

Severe Cutaneous Reaction to Sorafenib: Induction of Tolerance

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Accepted May 9, 2008.

Sir,

Sorafenib (Nexavar®, Bayer, Leverkusen, Germany) is a small molecule kinase inhibitor that has been approved for treatment of metastatic renal cancer in Germany since August 2006. Adverse drug reactions to sorafenib occur particularly in the cardiovascular and gastrointestinal system, and may be also seen at the skin (1). Severe skin reactions may limit the applicable dose and require either dose reduction or discontinuation of therapy (2). We report here the case of a patient in whom continuation of treatment with sorafenib was urgently required despite previous suspected sorafenib-induced eczema.

CASE REPORT

A 68-year-old woman presented with a severe generalized and confluent maculopapular rash with intense pruritus (Fig. 1). The patient had a metastatic renal



Fig. 1. Confluent maculopapular rash on the lower extremities.

cancer. Skin lesions had developed 2 weeks after the start of oral treatment with sorafenib, 800 mg/day. As a consequence, sorafenib was discontinued, and upon treatment with potent topical glucocorticoids and oral antihistamines, the skin cleared within 10 days. Because sorafenib treatment was felt to be needed urgently, it was decided to attempt an oral tolerance induction. As pre-medication the patient was given 24 mg methylprednisolone. One hour later incremental doses of sorafenib (0.4/0.8/1.6/3.2/6/12/24/50/100/200/400 mg) were administered at intervals of approximately 15 min, reaching a cumulative dose of 798 mg sorafenib within 3 h. One hour later, the patient developed a pruritic generalized erythema. She was given 4 mg dimethindene maleate intravenously, and the reaction subsided within 1 h. On the following day, after oral pre-medication with 24 mg methylprednisolone and 180 mg fexofenadine, sorafenib was given at doses of twice 100 mg and twice 200 mg (cumulative dose 600 mg). The time interval between those repeated applications was 2 h. From day 3 to day 5 sorafenib was given at four doses of 200 mg (cumulative dose 800 mg), again with a 2-h interval between each consecutive dose. From day 6 on, after sorafenib had been tolerated without any visible side-effects, the intended application of 400 mg twice daily (administered in the morning and in the evening) was started and continued. Methylprednisolone was slowly tapered and discontinued after 12 days, and fexofenadine was used only if needed and was finally discontinued after 6 weeks. So far, the patient has been tolerating the ongoing therapy well and no further rash occurred. Computer tomography revealed a very good response to the treatment with a significant reduction in metastasis size.

DISCUSSION

Skin rashes are well known adverse events during the early period of small molecule kinase inhibitor therapy. These drugs are toxic by nature, and their skin toxicity correlates with clinical anti-tumour efficacy (3). It is thought that skin reactions indicate a relevant *in vivo* targeting of the epidermal growth factor receptor (4). These skin reactions are usually taken as a positive indicator of drug efficacy. Therefore, an allergological work-up is not done. Consequently there are also no data describing skin test reactions to tyrosine kinase inhibitors. However, one should also consider the

possibility that reactions to kinase inhibitors are of an allergic origin.

Unfortunately it was not possible to perform allergological testing in our patient. After the rash had cleared sorafenib treatment with anti-allergic co-medication had to be restarted immediately. We assess the rash, which appeared on the first day of tolerance induction, as a positive reaction indicating the causal relationship between the previous eczema and sorafenib.

The National Cancer Institute has defined common toxicity criteria of skin reactions. According to these criteria our patient had a grade 3 reaction with involvement of more than 50% of the body surface area (4). In patients in whom no other treatment option for a malignant tumour exists, a continuation of tyrosine kinase inhibitor therapy is highly desired. An expert panel released recommendations on how to continue tyrosine kinase treatment in patients with mild to moderate skin reactions (4). In patients with grade 3 reactions it is recommended to discontinue therapy until the patients has largely recovered. After recovery therapy may resumed using a reduced dose. For erlotinib a dose of 100 mg was recommended, which represents two-thirds of the usual therapeutic dose. In some cases one may also switch to another class of kinase inhibitors.

The concept of tolerance induction differs significantly from that recommended for a therapeutic restart. Tolerance inductions begins with a very low dose of the drug (corresponding to 0.01–0.001 of the routine single

dose), and aims to reach the full therapeutic dose. Successful oral tolerance induction is possible with tyrosine kinase inhibitors, and has been demonstrated in patients with leukaemia who experienced cutaneous side-effects to imatinib (5). Also in our patient tolerance to sorafenib could be achieved, thus allowing a continuation of the urgently needed treatment. It remains to be assessed which aspect of our therapy (oral desensitization or concomitant anti-inflammatory treatment) contributed more to its final success.

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