Cutaneous toxicity as a predictive biomarker for clinical outcome in patients receiving anticancer therapy

Alexandra K. Rzepecki, BS,[a] Haiying Cheng, MD, PhD,[b] and Beth N. McLellan, MD[c]
Ann Arbor, Michigan, and Bronx, New York

The relationship between treatment outcome and cutaneous toxicity induced by anticancer therapy has gained attention in the past decade. In this article, we have provided an overview of the 3 main classes of anticancer agents—specifically, molecularly targeted kinase inhibitors, immune checkpoint inhibitors, and cytotoxic chemotherapeutics—and described the data evaluating the association between cutaneous toxicity induced by these agents and survival benefit. Although preliminary studies are promising with regard to the potential role of cutaneous toxicities as a surrogate biomarker of efficacy of treatment, larger prospective studies are needed to confirm this relationship. Dermatologists have a unique opportunity to collaborate with oncologists in the multidisciplinary treatment paradigm by helping to identify and manage these dermatologic events in patients with cancer. A heightened awareness of these toxicities is critical, as it can potentially allow recognition of the efficacy of anticancer therapy and may influence treatment decisions and patient outcomes. (J Am Acad Dermatol 2018;79:545-55.)

Key words: biomarker; cancer outcome; cutaneous adverse event; cutaneous toxicity; oncodermatology; prognostic marker; survival.

The relationship between treatment outcome and cutaneous toxicity induced by anticancer therapy has gained attention in the past decade. Development of certain toxicities, such as an acneiform eruption induced by epidermal growth factor receptor (EGFR) inhibitors, and the association with efficacy of treatment are already well established.[1,2] However, less is known about the association between clinical outcomes and development of cutaneous toxicities due to cytotoxic chemotherapy[3-6]; an association for several toxicities caused by immunotherapy is also beginning to emerge.[7-9]

This article provides an overview of the 3 main classes of anticancer agents—molecularly targeted kinase inhibitors, immune checkpoint inhibitors, and cytotoxic chemotherapeutics—and it describes the data evaluating the association between cutaneous toxicities induced by these agents and survival benefits. Our goals are to (1) reinforce the well-established association between kinase inhibitor–induced cutaneous toxicity and survival benefit and (2) perform a comprehensive review of the literature for a similar but less well-known association induced by immunotherapeutic and systemic chemotherapeutic agents.

Abbreviations used:

HFS:	hand foot syndrome
HFSR:	hand–foot skin reaction
HR:	hazard ratio
irAE:	immune-related adverse effect
NSCLC:	non–small cell lung cancer
OS:	overall survival
PD-1:	programmed death receptor 1
PD-L1:	programmed cell death ligand 1
PFS:	progression-free survival

METHODS

We conducted a literature search in the MEDLINE (via PubMed) and Scopus databases from January

From the Department of Dermatology, University of Michigan Medical School, Ann Arbor,[a] and Department of Oncology, Montefiore Medical Center,[b] and Division of Dermatology, Department of Medicine, Albert Einstein College of Medicine, Bronx.[c]

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Correspondence to: Alexandra K. Rzepecki, BS, Albert Einstein College of Medicine, Montefiore Medical Center, 111 E 210th St, Bronx, NY 10467. E-mail: arzepeck@umich.edu.

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1960 to January 2018 by using the key terms *cutaneous toxicity*, *cutaneous adverse event*, *skin toxicity*, *alopecia*, *rash*, *vitiligo*, *lichenoid*, *immunotherapy*, *chemotherapy*, *immune checkpoint inhibitor*, *CTLA4*, *PD-L1*, *PD-1*, *EGFR inhibitor*, *kinase inhibitor*, *prognosis*, *survival outcome*, and *biomarker*, as well as the individual drug names of kinase inhibitors, immune checkpoint inhibitors, and chemotherapeutic agents. Additionally, published abstracts from the American Society of Clinical Oncology annual conferences were searched. A manual search of references from key articles was also performed to find studies missed by the computer search. An investigator reviewed the search results by way of title and abstract screening; articles were included if the abstract commented on a possible association between cutaneous toxicity during anticancer therapy and clinical outcome. Case reports and articles not available in the English language were excluded.

CAPSULE SUMMARY

- There is an association between clinical outcomes and development of cutaneous toxicities due to anticancer therapeutics.
- Vitiligo, rash, nail toxicity, or alopecia induced by anticancer therapeutics may be potential biomarkers in predicting efficacy of treatment.
- Identification of cutaneous toxicities may be an early and noninvasive way to determine efficacy of cancer treatment.

RESULTS

All studies reporting an association between cutaneous toxicity and clinical outcome, such as overall survival (OS) or progression-free survival (PFS), were reviewed. The 3 main classes of anticancer agents, including molecularly targeted kinase inhibitors (Table I),[1,10-50] immune checkpoint inhibitors (Table II),[3-5,51-62] and cytotoxic chemotherapeutics (Table III),[6-9,63-71] are responsible for a variety of cutaneous adverse events (AEs); several of these have been shown to be associated with favorable clinical outcomes of varying degrees.

Molecularly targeted kinase inhibitors

The inhibition of kinase signaling is an established treatment approach in several tumor types.[11,72] Therapeutic strategies include use of agents such as cetuximab and erlotinib (which target EGFR [a member of the receptor tyrosine kinase family]) or use of sorafenib and sunitinib (which target multiple kinase receptors) (Table I).[10,18,32,35,39,41,43,73] Several review articles describing the association between the cutaneous adverse effects caused by these agents and their association with survival have been published.[44,45,74-82]

EGFR inhibitors. The association between the efficacy of EGFR inhibitors and severity of a rash was first reported in 2003 in 4 phase II studies, including studies of patients with colorectal cancer, squamous cell cancer of the head and neck, and pancreatic cancer who were undergoing therapy with cetuximab.[83] In all 4 studies, patients who developed the rash survived longer than those who did not, and those with more intense rash survived longer still ($P < .05$ for all 4 trials). Since then, the association between the onset or severity of rash and survival benefit after treatment with an EGFR inhibitor has been increasingly analyzed and reported in a large number of clinical trials.[19,20,29,84-86] For instance, 1 study found that in patients with non–small cell lung cancer (NSCLC) who were receiving erlotinib, the median survival time was 46.5 days in those with no rash compared with 257 days in those with grade 1 rash ($P < .0001$) and 597 days in those with grade 2 or 3 rash ($P < .0001$).[19]

Multikinase inhibitors. Multikinase inhibitors, on the other hand, can commonly lead to development of a painful eruption on the hands and feet that is termed *hand–foot skin reaction* (HFSR).[87,88] HFSR has also been shown to be associated with survival.[2,33,34,46] For instance, 1 study found that patients with hepatocellular carcinoma treated with sorafenib who developed HFSR or rash had significantly better tumor control than did patients without cutaneous side effects (48.3% vs 19.4% [$P = .028$]).[2] Additionally, a recent systematic review and meta-analysis of 12 cohort studies of patients with hepatocellular carcinoma treated with sorafenib reported that development of HFSR was significantly associated with reduced risk of death ($P < .00001$; hazard ratio [HR], 0.45).[44]

Although the majority of studies describe rash as the cutaneous toxicity found to be significantly associated with improved survival in patients receiving kinase inhibitors,[1,11-16,19-27,29-31,36,37] there are reports that further specify mucocutaneous toxicities, including the following, as having an association with clinical outcome: xerosis[16] and skin toxicity[17] in patients receiving cetuximab; leukocytoclastic vasculitis,[28] pruritus,[21] and paronychia[21] in patients receiving erlotinib; hand-foot syndrome (HFS)[38] in patients receiving lapatinib; stomatitis[40] in patients receiving everolimus; xerosis[16] and skin toxicity[42] in patients receiving