Risk Factors for Sorafenib-Induced Erythema Multiforme in Japanese Patients with Advanced Renal Cell Carcinoma

Introduction and Objective: It is reported that the incidence of erythema multiforme (EM) in patients with renal cell carcinoma (RCC) treated with sorafenib is rare but treatment limiting adverse event. In this retrospective study, clinical factors, drug-related genetic, and HLA type were assessed in RCC patients to determine the association with sorafenib-induced EM.
Materials and Methods: A total of 55 consecutive RCC patients treated with sorafenib were enrolled in this study. Of the patients, 33 patients were subjected to HLA typing and polymorphism analyses of *CYP3A5* and *ABCB1*.
Results: EM developed 12 of 55 patients (21.8%) and the median time to occurrence of EM was 10 days with a range of 7 to 17 days after sorafenib administration. All the patients had complete resolution of the erythema after discontinuation of sorafenib. Two patients who were re-challenged with sorafenib 200 mg bid have not experienced recurrent EM. A higher incidence was observed in female than male patients (40.0% vs. 15.0%, *P*=0.046). Initial dose (ID), ID per body weight (BW), and ID per body surface area (BSA) in EM (+) patients were significantly higher than those in EM (-) patients (733 vs 577 mg/day, *P*=0.032, 13.4 vs 10.2 mg/day/kg, *P*=0.012, and 483 vs 373 mg/day/m^2, *P*=0.007, respectively). With regard to HLA types in HLA –A, B, and DR loci, the incidence of EM was significantly higher in patients with HLA-A*24 than those without HLA-A*24 (7/19 [36.8%] vs 1/14 [7.1%], *P*=0.046). The *CYP3A5* and *ABCB1* polymorphisms were not associated with EM.
Conclusions: In Japanese RCC patients, the higher frequency of sorafenib-induced EM was observed in females, patients administered higher initial dose of sorafenib per BW or BSA, and patients with HLA-A*24. A reduction of initial sorafenib dose may be recommended for patients with lower BW/ BSA, or HLA-A*24 to prevent EM.

Table 1. Association of sorafenib-induced erythema multiforme with patient demographics, initial sorafenib dose, and HLA-A*24

Variables		EM (+)	EM (-)	*P*
Sex	Male	6 (50)	34 (79)	
	Female	6 (50)	9 (21)	0.046
Initial dose (mg/day)	≤ 400	2 (17)	21 (49)	
	800	10 (83)	22 (51)	0.046
Initial dose (mg/day)		733 ± 156	577 ± 232	0.032
Initial dose per BW (mg/day/kg)		13.4 ± 3.3	10.2 ± 4.3	0.012
Initial dose per BSA (mg/day/ m^2)		483 ± 105	373 ± 141	0.007
HLA-A*24	+	7 (37)	12 (63)	
	-	1 (7)	13 (93)	0.046

EM; erythema multiforme, BW; body weight, BSA; body surface area