Sorafenib-induced erythema multiforme for metastatic renal cell carcinoma

Sorafenib is an active agent for cytokine-refractory renal cell carcinoma (RCC) patients [1]. Skin toxicity such as hand–foot syndrome (HFS) is one of the frequent adverse events of sorafenib. In the phase II study conducted in Japan, grade 3 skin toxicity occurred in 13.7% of 131 patients with RCC, but all of those skin toxic effects were HFS or rash/desquamation [2]. We here report three cases of erythema multiforme (EM) associated with sorafenib therapy. EM, Stevens–Johnson syndrome, and toxic epidermal necrolysis are mucocutaneous diseases associated with significant morbidity and mortality. The term 'Stevens–Johnson syndrome' has been widely accepted as a synonym for EM major [3].
case 1

A 25-year-old female with pulmonary metastases of papillary RCC received sorafenib 800 mg/day. At day 8, erythema appeared on lower legs and spread over 50% of body surface area in 2 days (Figure 1A) with HFS. She also suffered intermittent fever up to 39.5°C from day 8. Serum examination excluded the viral infection, including measles, herpes simplex, or herpes zoster. Skin biopsy of femoral region at day 12 revealed superficial and perivascular lymphocyte infiltration and necrotic keratinocytes, compatible with EM. Skin rash disappeared within days after discontinuation of sorafenib without steroid treatment or antimicrobial treatment.

case 2

An 80-year-old man with multiple pulmonary metastases of papillary RCC was treated with sorafenib 800 mg/day. From the 8th to 12th day of sorafenib, erythema spread over his whole body (Figure 1B) with grade 2 HFS, mild stomatitis, and grade 3 fatigue. EM and HFS disappeared within 2 weeks after discontinuation of sorafenib and oral predonisolone 10 mg/day. When sorafenib (400 mg/day) was rechallenged, EM with high fever reappeared within 24 h and the sorafenib was discontinued at once.

case 3

A 70-year-old female with metastatic clear cell RCC developed erythema spread to whole body 15 days after starting sorafenib 800 mg/day (Figure 1C). Eruption disappeared within 2 weeks after discontinuation of sorafenib and topical treatment without steroid. She was treated with sunitinib 50 mg/day and EM has not appeared.

Furthermore, postmarketing surveillance of sorafenib-treated patients in Japan reported that 108 cases of so-called EM occurred in 2889 cases from February 2008 to October 2009, so occurrence rate of EM might be different between Japanese and Caucasians. A recent study suggests that polymorphisms in specific genes encoding for metabolizing enzymes, efflux transporters, and drug targets are associated with toxic effects of sunitinib, another angiogenesis inhibitor [7]. In addition, the population-related pharmacogenomics might contribute to differences in adverse events and responses of antitumor agents between patients in Japan and those in the United States [8]. Further study is necessary to elucidate this discrepancy of EM occurrence rate between Japanese and Caucasians.

In clinical practice, it is very difficult to diagnose whether the drug-induced skin rash is caused by allergic or toxic mechanisms. To use sorafenib safely, restarting of sorafenib needs careful monitoring because the possibility of an allergic mechanism cannot be ruled out. Patients with skin lesions due to allergic mechanisms may not have benefits from sorafenib treatment because of early treatment failure. At present, we cannot recommend the rechallenge of sorafenib for these patients as two of three patients including our case recurred EM.

Sorafenib is now one of few standard agents for metastatic RCC. Molecular mechanism of this type of toxicity remains unknown. Further investigation is necessary to disclose the mechanism and establish the effective therapy for sorafenib-induced EM, which might not be a rare adverse event in Japanese patients.

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disclosure

None of the authors declare conflicts of interest.

references


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