Non-Rash Dermatologic Adverse Events Related to Targeted Therapies

Jane Bryce and Christine B. Boers-Doets

Objectives: *To provide background information and management strategies for non-rash dermatological adverse events.*

Data Sources: *Peer-reviewed journal articles, professional manuals, online sources.*

Conclusion: *During the last decade, many dermatological adverse events of targeted therapy have been reported, including xerosis, skin fissures, pruritus, photosensitivity, pigmentation changes, hair and nail changes, hand-foot skin reaction, squamoproliferative lesions, Stevens-Johnsons syndrome, and toxic epidermal necrolysis. Although evidenced-based treatment options are scarce, many recommendations have been described in the literature that should be considered to apply in daily practice.*

Implications for Nursing Practice: *Nursing practice will be enhanced by education, assessment, and management recommendations.*

Key Words: *Targeted therapy, non-rash adverse events, education, assessment, management*

THE targeted agents used in oncology rely on specific inhibition of one or more events along the signaling pathways that control cell differentiation. This inhibition aims to stop the aberrations in the pathway that have allowed proliferation of tumor cells. However, the effects of targeted inhibition are not limited to cancer cells, and thus, adverse events of targeted therapy have been described across various systems.[1] Dermatologic adverse events are among the most frequently occurring, and have been reported in epidermal growth factor receptor (EGFR), multi tyrosine-kinase, mammalian target of rapamycin (mTOR), and RAS/RAF/MEK/ERK inhibitors, as well as with monoclonal antibodies to immune targets CD 20 and CTLA-4.[1-6] Although rash has been the adverse event most often described, and for which

Jane Bryce, MSN, AOCNS®: *Research Nurse, Department of Research, Clinical Trials Unit, National Cancer Institute-Fondazione G. Pascale, via Mariano Semmola, Naples, Italy*. Christine Bettine Boers-Doets, RN, MSc: *Director, IMPAQTT Research & Consultancy, Wormer, The Netherlands, and PhD candidate, Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands*.

Address correspondence to Jane Bryce, MSN, AOCNS®, National Cancer Institute-Fondazione G. Pascale, via Mariano Semmola, 80131 Naples, Italy. e-mail: jane.bryce@usc-intnapoli.net

0749-2081/3003-$36.00/0.
http://dx.doi.org/10.1016/j.soncn.2014.05.003

prevention and treatment measures have more often been tested, it is only one of a number of adverse events that comprise a distinct profile of dermatologic adverse events observed with these agents. Dermatologic adverse events can be categorized as those that affect the pilo-sebaceous follicle (rash), and several non-rash adverse events due to alteration of the skin barrier (xerosis and skin fissures, pruritus, photosensitivity, pigmentation disorders), lesions of the skin appendages (paronychia, hair changes, hypertrichosis of the face, trichomegaly), hyperkeratosis, and hand foot skin reactions (HFSR), and the development of epithelial benign and malignant skin tumors.[1,7]

Dermatologic adverse events from targeted agents have been associated with poorer quality of life (QoL), in particular in relation to presence of rash, pruritus, or HFSR.[8,9] Unlike rash, many of the non-rash dermatologic adverse events persist with treatment, and may adversely impact psychosocial functioning, activities of daily living (ADL), and potentially interfere with the patient receiving optimal dose of therapy.[10-12] With the integration of targeted therapies into the treatment of many types of cancer, nurses are being challenged to deal with various dermatologic events with which they may be unfamiliar.[13-15] Though many of these adverse events are predictable, the lack of evidence-based guidelines makes their effective management more challenging, particularly in settings where a dermatologist is not present.

This review will discuss the etiology and treatment of non-rash dermatologic adverse events associated with targeted anticancer therapies, and focus on the nursing role of identifying risk factors, providing patient education and clinical assessment, and implementing measures to reduce the impact of these adverse events.

Dermatologic Assessment

Before starting therapy with a targeted agent, patients should be assessed for risk factors, including previous cancer therapies, history of dermatologic disorders, routine exposure of skin to sun or harsh substances, and occupational history of skin, hand, or foot injury. A full body skin exam should be included in the clinical assessment at each visit. Grading of dermatologic adverse events should be documented within the clinical record and the same grading scale should be used throughout therapy. The scale most commonly used by dermatology and oncology is the Common Terminology Criteria for Adverse Events (CTCAE).[16,17] The adverse events discussed here are listed in Table 1. The CTCAE dermatology scale is designed to broadly define and grade adverse reactions that may occur from a variety of causes. The Multinational Association of Supportive Care in Cancer (MASCC) EGFRI Skin Toxicity Tool (MESTT) was developed to better define and grade these class-specific dermatologic adverse events. Though it has not been widely reported in clinical trials, the MESTT is more sensitive and highly specific, making it useful when comparing adverse events of agents of the same class, or when evaluating the effect of supportive care measures.[18]

Assessment of skin adverse events should also include patient-reported outcomes, including impact on function and QoL. Patients should be questioned about the interference of dermatologic adverse events on ADL, and any other psychosocial impact. Dermatology-specific QoL instruments, such as the Skindex-16 and the Dermatology Life Quality Index, have been used to study impact on physical and social functioning in patients receiving targeted therapy.[10] The impact of EGFR inhibitor-associated mucocutaneous adverse events on QoL can be evaluated with the Functional Assessment of Cancer Therapy Epidermal Growth Factor Receptor Inhibitor 18 (FACT-EGFRI-18) scale.[19,20] Incorporating patient self-reporting of CTCAE adverse events (PRO-CTCAE) is also under development, with a substantial focus on dermatologic adverse events.[21] Patient education regarding proper skin care should be given at the start of therapy. Patients should be informed of the likelihood of dermatologic adverse events, and what to monitor and report between visits.

Non-Rash Adverse Events

Xerosis and Fissures

Xerosis, or dry skin, has been reported in patients receiving inhibitors of EGFR, multikinases, mTOR, RAS/RAF/MEK/ERK, and CTLA-4.[1,6,22-24] EGFR helps regulate epidermal homeostasis, and its inhibition results in an abnormal differentiation of keratinocytes, leading to changes in the stratum corneum and its protein, thereby weakening the epidermal barrier