Cutaneous reactions to chemotherapeutic drugs and targeted therapies for cancer

Part I. Conventional chemotherapeutic drugs

Claire Marie Reyes-Habito, MD,[a] and Ellen K. Roh, MD[b]
Laguna, Philippines, and Boston, Massachusetts

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3. Achievement of a 70% or higher on the online Case-based Post Test
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Learning Objectives
After the completing this learning activity, participants should be able to identify the mechanism of action of conventional chemotherapeutic drugs, recognize cutaneous reactions from conventional chemotherapeutic drugs, and plan the appropriate management of cutaneous reactions.

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Conventional chemotherapy continues to be an important part of cancer management, but may cause various cutaneous reactions because it disturbs specific cell cycle phases. The alkylating agents cyclophosphamide, ifosfamide, and thiotepa can produce hyperpigmentation, while hypersensitivity reactions can be seen with platinum alkylating agents. Antimetabolites vary in reactions from exanthematous to bullous skin lesions. 5-fluorouracil and its derivatives and liposomal doxorubicin and daunorubicin are characteristically known to cause hand-foot syndrome, while bleomycin can cause fibrosis and flagellate dermatitis. Several hypersensitivity reactions may also occur from mitotic inhibitors and topoisomerase inhibitors. These different characteristic presentations are important to dermatologists in identifying the correct diagnosis and management for the cancer patient. (J Am Acad Dermatol 2014;71:203.e1-12.)

Key words: cancer; chemotherapy; cutaneous reactions; cytotoxic therapy; drug hypersensitivity; rash.

Cancer therapy has always been a challenging focus in clinical medicine and research. Traditionally, chemotherapeutic drugs have worked by disrupting specific phases of the cell cycle in actively dividing cancer cells (Table I).[1] In doing so, it can cause multiple side effects, with the skin being one of the most commonly affected organs, manifesting as dermatitis, alopecia, stomatitis, and other adverse reactions. Characteristics of these cutaneous reactions vary depending on the chemotherapeutic drug. Identification of these reactions is important to both dermatologists and oncologists so that appropriate management and uninterrupted chemotherapy may be provided to cancer patients.

Abbreviations used:

5-FU:	5-flurouracil
CLL:	chronic lymphocytic leukemia
HFS:	hand–foot syndrome
NHL:	non-Hodgkin lymphoma
NSCLC:	non–small cell lung carcinoma

ALKYLATING AGENTS

Key points

- **Self-limiting hyperpigmentation may occur with alkylating agents, especially in occluded areas with the use of ifosfamide and thiotepa**
- **Type I immunoglobulin E–mediated hypersensitivity reactions can occur with platinum agents**

Cyclophosphamide, ifosfamide, and thiotepa

Classical alkylating agents attach an alkyl group to the guanine base of DNA, and are used to treat leukemia, lymphoma, Hodgkin disease, multiple myeloma, sarcoma, and cancers of the lung, breast, and ovary.[1] All can be administered intravenously, though cyclophosphamide also has an oral option, and thiotepa an intracavitary protocol.

Hyperpigmentation. Cyclophosphamide can cause hyperpigmented patches after 4 weeks of therapy that fade within 6 to 12 months after discontinuation. These patches can appear on the palms, soles, nails, teeth and, rarely, the gingiva. Nails can have diffuse, longitudinal, or transverse pigmentation, and may also present with onychodystrophy, onycholysis, Beau lines, or Muehrke lines.[2,3] Hyperpigmentation from ifosfamide often occurs in the flexural areas, on the hands, feet, and scrotum, and under occlusive dressings. Large areas of the trunk may also be affected in severe cases. This discoloration can occur after a single course or many months of therapy, and has a more unpredictable course than that from cyclophosphamide. Some cases may experience fading despite continued treatment, whereas others may persist even after completing treatment.[2,4,5]

Like ifosfamide, thiotepa can produce hyperpigmentation under occluded areas. Other commonly reported cutaneous side effects include erythema, desquamation, and pruritus.[6] Horn et al[7] found that thiopeta is excreted in sweat, and it has been postulated that this mechanism is responsible for the drug's toxicity.

From Los Banos Doctors Hospital and Medical Center,[a] Los Banos, Laguna, and Harvard Medical School and Department of Dermatology,[b] Massachusetts General Hospital, Boston.

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Reprint requests: Ellen K. Roh, MD, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, 50 Staniford St, Boston, MA 02114. E-mail: ekroh@partners.org.

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