic targets that include subtypes of VEGFR and EGFR, as well as other proto-oncogene targets (Table 1) (12,13,15–21).

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TABLE 1. INCIDENCE OF DERMATOLOGIC ADVERSE EVENTS ASSOCIATED WITH TKI TREATMENT IN CLINICAL TRIALS OF PATIENTS WITH LOCALLY ADVANCED OR METASTATIC MTC

Drug	Pharmacologic targets	Authors	Type of study	Type of MTC	No. of patients	Dermatologic adverse events, % of patients	
						All grades	Grade ≥ 3
Vandetanib	EGFR	Robinson <i>et al.</i> 2010 (16)	Phase II, single arm, 100 mg/d	Hereditary	19	Rash	26
	VEGFR						NR
	RET	Wells <i>et al.</i> 2010 (17)	Phase II, single arm, 300 mg/d	Hereditary	30	Rash	67
	BRK						3
	TIE2	Wells <i>et al.</i> 2012 (18)	Phase III, vandetanib (300 mg/d) vs. placebo	Hereditary or sporadic	231	Rash	53
Cabozantinib	EPH	Caprelsa PI 2012 (13)				Dermatitis acneiform/acne	35
	Src (13)					Dry skin	15
						Photosensitivity reactions	13
						Pruritus	11
						Nail abnormalities	9
							0
							13
	VEGFR1	Cometriq PI 2012 (12)	Phase III, cabozantinib (140 mg/d) vs. placebo	Hereditary or sporadic (12)	214	HFSR	50
	VEGFR2					Hair color changes	34
	VEGFR3	Schoffski 2012 (19)				Rash	19
	RET					Dry skin	19
	MET					Alopecia	16
	KIT					Erythema	11
	FLT3						1
	TIE-2					Hyperkeratosis	7
	AXL						0
Sunitinib	TRKB (12)						
	VEGFR1	De Souza <i>et al.</i> 2010 (20)	Phase II	NS	25	HFSR	NR
	VEGFR2						17
	VEGFR3						
	RET						
	RET/PTC subtype1						
	RET/PTC subtype3 (15)						
Sorafenib	VEGFR2	Lam <i>et al.</i> 2010 (21)	Phase II, single arm, 400 mg twice daily	Hereditary or sporadic	21	HFSR	14
	VEGFR3					Alopecia	76
	RET					Rash (non-HFSR)	67
						Nail changes	48
	BRAF (15)					Dry skin/scalp	48
						Skin lesions/sores (non-HFSR)	38
						Scalp pruritus	33
						Photosensitivity	14
						Ruddy complexion	5
							0

EGFR, epidermal growth factor receptor; HFSR, hand-foot skin reaction; MTC, medullary thyroid cancer; NR, not reported; NS, not specified; RET, Rearranged during Transfection; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

The present article focuses on the assessment and management of TKI-associated dermatologic events in patients with MTC. The rationale and data to support the use of TKIs in MTC, the dermatologic adverse events (AEs) associated with this treatment, and recommendations for prevention, management, nursing assessments, and patient education are described.

Review

Rationale for using TKIs in MTC

In the early 1990s, investigators found that mutations in the *RET* proto-oncogene are linked to the development of MEN2A, MEN2B, and FMTC (22–25). Somatic mutations in *RET* are also common in sporadic MTC (26) and correlate with the risk of having lymph-node metastases at diagnosis, persistent disease, and shorter survival (27).

The *RET* gene encodes a transmembrane receptor tyrosine kinase that has important roles in cell growth, differentiation, and survival (5). The *RET* receptor is recognized by the persephin, artemin, and neurturin ligands that belong to the glial cell-derived neurotrophic factor family. The *RET* receptor is expressed by noradrenergic and dopaminergic neurons, thyroid C cells, and adrenal medulla. Gain of function or activating mutations in the *RET* gene are the primary cause of all hereditary MTC cases and between 25% and 50% of sporadic cases (5).

The vascular endothelial growth factor A (VEGF-A) and its VEGFRs, which have major roles in angiogenesis in normal tissues and malignant tumors, may also be involved in the development and maintenance of sporadic and hereditary MTC (28). VEGF-A and several VEGFRs are overexpressed in MTC biopsy specimens (28,29). In addition, VEGFR2 and EGFR are overexpressed in some metastases, while they are not expressed within the primary tumor, suggesting a role for these receptors in the progression of MTC (30). In preclinical studies using human thyroid tumor cell lines, high VEGF expression correlated with increased tumorigenic potential (31). Increased expression of MET has been observed in some MTC tumors (11,32).

Members of the RAS family of low-molecular weight GTP-binding proteins are important downstream mediators of effects occurring through these tyrosine kinases (33). RAS proteins are essential mediators in a variety of pathways that regulate normal and malignant cell proliferation (33). The RAS pathway, particularly through downstream effects at the *RET* receptor, has been implicated in MTC (34). In addition, a recent study in which the exomes of 17 sporadic MTCs were sequenced and compared with corresponding findings in an independent cohort of 40 sporadic and hereditary MTCs revealed that approximately 90% of MTCs have mutations in either *RET* or *RAS* (35). These mutations were found to be mutually exclusive, and few other types of mutations were identified.

In a phase III randomized double-blind study, vandetanib treatment (300 mg, administered orally, once daily) (13) compared with placebo significantly prolonged progression-free survival (PFS) in patients with symptomatic or progressive locally advanced or metastatic MTC (hazard ratio [HR] 0.46; 95% confidence interval [CI] 0.31–0.69; $p < 0.001$) (18). Patients treated with vandetanib also showed improved objective response rates, disease control rates, and calcitonin

and carcinoembryonic antigen biochemical response rates. Overall survival data are not yet available. The most common all-grade AEs (occurring at a frequency of $\geq 5\%$) reported for the vandetanib and placebo groups respectively were diarrhea (57% vs. 27%), rash (53% vs. 12%), dermatitis acneiform/acne (35% vs. 7%), nausea (33% vs. 16%), hypertension (33% vs. 5%), fatigue (24% vs. 23%), headache (26% vs. 9%), upper respiratory infection (23% vs. 16%), decreased appetite (21% vs. 12%), and abdominal pain (21% vs. 11%) (13). The study protocol mandated dose reduction from 300 mg/d to 200 mg/d for a grade 3 or 4 dermatologic AE (as well as for grade 3 or 4 gastrointestinal AEs and QTc prolongation) and another reduction to 100 mg/d if an additional grade 3 or 4 AE occurred (18).

Another phase III, double-blind, placebo-controlled study evaluated cabozantinib (140 mg, administered orally, once daily) compared with placebo in patients with actively progressive MTC within 14 months of screening (19). Median PFS was 11.2 months and 4.0 months in the cabozantinib and placebo arms respectively (HR 0.28; [CI 0.19–0.40]; $p < 0.0001$) (12). An improvement in partial response rate was also observed in the group receiving cabozantinib compared with those receiving placebo. No statistically significant difference in overall survival was seen at the planned interim analysis. The most common all-grade AEs in the cabozantinib arm compared with the placebo arm were diarrhea (63% vs. 33%), stomatitis (51% vs. 6%), palmar-plantar erythrodysesthesia syndrome (i.e., hand-foot skin reaction [HFSR]; 50% vs. 2%), decreased weight (48% vs. 10%), decreased appetite (46% vs. 16%), nausea (43% vs. 21%), fatigue (41% vs. 28%), oral pain (36% vs. 6%), hair color changes (34% vs. 1%), dysgeusia (34% vs. 6%), hypertension (33% vs. 4%), constipation (27% vs. 6%), abdominal pain (27% vs. 13%), vomiting (24% vs. 2%), asthenia (21% vs. 15%), and dysphonia (20% vs. 9%) (12).

Dermatologic AEs associated with TKIs

Dermatologic AEs have been well characterized for TKIs that target the VEGFR or EGFR pathways. Patients treated with TKIs may experience cutaneous AEs such as rash, erythema, pruritus, acneiform rash, paronychia, telangiectasia, alopecia, changes in hair growth or pigmentation, skin discoloration, xerosis (dryness), and HFSR (36,37). Incidence and severity of dermatologic AEs vary across the specific targeted therapies used and prescribed doses. While the factors that determine the profile of AEs have not been fully elucidated, risk factors that may be associated with skin reactions subsequent to EGFR inhibition include age, smoking status, and exposure to ionizing and ultraviolet (UV) radiation (e.g., sunlight) (38).

Putative mechanisms. The EGFR, which is thought to play an important role in the proliferation of the basal epidermal layer, is expressed at high levels in the basal and suprabasal layers of the skin, and in the outer layers of hair follicles (37). In experimental systems, inhibition of EGFR signaling in keratinocytes causes growth arrest, initiation of differentiation, and apoptosis. In patients treated with EGFR inhibitors, histologic analysis of the skin has revealed marked downregulation of phosphorylated EGFR and decreased proliferation and premature differentiation of basal keratinocytes (37). Thus, skin AEs associated with EGFR-inhibitor

treatment are likely to be linked to the overall inhibition of EGFR signaling in basal keratinocytes, leading to alterations in keratinocyte survival, proliferation, differentiation, migration, and attachment (37,39). EGFR inhibition can also cause an inflammatory response by triggering the release of cytokines and the resultant recruitment and activation of neutrophils, monocytes, and lymphocytes (39). Inflammation is a secondary but important contributor to the development of these dermatologic AEs (39). The pathogenic mechanism for the development of HFSR is thought to involve combined inhibition of the VEGFR and platelet-derived growth factor receptor (PDGFR) proangiogenic pathways, possibly preventing the proper implementation of vascular repair mechanisms in these high-pressure areas (36).

Types of skin AEs linked to specific drugs. Table 1 lists the incidence of dermatologic AEs associated with the TKIs vandetanib, sunitinib, sorafenib, and cabozantinib in clinical trials of patients with locally advanced or metastatic MTC

(12,13,15–21). Table 2 presents a grading scale on the severity of these AEs provided in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (40).

In the placebo-controlled phase III study of patients with MTC, dermatologic AEs of vandetanib were, in decreasing order of incidence, rash, dermatitis acneiform or acne, dry skin, photosensitivity reactions, pruritus, and nail abnormalities (Table 1) (13). Severe skin reactions, such as Stevens–Johnson syndrome, were rare, although some led to death or permanent treatment discontinuation (13). A systematic review and meta-analysis of nine studies of single-agent vandetanib in 2961 patients found a 46.1% incidence of all-grade skin rash and 3.5% high-grade skin rash (41). The same analysis reported that, when compared with controls in randomized studies, patients treated with vandetanib had a 2.43 relative risk ([CI 1.37–4.29]; $p=0.002$) of developing an all-grade rash. An analysis of the skin toxic effects observed in three clinical trials of patients receiving vandetanib for the treatment of advanced MTC revealed two additional

TABLE 2. CTCAE GRADING OF SELECTED TKI-ASSOCIATED DERMATOLOGIC AEs*

AE	Grade				
	1	2	3	4	5
Palmar-plantar erythrodysesthesia syndrome (hand-foot skin reaction) <i>Definition:</i> A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	—	—
Photosensitivity <i>Definition:</i> A disorder characterized by an increase in sensitivity of the skin to light	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10–30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Acneiform rash <i>Definition:</i> A disorder characterized by an eruption of papules and pustules, typically appearing in the face, scalp, upper chest, and back	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death

*National Cancer Institute Common Terminology Criteria for Adverse Events (40).

ADL, activities of daily living; AEs, adverse events; BSA, body surface area; CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.

dermatologic AEs: photodistributed erythematous eruptions and skin pigmentation changes (e.g., appearance of gray-blue macules on the face, scalp, or trunk) (42). Discontinuation of therapy was associated with rapid improvement in almost all patients with skin phototoxic effects, and reinitiation of therapy at a lower dose accompanied by strict photoprotection measures was successful in preventing a recurrence of this AE (42). A gradual disappearance of pigmented macules over a three- to six-month period was noted upon treatment discontinuation (42).

Dermatologic AEs associated with cabozantinib treatment in patients with MTC from the placebo-controlled phase III study were, in descending order, HFSR, hair color changes, rash, dry skin, alopecia, erythema, and hyperkeratosis (Table 1) (12).

Data from trials in MTC represent relatively small numbers of patients. Hence, the occurrence and incidence of these skin reactions may not be representative of experience in the overall population of patients treated with TKIs for all forms of cancer.

In registration studies for sunitinib, rash (29%), HFSR (29%), skin discoloration (25%), dry skin (23%), and hair color changes (20%) were among the most common AEs

experienced by patients with renal cell carcinomas. Similar dermatologic AEs were reported in patients with gastrointestinal stromal tumors or pancreatic neuroendocrine tumors (43). Warning notices or precautions for dermatologic AEs are not listed in the manufacturer's prescribing information.

In patients with renal cell cancer and hepatocellular cancer, HFSR and rash are the most common dermatologic AEs associated with sorafenib treatment. They are usually grade 1 or 2 according to the National Cancer Institute's CTCAE grading scale and typically occur during the first six weeks of treatment (40,44). In registration studies of sorafenib in patients with hepatocellular carcinoma and renal cell carcinoma, up to about 1% of patients had to permanently discontinue treatment due to HFSR. In the sorafenib prescribing information for dermatologic events reported from multiple clinical trials, erythema occurred in $\geq 10\%$ of patients, and exfoliative dermatitis, acne, and flushing in 1% to $\leq 10\%$ of patients (44).

Photographs of representative patients exhibiting some of the skin reactions associated with TKI therapy are shown in Figure 1.

FIG. 1. Photographs of representative patients exhibiting skin reactions associated with tyrosine kinase inhibitor (TKI) therapy. (A) acneiform rash, grade 2 (vandetanib); (B) gray and curly hair, grade 1 (sunitinib); (C) hand-foot skin reaction, grade 2 (cabozantinib); (D) stomatitis, grade 2 (cabozantinib); (E) photosensitivity, grade 1 (vandetanib); (F) photosensitivity, grade 1 (vandetanib). Photos courtesy of Mario E. Lacouture, MD.

Impact of dermatologic events on QoL. Dermatologic events can cause physical discomfort such as pain, burning, and increased skin sensitivity (45). These symptoms can affect a patient's ability to perform activities of daily living such as eating, grooming, exercise, and work. The effects of EGFR inhibitor-induced dermatologic AEs on QoL (46), including xerosis, rash, pruritus, and paronychia, resulted in decreased QoL, with rash having the highest impact. Younger patients reported decreased overall QoL compared with older patients for the same AEs (46).

Symptoms from ineffectively managed dermatologic AEs may also cause depression, frustration, worry, and withdrawal from certain social activities, thereby affecting a patient's physical, functional, emotional, and social well-being (45). Moreover, HFSR results in decreased QoL due to the associated symptoms of pain and tenderness (47).

Although data are limited, it is important to note the financial impact of managing dermatologic AEs to the economic burden of cancer care. Assessment and management may involve ongoing long-term care from multiple health-care professionals over multiple visits to the clinic or office.

Management

Guidelines and recommendations. Prior to starting an oncology patient on any type of treatment, a thorough medical history must be taken to document the patient's history of cancer treatments and past skin disorders, their current medication profile, and presence of current skin disorders or symptoms (48). Patients with skin symptoms should be asked specific questions regarding the location, onset, duration, relieving factors, severity, and history of medications (Fig. 2) (49,50).

Various recommendations exist for the management of TKI-associated dermatologic AEs (36,38,51–54). Figures 3 (51–53), 4 (55), 5 (38), and 6 (12,13) also provide specific guidance. There have not been any prospective randomized trials to evaluate the best management strategies for these dermatologic AEs in patients with MTC. Recommendations are based on the evaluation of existing data and clinical experience (36). An important message from all these publications is the need for practitioners to develop and consistently implement effective algorithms for AE management (see Figs. 3–5 for examples of effective algorithms for management of photosensitivity, HFSR, and acneiform

rash, respectively). Careful management is critical in allowing the patient to gain the most benefit from therapy by avoiding or limiting dose interruptions and modifications (36). However, these considerations must be balanced with the important goal of maintaining patients' QoL by minimizing the negative effects of debilitating AEs, particularly dermatologic AEs. In the case of serious drug-related dermatologic AEs, dose reductions, modifications, or interruptions might be necessary, as recommended by the product prescribing information. For example, in the cabozantinib prescribing information, dose interruptions are recommended for patients experiencing intolerable grade 2, grade 3, or higher grade skin toxicities, and some patients may require dose modifications at treatment reinitiation. These recommendations are described in Figure 6 (12,13).

Preventive measures. Results from a randomized study in 95 patients with metastatic colorectal cancer undergoing treatment with the EGFR monoclonal antibody inhibitor panitumumab suggest that preventive therapy may be more effective than reactive therapy in the management of dermatologic AEs with EGFR inhibitors (56). Patients in this study were randomized to pre-emptive treatment, consisting of skin moisturizers, sunscreen, topical steroid, and doxycycline, or reactive treatment begun after dermatologic AE development. The primary objective of the study was to assess the difference in the incidence of protocol-defined grade ≥ 2 skin AEs between the two groups during the six-week dermatologic treatment period. An approximate 50% reduction in skin AEs was observed in the pre-emptive versus reactive groups (56). Another study has demonstrated the effectiveness of prophylaxis in reducing the incidence or severity of grade ≤ 2 skin toxicities linked to treatment with the anti-EGFR monoclonal antibody cetuximab in patients with metastatic colorectal cancer (56,57).

Of 868 patients treated with sorafenib for hepatocellular carcinoma, a reduction was seen in the incidence of all-grade HFSR (56% in treatment arm vs. 73.6% in controls; $p < 0.0001$), and a 2.5-fold increase in the median time-to-first onset of HFSR (84 days in the treatment arm vs. 34 days in controls; $p < 0.001$), with the preventive daily use of urea-based cream (58). Figures 4 (55) and 5 (38) provide recommendations for the prevention of HFSR and acneiform rash respectively.

Stomatitis from targeted therapies is characterized by well-defined round plaques < 0.5 cm in diameter affecting the lips, tongue, and oral mucosa (59,60). The lesions are very painful and may impair the ability to eat, drink, or speak (59,61). These aphthous-stomatitis-like lesions are treated with topical corticosteroids (e.g., clobetasol 0.05% cream) applied onto the lesions or dexamethasone solution swish and spit, taken three times daily with avoidance of eating or drinking for 30 minutes afterward (59,61). In addition, topical lidocaine 2–4% jelly applied onto the lesions, or one tablespoon or less of lidocaine viscous swished around in the mouth and spat out (taken no more than every 3 h), will help mitigate the pain so that patients can eat or drink (38).

General supportive measures. Supportive measures should include advice for patients on how to manage dry skin. A thick alcohol-free emollient (e.g., Vanicream®, Pharmaceutical Specialties, Inc., Rochester, MN; Eucerin®, Beiersdorf

- When did the skin reaction start?
- Does the skin itch or hurt?
- What did the reaction first look like?
- Before this reaction occurred, have you made changes to any of your daily medications?
- Have you had any blisters in your skin, eyes, mouth, or genitals?
- Have you changed soap, detergents, lotions, etc, before you noticed the skin reaction?
- Have you previously experienced any similar symptoms?
- Have you tried any treatments (including over-the-counter treatments) and have they made the skin reaction better or worse?

FIG. 2. Triage questions that may be used to assess skin reactions during treatment (49,50). Republished with permission of Jannetti Publications, Inc., from Johannsen L 2005 Dermatology nursing essentials: a core curriculum. *Dermatol Nurs* 17:165–166; via Copyright Clearance Center, Inc.

^aExamples of topical steroids include hydrocortisone 2.5% cream or alclometasone 0.05% cream to the face and fluocinonide 0.05% or mometasone 0.1% to the body twice daily.

FIG. 3. Intervention algorithm for photosensitivity (51–53). CTCAE, National Cancer Institute’s Common Terminology Criteria for Adverse Events; SPF, sun protection factor.

AG, Hamburg, Germany) is recommended for moisturizing dry areas of the body (62,63). When xerotic skin is very dry and scaly, and for xerosis in the palms and soles, moisturizing creams or lotions containing salicylic acid 3–6%, respectively, or ammonium lactate 12%/lactic acid 12% (ammonium lactate topical) are recommended. Figure 7 (49,59,61,64,65) provides measures that may be helpful in preventing and managing xerosis and stomatitis.

Patient education

Patient and caregiver education is extremely important for the prevention, early recognition, and management of dermatologic AEs. It is recommended that this education start at the beginning and be reinforced throughout treatment by dermatology and oncology specialists. A patient-appropriate guide

can be provided describing the common side effects experienced with a particular TKI. Specific instructions on when to call a doctor’s office to discuss onset or exacerbation of symptoms should also be provided. Patients should keep documentation of the location, onset, symptoms/quality, treatment, and self-evaluation of all their AEs and bring concomitant medications to the clinic so the healthcare team can determine if they may be causing or worsening AEs. For example, topical and oral retinoids may lead to dryness and may worsen burning or irritation of skin rashes caused by EGFR inhibitors (51).

Nurses have an important role in patient education related to dermatologic AEs. Both healthcare providers and patients may view nurses as spending more time with patients and giving more in-depth treatment instructions than other professionals (66). Therefore, to prevent alteration of anticancer treatment administration and produce optimal results for

FIG. 4. Intervention algorithm for hand-foot skin reaction (55). Published in Balagula Y 2010J Support Oncol 8:149–161. Copyright © 2010; Elsevier. ^aFrom Ren Z, *et al.* 2012 Clin Oncol 30: Abstract 4008 (58). GABA, gamma-aminobutyric acid; NSAIDs, nonsteroidal anti-inflammatory drugs.

FIG. 5. Intervention algorithm for acneiform rash (38). Published in Balagula Y 2011 Int J Dermatol 50:129–146. Copyright © 2011; John Wiley & Sons, Inc. EGFR, epidermal growth factor receptor.

Vandetanib	Cabozantinib
<ul style="list-style-type: none"> Treatment should be stopped for CTCAE grade 3 or greater toxicity. Vandetanib should be resumed at a reduced dose when the toxicity resolves or improves to CTCAE grade 1 The 300-mg daily dose can be reduced to 200 mg and then to 100 mg 	<ul style="list-style-type: none"> Withhold cabozantinib in patients who develop grade 3 or greater nonhematologic adverse reactions or intolerable grade 2 adverse reactions (eg, intolerable grade 2 HFSR, grade 3 or 4 HFSR) until improvement to grade 1 Institute AE-specific intervention during treatment, hold and continue upon rechallenge for at least 2 weeks Upon resolution/improvement of the adverse reaction reduce the dose as follows: <ul style="list-style-type: none"> If previously receiving 140-mg daily dose, resume treatment at 100 mg daily If previously receiving 100-mg daily dose, resume treatment at 60 mg daily If previously receiving 60-mg daily dose, resume at 60 mg if tolerated, otherwise, discontinue cabozantinib

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; HFS, hand-foot skin reaction.

FIG. 6. Skin toxicities requiring dose interruption and strategies for reintroducing TKI therapy (12,13).

patient care, nurses must understand the basis of side effects, impact on QoL, and pre-emptive measures, and must be able to provide optimal psychosocial support.

According to one survey, prior to treatment initiation, cancer survivors considered skin irritation and dry skin to be minor concerns compared with AEs such as a weaker immune system, hair loss, and fatigue (67). However, after undergoing treatment, most patients reported that dry skin and skin irritation were important concerns that heavily impacted their lives. Most respondents said that skin AEs were worse than expected, indicating they had either under-

estimated the potential impact of dermatologic AEs prior to initiation of therapy or had not been sufficiently informed. These data emphasize the importance of patient education.

Conversations with your patients. Conversations between the treatment team and patients should enhance patients' control over disease management. The cause, course, treatment, and management of disease side effects should be discussed (68). Emotional and informational support for patients with cancer is likely to have a beneficial impact on psychological adjustment (68). Such educational interventions may also help increase patient self-esteem and outlook, especially when management strategies are implemented effectively. More data are needed on the psychological needs of patients with dermatologic AEs linked to treatment with targeted therapies to improve the accuracy of assessments and to develop even more effective patient education (69). Oncology nurses provide an easily accessible sounding board for patients to express their psychological as well as physical concerns (70). Therefore, in addition to educating patients on interventions to ease the physical impact of the AEs, nurses can help determine when referral for psychosocial counseling is appropriate.

Patient education on specific topics: protection from UV radiation. Thick application of sunscreen and wearing protective clothing whenever possible should be emphasized, since UV radiation can trigger rash and photosensitivity in patients treated with vandetanib and sorafenib (44,51). Nonalcohol-based physical sunblocks (e.g., zinc oxide, titanium dioxide) with a sun protection factor of 30 that inhibit both UVA and UVB radiation are recommended because they are effective and cause less irritation than other types of sunscreen. To provide the best sun protection, patients should also be advised to be in the shade between 10:00 AM and 4:00 PM, and to wear a broad hat and appropriate clothing (65). In addition, patients should be counseled to apply an appropriate amount of sunscreen—at least 35 mL to cover the body of an average adult, and should be repeated every two hours or every hour if swimming or sweating.

Patient education on specific topics: typical timing for development of acneiform rash and HFSR. It is critical to inform patients that both the acneiform rash and HFSR typically develop within the first eight weeks of therapy (71). Knowing that these events peak in severity during this time ensures close follow-up and care during this time, while reassuring patients that they will not endure these toxicities during the entire duration of their therapy.

Summary and Conclusions

The treatment options available for patients with metastatic MTC have been expanded with the FDA approval of vandetanib and cabozantinib. Other TKIs are under clinical investigation for MTC, including some currently marketed for other indications. Patients treated with TKIs are at risk of developing dermatologic AEs, a common type of AE associated with this class of agents. The risk of developing these dermatologic AEs can be reduced and their impact may be diminished through development and implementation of preventive and management algorithms. These algorithms

<p>Xerosis</p> <ul style="list-style-type: none"> Restrict time in shower or bathtub Bathe in cool or warm water instead of hot Use mild soaps and low pH cleansers and moisturizers Avoid cleansers containing alcohol Apply moisturizers twice daily, including immediately after bathing when skin is still damp Reduce friction on the skin, such as by patting with a towel instead of rubbing Maintain humidity in the home by lowering the heat or using a humidifier Maintain short fingernails to prevent skin damage in cases where the patient is unable to avoid scratching Wear gloves or socks when exercising Protect the skin from cold weather by using hats and gloves Protect lips with fragrance-free, vitamin-free lip balm When xerotic skin is very dry and scaly, and for xerosis in the palms and soles, moisturizing creams or lotions containing salicylic acid 3% to 6%, respectively, or ammonium lactate 12%/lactic acid 12% (ammonium lactate topical) are recommended <p>Stomatitis</p> <ul style="list-style-type: none"> Stomatitis/mucositis is treated with topical corticosteroids (clobetasol 0.05% cream) applied onto the lesions or dexamethasone solution swish and spit, thrice daily with avoidance of eating or drinking for 30 minutes afterward In addition, topical lidocaine 2% to 4% jelly applied onto the lesions or 1 tablespoon or less of lidocaine viscous swished around in the mouth and spit out (taken no more than every 3 hours) will help mitigate the pain so that patients can eat or drink
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FIG. 7. Supportive and preventive measures in the management of dermatologic adverse events (49,59,61,64,65).

combine nonpharmaceutical and pharmaceutical treatment modalities that are best implemented by a multidisciplinary effort, incorporating nursing interventions, patient education, and referrals to pain-management and dermatologic specialists, as appropriate. Effective AE prevention and management reduces dose interruptions and modifications, enabling patients to derive the most benefit from anticancer therapy, while maintaining a good QoL. Effective management of targeted therapies in the treatment of MTC strongly relies on patient education, interdisciplinary communication, and encouragement to minimize interruption of otherwise effective treatment.

Acknowledgments

We thank Monica Nicosia, PhD, and Antoinette Campo from SCI Scientific Communications & Information (SCI), and Jennifer Steeber, PhD, and Susan Moench, PhD, PA-C, formerly of SCI, who provided medical writing support funded by AstraZeneca LP.

Author Disclosure Statement

Mario E. Lacouture is a consultant for AstraZeneca. Richard T. Kloos is an employee and stockholder in Veracyte, Inc. The remaining authors have no competing financial interests.

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