Tohoku J. Exp. Med., 2014, **233**, 95-102

HLA-DR9 and DR14 Are Associated with the Allopurinol-Induced Hypersensitivity in Hematologic Malignancy

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Allopurinol, a widely used urate-lowering agent, is a leading cause of severe cutaneous adverse reactions (SCARs), especially in patients with HLA-B*58:01. Despite its routine use for the prevention of tumor lysis-related hyperuricemia prior to chemotherapy, the risk of allopurinol-induced hypersensitivity has not been investigated in patients with hematologic malignancies. This retrospective cohort study was conducted to investigate the incidence and risk factors of allopurinol-induced hypersensitivity in patients at least 18 years of age with hematologic malignancies. We reviewed 463 patients who had ever taken allopurinol for the prevention of hyperuricemia prior to chemotherapy and had undergone serologic HLA typing as a pre-transplant evaluation from January 2000 to May 2010. Thirteen (2.8%) patients experienced maculopapular eruptions (MPE) and none experienced SCARs. Among subtypes of underlying hematologic malignancies, percentage of chronic myeloid leukemia was significantly higher in the allopurinol hypersensitivity group compared with the tolerant group (23.1% (3/13) vs. 5.9% (26/440), P = 0.044). According to HLA subtypes, the incidence of allopurinol-induced MPE was 4.0% in HLA-B58 (+) patients (2/50) and 2.7% in HLA-B58 (−) patients (11/403) but this difference was statistically insignificant. In contrast to HLA-B58, the frequencies of DR9 and DR14 were significantly higher in the allopurinol-induced MPE group compared with the allopurinol tolerant group (38.5% (5/13) vs. 13.6% (53/443), P = 0.019, and 38.5% (5/13) vs. 15.6% (41/440), P = 0.038, respectively). In conclusion, HLA-DR9 and DR14, but not HLA-B58, are associated with hypersensitivity reaction by allopurinol when administered in patients with hematologic malignancy prior to chemotherapy.

Keywords: allopurinol; hematologic malignancy; human leukocyte antigen; Koreans; maculopapular eruptions
Tohoku J. Exp. Med., 2014 June, **233** (2), 95-102.

Introduction

Allopurinol is a generally well tolerated urate-lowering agent but has a relatively high rate of hypersensitivity reactions (Wortmann 2002) and is known as one of the major causative agents of severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug hypersensitivity syndrome (DHS) (Singer and Wallace 1986; Gutierrez-Macias et al. 2005; Tassaneeyakul et al. 2009; Jung et al. 2011). Until now, many studies have shown strong association between allopurinol-induced SCARs and the human leukocyte antigen (HLA)-B*58:01 allele (Hung et al. 2005; Alfirevic et al. 2006; Lonjou et al. 2008; Tassaneeyakul et al. 2009) and HLA-B*58:01 is also known as a risk marker for the development of allopurinol-induced SCAR in Koreans (Kang et al. 2011; Jung et al. 2011).

Allopurinol is widely used in the management of hyperuricemia in patients with impaired renal function and for the prevention of recurrent gout in clinical practice. It is also commonly used for the prevention of hyperuricemia associated with tumor lysis syndrome before starting chemotherapy in patients with hematologic malignancies (Davidson et al. 2004; Coiffier et al. 2008). However, the risk of allopurinol-induced hypersensitivity reaction in patients with hematologic malignancies, especially in patients with B*58:01 allele, has not yet been evaluated.

Therefore, we investigated the risk of allopurinol-induced hypersensitivity reactions in hematologic malignancy patients taking short-term allopurinol for the prevention of tumor lysis syndrome and the association with HLA subtypes including the previously reported risk marker HLA-B58.

Received September 5, 2013; revised and accepted May 2, 2014. Published online May 24, 2014; doi: 10.1620/tjem.233.95.
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Methods

Study Design, Setting and Participants

This retrospective cohort study was approved by the institutional review board of Seoul National University Hospital and informed consent was waived. We retrospectively searched electronic medical records of the patients with hematologic malignancy who underwent HLA testing for pre-transplant evaluation and had a history of allopurinol use. Among these patients, we chose patients at least 18 years of age who had taken allopurinol for the purpose of preventing tumor lysis syndrome prior to chemotherapy. Those who had taken allopurinol for the treatment of hyperuricemia related with other causes or underlying gout were excluded.

The information of underlying hematologic malignancies and the serologic HLA types tested as a pre-transplant evaluation were investigated for analysis. Other clinical characteristics were also collected such as age, sex, height, weight, daily allopurinol dose, duration of allopurinol use, and the following laboratory test results before allopurinol use: white blood cell (WBC) counts with differentials, liver function tests, renal function tests, and uric acid levels.

We reviewed the medical records during the period between initiation and one month after discontinuation of allopurinol administration and screened cases suspicious of hypersensitivity reactions. For screened cases, the causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC) was applied by two allergy specialists trained for adverse drug reaction monitoring (Meyboom et al. 1997). We categorized drug hypersensitivity reaction into one of 3 entities: maculopapular eruptions (MPE), SJS/TEN, or DHS. Of these three, SJS/TEN and DHS were classified as SCARs. The subjects who had no such event during the period were classified as allopurinol tolerant.

HLA typing

Serologic HLA typing was performed by Terasaki Oriental HLA-ABC well tray (One Lambda, Canoga Park, CA, USA) using the microlymphocytotoxicity method. For HLA data of the general Korean population, we converted the previously reported HLA-A, -B, -C, and -DRB1 allele frequencies into serologic type frequencies (Lee et al. 2005). Since the previous study on the Korean population showed 100% coincidence of HLA-B*58:01 corresponding serologic type HLA-B58, we considered them identical. The frequencies of HLA-Cw8 were counted as the sum of the frequency of three Cw alleles (Cw*08:01, Cw*08:02, Cw*08:03) (Lee et al. 2005).

Data Analysis

Statistical analyses were performed using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). Values are expressed as mean ± standard deviation (S.D.) for continuous variables. Comparisons of categorical variables were made with Chi-square test and Fischer's exact test. The student's *t* test was used for continuous data and Mann-Whitney test for ordinal data. For comparing allele frequency, data of HLA-A, -B, -C and -DRB1 genes in the Korean population from a previous study were used as general population controls (Lee et al. 2005). Risks of allopurinol hypersensitivity according to the underlying diseases and HLA types were evaluated by binary logistic regression and expressed as odds ratio (OR) and 95% confidence intervals (CI). Multiple logistic regression was used to adjust for confounding variables. A P value of < 0.05 was considered statistically significant.

Results

Characteristics of Study Patients

Of the total 453 patients, the mean age was found to be 42.1 ± 14.5 years and the group consisted of 279 males (61.6%) (Table 1). The mean duration of allopurinol use was 16.4 ± 14.3 days with a mean dosage of 282.8 ± 56.9 mg/day (range, 100-600 mg/day). Pre-allopurinol levels of WBC and uric acid were 32,847 ± 68,246/mm^3 and 5.0 ± 2.8 mg/dL, respectively. The most common underlying hematologic malignancy was acute myeloid leukemia (AML) consisting of 229 patients (50.6%) followed by lymphoma with 75 patients (16.6%).

Clinical characteristics according to the presence of allopurinol hypersensitivity reactions

Of a total 453 patients, 13 had allopurinol hypersensitivity reactions, showing an incidence of 2.9% (Table 2). Males had an incidence of 2.2% (6/279) and females 4.0% (7/174). Among these patients, none had SCARs and all hypersensitivity reactions were assessed as MPE.

When the tolerant group was compared with the hypersensitivity group, there were no significant differences in age, sex, duration of allopurinol use, or allopurinol dose. Both groups had elevated WBC counts of over 30,000/mm^3 without any significant difference ($P > 0.05$). The hypersensitivity group had a four-fold elevation in eosinophils compared with the tolerant group (1,295 ± 3,747/mm^3 vs. 319 ± 1,564/mm^3) and they also had a relatively lower number of lymphocytes and higher number of neutrophils

Table 1. Clinical characteristics in total patients.

	$N = 453$
Sex (Male %)	279 (61.6%)
Age (median, yr)	42.1 ± 14.5
Body mass index	22.3 ± 3.6
Duration of allopurinol exposure (day)	16.4 ± 14.3
Dosage of allopurinol (mg/day)	282.8 ± 56.9
Blood WBC counts (/μl)	32,847 ± 68,246
Blood eosinophil counts (/μl)	354.2 ± 1,672
Blood lymphocyte counts (/μl)	11,407 ± 36,563
Blood neutrophil counts (/μl)	v9,031 ± 29,430
Alanine transaminase (IU/L)	42.2 ± 129.2
Creatinine (mg/dL)	1.0 ± 0.6
Uric acid (mg/dL)	5.0 ± 2.8
Underlying diseases (%)	
Acute myeloid leukemia	229 (50.6%)
Lymphoma	75 (16.6%)
Acute lymphoblastic leukemia	55 (12.1%)
Multiple myeloma	32 (7.1%)
Chronic myeloid leukemia	29 (6.4%)
Myelodysplastic syndrome	21 (4.6%)
Others	12 (2.6%)

Table 2. Clinical characteristics according to allopurinol hypersensitivity.

	Allopurinol hypersensitive group n = 13 (2.9%)	Allopurinol tolerant group n = 440 (97.1%)
Sex (Male %)	6 (46.2%)	273 (62.0%)
Age (median, yr)	40.3 ± 13.4	42.1 ± 14.5
Duration of allopurinol exposure (day)	16.1 ± 9.9	16.4 ± 14.4
Dosage of allopurinol (mg/day)	273.1 ± 66.5	283.1 ± 56.6
Blood WBC counts (/μl)	60,598 ± 107,688	32,024 ± 66,738
Blood eosinophil counts (/μl)	1,534 ± 3,758	319.2 ± 1,564
Blood lymphocyte counts (/μl)	24,800 ± 79,794	11,010 ± 34,587
Blood neutrophil counts (/μl)	16,741 ± 30,688	8,810 ± 29,402
Alanine transaminase (IU/L)	43.8 ± 41.1	43.2 ± 131.0
Creatinine (mg/dL)	1.1 ± 0.6	1.0 ± 0.6
Uric acid (mg/dL)	4.6 ± 3.4	5.0 ± 2.8
Underlying diseases (%)		
Acute myeloid leukemia	8 (61.5%)	221 (50.2%)
Lymphoma	2 (15.4%)	73 (16.6%)
Acute lymphoblastic leukemia	0 (0%)	55 (12.5%)
Multiple myeloma	0 (0%)	32 (7.3%)
Chronic myeloid leukemia*	3 (23.1%)	26 (5.9%)
Myelodysplastic syndrome	0 (0%)	22 (5.0%)
Others	0 (0%)	12 (2.7%)

*P = 0.044, compared between allopurinol hypersensitivity group and allopurinol tolerant group.

compared with the tolerant group, but all these differences were not statistically significant. Both groups showed similar findings in the number of blasts, alanine aminotransferase, and creatinine levels in peripheral blood.

Of the 13 patients with hypersensitivity, 8 had underlying AML, 3 had chronic myeloid leukemia (CML), and 2 had lymphoma. When the incidence rate of allopurinol hypersensitivity according to each hematologic malignancy was calculated, CML showed a rate of 10.3% (3/29), which was significantly higher than the combined rate of 2.4% (10/424) shown by hematologic malignancies other than CML (P = 0.044) (Fig. 1). CML has a higher risk of developing allopurinol hypersensitivity reactions with an odds ratio (OR) of 4.777 (95% CI: 1.239-18.421, P = 0.023). The risk became more significant after adjustment for age and sex (OR = 5.441, 95% CI: 1.365-21.687, P = 0.016). Comparing the proportion of individual subtypes of hematologic malignancies, the allopurinol hypersensitivity group consisted of a higher percentage of CML patients, showing significant difference compared with the tolerant group (23.1% (3/13) vs. 5.9% (26/440), P = 0.044).

The clinical manifestations of the 13 patients with allopurinol hypersensitivity reactions are displayed in Table 3. The mean interval from allopurinol initiation to symptom onset was 5.5 ± 1.2 days (range, 4-8 days). As allopurinol was administered for preventive measures during chemotherapy, it was not taken continuously but rather repeatedly in accordance with the chemotherapy cycle. Nine patients (69.2%) developed MPE during the first cycle, 3 patients (23.1%) in the second cycle, and 1 patient (7.7%) in the fourth cycle of allopurinol use. Among these patients with MPE, allopurinol was readministered in 6 patients but the hypersensitivity reaction did not recur.

Allopurinol hypersensitivity according to HLA alleles

There were 84 HLA subtypes discovered in 453 study subjects. When compared with the Korean general population, no significant difference was found in HLA allele frequency of the study subjects (Fig. 2). To determine the association of specific HLA subtypes and the development of allopurinol-induced hypersensitivity, we compared the frequency of the HLA subtypes between the allopurinol tolerant and the allopurinol hypersensitive groups (Table 4).

The frequency of the HLA-B58 allele, which had been previously reported to have a strong association with allopurinol-induced SCARs, did not show any significant difference between the hypersensitivity group and the tolerant group. Instead, HLA-B48 frequency was significantly higher in the hypersensitivity group (23.1%) than in the tolerant group (7.7%) and the Korean general population (6.8%). HLA-B48 was found to increase the risk of allopurinol hypersensitivity reaction with an OR of 4.109 (95% CI: 1.078-15.657, P = 0.038). As for HLA-DRB1, patients in the hypersensitivity group had higher DR9 positive rates (38.5%) compared with the tolerant group (13.6%), showing an OR of 3.986 (95% CI: 1.257-12.642, P = 0.019). The frequency of DR14 was also higher in the hypersensitivity group (38.5%) compared with the tolerant group

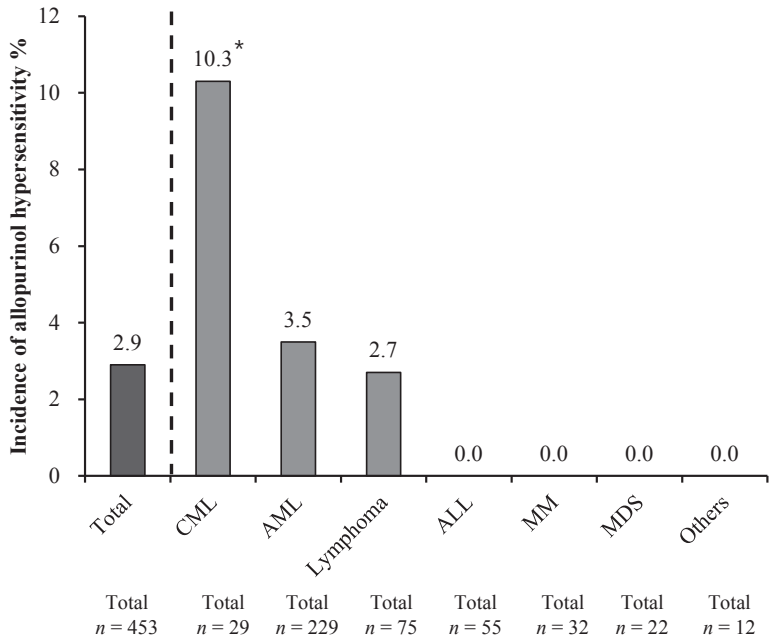

Fig. 1. Incidence of allopurinol hypersensitivity according to underlying hematologic malignancies. CML showed a rate of 10.3% (3/29), significantly higher than the combined rate shown by hematologic malignancies other than CML (P = 0.044).
*$P < 0.05$, compared to incidence of allopurinol hypersensitivity in other patients with hematologic malignancies other than CML.

Table 3. Clinical manifestations of allopurinol hypersensitivity reactions (13 cases).

Sex/Age	HLA-B	HLA-Cw	HLA-A	HLA-DR	Comorbidity	Allopurinol dose (mg)	Days to hypersensitivity reaction	At the initiation of allopurinol administration (/mm^3)				
								WBC	ANC*	Eosinophils	Lymphocytes	Blast
F/32	60	3, 7	1, 2	4, 8	AML	300	6	5,450	3,924	0	1,145	327
M/51	60, 62	3	24, 33	8, 14	AML	300	6	5,360	3,570	11	1,281	0
M/42	61, 62	3, 8	11, 26	12, 14	AML	300	6	1,020	90	30	830	0
F/25	60	3	24	9, 14	AML	300	4	10,460	523	0	1,360	8,368
M/49	37, 48	6, 8	1, 2	12, 15	AML	300	6	5,550	1,055	0	0	0
M/45	13, 61	3	11, 24	9, 14	AML	300	5	2,180	545	0	458	458
F/47	51, 58	3	2, 33	4, 13	AML	300	4	16,430	0	493	164	164
F/34	48, 58	3, 8	2	9, 13	AML	300	7	311,800	9,354	3,118	289,974	7,015
F/64	54, 67	1, 7	2	8, 16	CML	150	8	27,200	13,872	0	5,712	5,168
F/23	27, 54	1, 2	24	4	CML	300	5	271,400	86,848	13,570	16,284	16,284
M/31	27, 61	1, 8	2, 24	8, 9	CML	300	4	121,500	76,545	2,430	2,430	2,430
F/58	39, 54	1, 7	2, 26	4, 9	Lymphoma	300	6	5,530	1,770	277	2,765	0
M/23	35, 48	3, 8	11, 24	14	Lymphoma	100	5	3,900	2,796	20	0	0

*ANC, absolute neutrophil counts.

(15.6%) (OR = 3.381, 95% CI: 1.070-10.681, P = 0.038).

On investigation of HLA haplotype frequency, B48-Cw8 showed significantly higher frequency in the hypersensitivity group (23.1%) than in the tolerant group (5.7%) (OR = 4.980, 95% CI: 1.289-19.246, P = 0.020) and in the general population (6.0%) (OR = 4.717, 95% CI: 1.231-18.082, P = 0.024). Cw9-DR9 was also more frequent in the hypersensitivity group than in the tolerant group (OR = 5.742, 95% CI: 1.145-28.801, P = 0.034).

Fig. 3 shows the incidence of allopurinol hypersensitivity reactions according to the presence of specific HLA. Similar to the results described above, patients with HLA-DR9 (8.6% vs. 2.3%, P = 0.012), HLA-DR14 (7.6% vs. 2.4%, P = 0.028), B48-Cw8 (10.7% vs. 2.4%, P = 0.010), or Cw8-DR9 (14.3% vs. 2.8%, P = 0.010) had significantly higher incidence of allopurinol hypersensitivity reactions than those without.

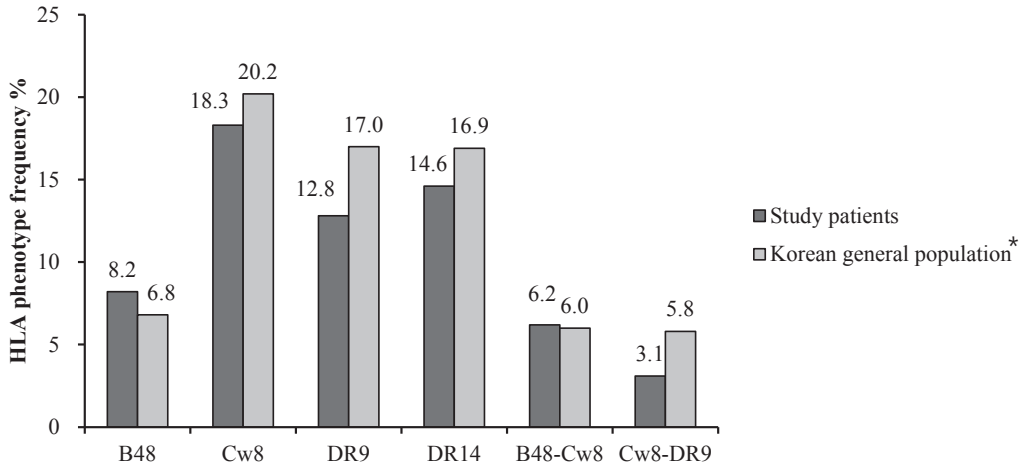

Fig. 2. HLA phenotype frequency in the study patients and the Korean general population. When compared with the Korean general population, no significant difference was found in HLA allele frequency of study subjects.
*From Lee et al. 2005.

Table 4. Frequencies of the HLA phenotypes in the simple rash group, tolerant group and the Korean general population.

HLA Types	Hypersensitivity group n = 13 (%)	Tolerant group n = 440 (%)	Korean general population* n = 485 (%)	Hypersensitivity group vs. Tolerant group OR (95% CI), P value	Hypersensitivity group vs. Korean general population* OR (95% CI), P value
DR9	5 (38.5%)	53 (13.6%)	86 (17.7%)	3.986 (1.257-12.642), 0.019	2.900 (0.926-9.079), 0.068
DR14	5 (38.5%)	61 (15.6%)	82 (16.9%)	3.381 (1.070-10.681), 0.038	3.072 (0.980-9.626), 0.054
B48	3 (23.1)	34 (7.7)	33 (6.8%)	3.582 (0.941-13.638), 0.061	4.109 (1.078-15.657), 0.038
Cw8	5 (38.5)	78 (17.7)	98 (20.2%)	2.901 (0.924-9.104), 0.068	2.468 (0.790-7.710), 0.120
B48-Cw8	3 (23.1%)	25 (5.7%)	29 (6.0%)	4.980 (1.289-19.246), 0.020	4.717 (1.231-18.082), 0.024
Cw8-DR9	2 (15.4%)	12 (3.1%)	28 (5.8%)	5.742 (1.145-28.801), 0.034	2.968 (0.627-14.040), 0.170

*From Lee et al. 2005.

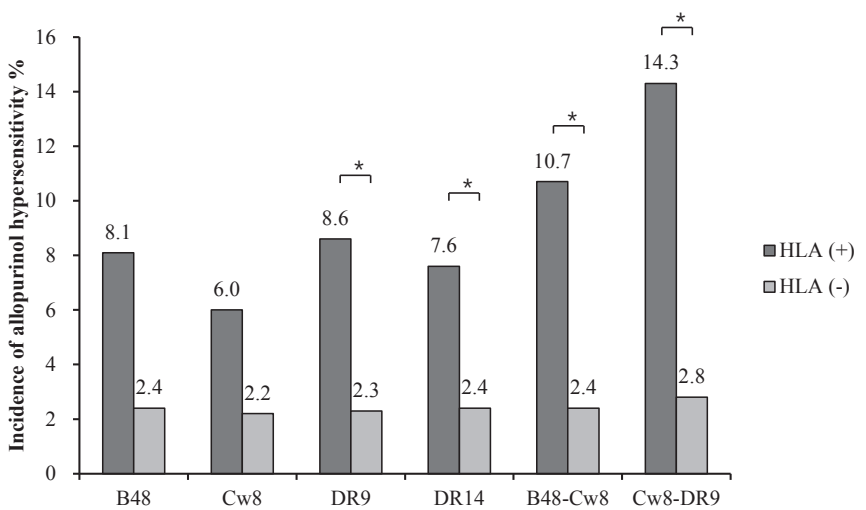

Fig. 3. Incidence of allupurinol hypersensitivity according to HLA phenotypes. Patients with HLA-DR9 (8.6% vs. 2.3%, P = 0.012), HLA-DR14 (7.6% vs. 2.4%, P = 0.028), B48-Cw8 (10.7% vs. 2.4%, P = 0.010), or Cw8-DR9 (14.3% vs. 2.8%, P = 0.010) had significantly higher incidence of allopurinol hypersensitivity reactions than those without.
*P < 0.05, compared according to presence of HLA phenotype.

Discussion

Allopurinol, a xanthine oxidase inhibitor, is the most commonly used agent for effectively lowering urate levels in hyperuricemia. Cutaneous adverse reactions from allopurinol use is relatively common, occurring in 2% of administered patients (Wortmann 2002). Allopurinol hypersensitivity syndrome, a severe form of cutaneous adverse reaction, occurs in 0.4% of administered patients and has a mortality rate of 25%, which is higher than that of hypersensitivity reactions induced by other drugs (Singer and Wallace 1986; Pluim et al. 1998).

Tumor lysis syndrome is a hematologic emergency that occurs in patients 1~3 days following the initiation of chemotherapy, characterized by acute hyperuricemia, hyperkalemia, and other severe electrolyte abnormalities often leading to acute renal failure. Allopurinol is very useful for the prevention of acute hyperuricemia related with tumor lysis syndrome (Davidson et al. 2004; Coiffier et al. 2008).

In our study, the incidence of hypersensitivity reactions caused by allopurinol, administered for the prevention of tumor lysis syndrome, was 2.9%, which was similar to the previously reported general incidence rate of 2% (Wortmann 2002). Considering the 0.4% incidence of allopurinol-induced SCARs in the general population (Gutierrez-Macias et al. 2005), there was a probability of 1.8 patients developing SCARs in our study group, but actually none was found. This is possibly due to the limited number of study subjects but other possibilities cannot be ruled out; the relatively short duration of administration (average 16 days) considering the average onset of allopurinol hypersensitivity syndrome (2 weeks ~ 2 months) (Hung et al. 2005; Kang et al. 2011) and impaired cell-mediated immunity related with their underlying hematologic malignancies (Hersh et al. 1971). In this study, hypersensitivity reactions did not occur in 6 patients despite allopurinol readministration in the following chemotherapy cycles. However, considering that their chemotherapy regimen and coadministered medications were not changed, it is unlikely that the hypersensitivity reactions had been caused by medications other than allopurinol. As we have presented in the results, incidence of hypersensitivity reactions were different according to underlying diseases. This suggests that immunologic susceptibility to hypersensitivity could be altered by the disease course even in the same subject.

On comparison of allopurinol hypersensitivity reactions according to hematologic malignancy, CML had a significantly higher incidence of 10.3%. CML patients on imatinib mesylate frequently have cutaneous adverse reactions even in the therapeutic ranges and the incidence of rash is reported up to 35% (Valeyrie et al. 2003). Although these cutaneous reactions by imatinib are mainly due to pharmacologic effects, hypersensitivity reactions seems to be play a role in some cases (Breccia et al. 2005). Our study has found that CML has a higher risk of allopurinol hypersensitivity reactions compared with other hematologic malignancies.

Cytotoxic CD8+ T cells have a primary role in the pathophysiology of SCARs by interaction of their surface T cell receptor and the HLA class I of the antigen presenting cells, inducing an immunologic response (Nassif et al. 2004). Many investigators have reported specific HLA class I genes having strong associations with certain drug-induced SCARs. Allopurinol-induced SCARs have strong associations with HLA class I genes, especially HLA-B*58:01 (Alfirevic et al. 2006; Lonjou et al. 2008; Tassaneeyakul et al. 2009). In Korea, China, and Taiwan where the frequency of HLA-B58 in the general population is relatively high, HLA-B*58:01 allele positivity in patients with allopurinol-induced SCARs was reported as high as 92-100%, showing an exceptionally strong association with the development of allopurinol-induced SCARs (Hung et al. 2005; Tassaneeyakul et al. 2009; Kang et al. 2011; Jung et al. 2011). We have previously performed a study on the association of HLA with the incidence of allopurinol-induced hypersensitivity reactions in patients with chronic renal insufficiency and have reported 3.6% incidence of allopurinol hypersensitivity reactions and 2% incidence of allopurinol-induced SCARs. In that study, all of the patients with SCARs were HLA-B58 positive and the patients with HLA-B58 positivity had 18% incidence of SCARs (Jung et al. 2011). If patients with underlying hematologic malignancy were to develop SCARs during chemotherapy, they would have dismal prognosis. Fortunately, no SCAR was found in our study, even in HLA-B58 positive patients. Based on our finding, short term use of allopurinol for the prevention of tumor lysis syndrome may be considered relatively safe in real practice situations. However, in patients with B48 or B48-Cw8, more attention must be paid for the possibility of MPE development.

In contrast to SCARs, MPE is a CD4+ T cell-mediated immune reaction where T-cells interact with HLA class II of the antigen presenting cells (Boehncke et al. 1993). Therefore, we speculated that HLA class II (HLA-DP, DQ, and DR) molecules may have some roles in the pathogenesis of MPE. Currently, the association between HLA class II genes and hypersensitivity reactions was revealed in part. For example, high frequency of DR9 was reported in Japanese patients with gelatin allergy (Kumagai et al. 2001). HLA-DRB gene association was also reported in penicillin allergy, especially with high frequency of DR9 in penicillin-allergic patients presenting with urticaria and DR14 in benzylpenicilloyl-hypersensitive patients (Yang et al. 2006). In addition, HLA-DR9 was found to have a positive association with ulcerative colitis (Stokkers et al. 1999). In our study, patients with HLA-DR9 and DR14 had a high incidence of allopurinol-induced MPE.

If allopurinol induces hypersensitivity in patients with hematologic malignancies, it could prohibit successful treatment by limiting scheduled chemotherapy as well as

increase the patient's suffering by the hypersensitivity symptom itself. Therefore, information on susceptibility to allopurinol hypersensitivity would help physicians diagnose and appropriately manage patients developing rash with allopurinol medication. For the patients with allopurinol hypersensitivity, other options such as rasburicase or febuxostat can be considered as a substitute (Coiffier et al. 2008).

As a retrospective study, there are potential limitations; the causality between allopurinol and hypersensitivity reactions was assessed by WHO-UMC causality system but not confirmed by skin test or drug provocation test and some reactions to allopurinol might not have been documented properly in the medical records.

Our study had a relatively short duration of allopurinol use by the study subjects. Since DHS usually develops after long-term allopurinol use, potential risk of DHS cannot be ruled out completely. However, considering that allopurinol is administered for a limited period for the prevention of hyperuricemia associated with tumor lysis syndrome in most patients with hematologic malignancies, the duration of allopurinol use in our study is long enough to investigate the safety of allopurinol for this use. Our study is based on serologic HLA subtypes. If HLA subtype data can be acquired by DNA sequencing methods, more specific HLA alleles responsible for the development of hypersensitivity reaction can be verified.

Incidence of allopurinol-induced hypersensitivity reactions was 2.9% and no case of SCARs was observed when allopurinol was administered to prevent tumor lysis syndrome before chemotherapy. In this setting, allopurinol hypersensitivity reactions were not associated with HLA-B*58:01, but rather had significant association with HLA-DR9 and DR14.

Acknowledgments

This study was supported by a grant of the National Project for Personalized Genomic Medicine, Ministry for Health & Welfare, Republic of Korea (A111218-PG01).

Conflict of Interest

The authors declare no conflict of interest.

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