Understanding Toxicities of Targeted Agents: Implications for Anti-tumor Activity and Management

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Targeted treatments have distinctive side effects: dermatologic problems (rash, hand-food skin reaction, skin/hair whitening), endocrine dysfunction (hyperglycemia, hypothyroidism, dyslipidemia), as well as hypertension, diarrhea, liver problems, ocular toxicity and proteinuria. Toxicities can be classified as: (1) on-target, mechanism-driven toxicities that are either related or unrelated to response; and (2) off-target side effects. Off-target toxicities may be specific to the class of agent, eg, small molecule tyrosine kinase inhibitor versus antibody versus cytotoxic; alternatively, they may also be mediated by metabolites or immune reactions. Both on- and off-target toxicities can be amplified or attenuated by drug concentrations or end-organ sensitivity, which in turn can be attributable to genetic polymorphisms regulating metabolism or tissue responsiveness. On-target side effects are important to identify as some are associated with response and, therefore, controlling these side effects is preferable to dose reduction or treatment discontinuation. Side effects caused by relevant target impact may be recognized when different types of agents, eg, small molecule inhibitors and antibodies, with the same target have the same side effect. These on-target effects may also correlate with better outcomes. We discuss toxicity of targeted agents in the context of understanding target impact, drug-drug interactions, and implications for optimized management.
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Toxicities are one of the foremost challenges in the field of drug development. Drug side effects can be classified into several subgroups: (1) on-target pharmacology (mechanism-related toxicity); (2) off-target pharmacology (side effects associated with the class of agent, eg small molecule tyrosine kinase inhibitor (TKI) versus antibody; (3) toxic metabolites; (4) hypersensitivity and other immunological reactions; and (5) rare or idiosyncratic toxicities.[1] Toxicities may reflect individual genetic predisposition that influence agent metabolism, disposition, immune responses, and end-organ responsiveness.[1] Toxicities sometimes correlate with anti-tumor activity, which has implications in regards to how to manage them.

Antibodies and tyrosine kinase inhibitors (TKIs) are major classes of targeted agents. They function by blocking signal transduction.[2,3] TKIs inhibit the function of the kinase enzyme. Antibodies often act on a ligand or a receptor, and are generally more specific than TKIs. Compared to cytotoxics, targeted therapies are better tolerated; however, they have distinctive toxicities. Some of these toxicities are associated with target impact and may serve as surrogates for anti-tumor response.[4] Other side effects may be due to the chemical structure of the class of agent administered, eg, antibodies versus small molecular inhibitors, or effects on targets not relevant to tumor response, or the impact of toxic metabolites. Accessory cells, such as those in the immune system or the vasculature or other microenvironment components, may also mediate toxicities. Finally, any or all of these effects may be modulated by individual polymorphisms that affect drug metabolism or tissue sensitivity. Herein, the current state of knowledge regarding major side effects associated with targeted therapy and their management will be reviewed.

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DERMATOLOGIC SIDE EFFECTS

Skin Rash

Skin rash is a common cutaneous adverse effect associated with a variety of targeted agents. It usually presents as acneiform, erythematous, papulopustular eruptions that are often seen on the face, and trunk, while rarely involving the palms or soles. Skin rash can be due to either target-related effects or to the class of drug. For example, epidermal growth factor receptor (EGFR) inhibitors (either antibodies or TKIs) result in skin rash (target EGFR-based effect); several other TKIs, such as MEK inhibitors, are also strongly associated with skin rash.

Characteristics and Pathogenesis of Skin Rash

EGFR-TKI–related skin rash occurs in 45%–100% of treated patients; grade 3–4, about 10%.[5] For cetuximab, an EGFR monoclonal antibody, the incidence of skin rash is almost 90%, with approximately 10% being grade 3/4.[6] The MEK inhibitors, such as trametinib and selumetinib, also frequently result in skin rash (up to 90% of patients).[7,8] Other targeted TKIs that commonly cause skin rash include, but are not limited to, inhibitors of Braf, Her2, PI3K/Akt/mTOR, multikinases, Abl, and Btk.

The pathogenesis of skin toxicity may involve inflammatory changes within epidermis as a reaction to inhibition of intracellular signaling pathways such as EGFR, RAS/RAF/MEK-ERK mitogen-activated protein kinase (MAPK), and PI3K/AKT/mTOR, leading to diminished/altered proliferation of basal keratinocytes, upregulation of proinflammatory cytokines, early infiltration of T lymphocytes, loss of skin barrier protection, and secondary infections.[9,10] These dose-dependent effects can also impact skin appendages causing paronychia, facial hypertrichosis, and trichomegaly.

Skin Rash and Outcome

There are well-established data to suggest that skin rash may be associated with a better outcome for EGFR inhibitors.[11–14] For example, Petrelli et al[11] did a meta-analysis that included 24 publications in patients with non-small cell lung cancer (NSCLC) receiving EGFR TKIs. Skin rash was found to be an independent predictive factor for overall survival ($P < .00001$) and progression-free survival ($P < .00001$). Patients who developed grade 2–4 rash were more likely to respond to treatment (response rate 42% *v* 7%; $P < .0001$). Similarly, studies on EGFR antibodies suggested the same trend between developing skin rash and better clinical outcome.[14–17] A meta-analysis based on 14 publications (3,833 patients) with colorectal cancer who received cetuximab or panitumumab showed that skin toxicity represented a predictive factor for survival and progression ($P < .00001$) (patients with rash did better). Patients with moderate or severe rash had an increased chance of response (35 vs 13 %; $P < .00001$).[17]

Skin Rash and Genetic Polymorphisms

Severity of skin rash may be affected by multiple clinical factors. A correlation between drug exposure and rash was suggested, indicating that polymorphisms in metabolizing enzymes mainly involving the cytochrome P450 3A4, 3A5, 1A2 family may play a role.[13] In addition, a variety of receptor polymorphisms,[18] such as EGFR intron 1 polymorphism (CA repeats)[19,20] and EFGR -216G/T mutation,[21] may also inference the occurrence of skin rashes.

Skin Rash Management

Management of skin rash associated with targeted therapy is largely based on clinical experience and consensus.[22,23] Because skin rash of EGFR inhibitors is probably due to impact on a target related to response, supportive care may be preferable to decreasing dose or drug discontinuation for EGFR inhibitors. In general, treatment should be individualized depending on the severity, location and patient's disease status. For grade I skin rash, topical corticosteroids and antibiotics (clindamycin, erythromycin, or metronidazole) can be used. For grade 2 rash, topical corticosteroids and oral antibiotics (such as tetracyclines, doxycycline, or minocycline) are commonly prescribed. For skin rash of grade 3 and above, dose reduction of target agent or temporary discontinuation may be warranted according to prescribing information of each drug. In addition, oral antibiotics plus a short course of systemic corticosteroid can be tried.[22]

Hand-Foot Skin Reaction

Hand-foot syndrome is commonly associated with multi-kinase angiogenesis inhibitors such as sorafenib, sunitinib, and some other vascular endothelial growth factor receptor (VEGFR)-targeting agents. It presents with local tender lesions, usually as hyperkeratosis or blisters in most cases. Symptoms include painful sensation in palm and soles, and burning, tingling, and hypersensitivity to hot objects. Biopsies of the skin lesion showed horizontal layers of keratinocyte necrosis, which correlated to time of drug exposure: early (<30 days from initiation) leading to stratum granulosum-spinosum alterations and late (≥30 days) resulting in stratum corneum pathology.[24]