Pigmentary changes in patients treated with targeted anticancer agents: A systematic review and meta-analysis

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Background: The discovery of signaling networks that drive oncogenic processes has led to the development of targeted anticancer agents. The burden of pigmentary adverse events from these drugs is unknown.

Objective: To conduct a systematic review and meta-analysis of published clinical trials and determine the incidence and risk of development of targeted therapy–induced pigmentary changes.

Methods: A comprehensive search was conducted to identify studies reporting targeted therapy–induced pigmentary changes. The incidence and relative risk were calculated. Case reports and series were reviewed to understand clinical characteristics.

Results: A total of 8052 patients from 36 clinical trials were included. The calculated overall incidences of targeted cancer therapy–induced all-grade pigmentary changes in the skin and hair were 17.7% (95% confidence interval [CI], 11.9-25.4) and 21.5% (95% CI, 14.9-30.1), respectively. The relative risk of all-grade pigmentary changes of skin and hair were 93.7 (95% CI, 5.86-1497.164) and 20.1 (95% CI, 8.35-48.248). Across 53 case reports/series (N = 75 patients), epidermal growth factor receptor and breakpoint cluster region–abelson inhibitors were the most common offending agents.

Limitations: Potential under-reporting and variability in oncologists reporting these events.

Conclusion: There is a significant risk of development of pigmentary changes during treatment with targeted anticancer therapies. Appropriate counseling and management are critical to minimize psychosocial impairment and deterioration in quality of life. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.06.044.)

Key words: cabozantinib; depigmentation; dyspigmentation; hyperpigmentation; hypopigmentation; imatinib; ipilimumab; nivolumab; pazopanib; pembrolizumab; pigmentary; repigmentation; sorafenib; sunitinib; vitiligo.

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The discovery of intracellular signaling networks that drive oncogenic processes when aberrantly activated has led to the development of molecularly targeted agents for the treatment of various cancers.[1,2] Their targeted action spares normal cells, thus improving efficacy and health-related quality of life (HRQoL). Although systemic adverse events (AEs) characteristic of conventional cytotoxic agents (eg, myelosuppression, nausea, vomiting)[3] are typically not encountered, dermatologic AEs (affecting the skin, hair, nails, and mucosae) are common because some of the signaling pathways inhibited are also essential for cutaneous homeostasis.[4]

Skin eruptions (rashes), xerosis, pruritus, photosensitivity, pigmentary changes, fissures, hand-foot skin reaction, and hair and/or nail changes are some of the most commonly encountered targeted therapy–induced dermatologic AEs.[5] Although not life threatening, they can negatively affect patients' HRQoL and impair psychosocial functioning and activities of daily living.[6,7] Furthermore, they often result in dose reductions, interruptions, or even discontinuation of therapy, which may lead to suboptimal management of the cancer itself and result in poorer outcomes.[8]

Whereas the incidence and risk of some of the targeted therapy–induced dermatologic AEs have been previously estimated,[9,10] that of dermatologic pigmentary AEs (dpAEs) is not known. The latter are of particular concern because of their persistence, resistance to therapy, and negative impact on psychosocial well-being and HRQoL. Therefore, we conducted a systematic review and meta-analysis of the literature to determine the incidence and risk of targeted therapy–induced dermatologic pigmentary AEs.

CAPSULE SUMMARY

- Dermatologic adverse events are a common occurrence in patients receiving targeted anticancer medications.
- There is an increased risk of development of targeted therapy–induced pigmentary changes, but the causal agents and specific risks are not well described.
- Understanding targeted therapy–induced pigmentary changes is critical for appropriate management to improve this psychosocially impactful adverse event.

METHODS

Data source

We searched all targeted anticancer agents (n = 64) approved by the US Food and Drug Administration (www.FDA.gov) in January 2017 (Appendix I; available at http://www.jaad.org). A PubMed search was conducted using the generic name of targeted agents (eg, afatinib) as the key word. The search was limited to phase II and phase III randomized clinical trials (RCTs) and nonrandomized clinical trials published in English (from January 1998 through January 2017). We also reviewed abstracts and virtual meeting presentations (from January 2004 through January 2017) posted on the American Society of Clinical Oncology website to further identify relevant clinical trials. In addition, an independent search on the Web of Science database was conducted to ensure that no other studies were missed. We reviewed each publication and retrieved data only from complete and/or the most recent reports if duplicate publications were identified. Extracted information included patient characteristics, study design, treatment regimen, study results, and safety data.

Study selection

The US Food and Drug Administration approves targeted therapies at a specific dose in the treatment of cancer. Therefore, we excluded clinical trials using drugs at unapproved doses (eg, phase I studies) to determine the incidence and risk of dpAEs at the dosing level meaningful for clinicians. We also excluded trials that combined targeted agents with other chemotherapeutic agents and/or treatment modalities.

The dpAEs in the studies were reported as: *hyperpigmentation*, *hypopigmentation*, *depigmentation*, *repigmentation*, *dyspigmentation*, *discoloration*, *color change*, and *vitiligo* of either the skin, hair, or nails. Studies that met the following criteria were selected for final analysis: (1) prospective phase II or III clinical trial in patients with cancer; (2) assignment of participants to treatment with the targeted agent at the approved dose; and (3) availability of data regarding the incidence of pigmentary changes.

Clinical end points

The clinical end points were extracted from the safety profile in each trial. The dpAEs for skin were recorded according to the National Cancer Institute's Common Toxicity Criteria (version 2.0), or the Common Terminology Criteria for AEs (versions 3.0 and v4.0). The grading of dpAEs in the skin in version 2.0 is described as follows: grade 0, none; grade 1, localized; and grade 2, generalized. In version 3.0, the description was updated to hyperpigmentation and hypopigmentation, as