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Clinical usefulness of testing for UDP glucuronosyltransferase 1 family, polypeptide A1 polymorphism prior to the inititation of irinotecan-based chemotherapy

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Abstract. An association between UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) polymorphisms and irinotecan-induced neutropenia has been previously reported. In this study, we assessed the clinical usefulness of testing for UGT1A1 polymorphisms prior to the initiation of irinotecan-based chemotherapy, as this remains a controversial subject. A total of 136 lung cancer patients who were treated with a combination of nedaplatin and irinotecan as initial chemotherapy were assessed. Following exclusion of patients exhibiting low UGT1A1 enzyme activity, 70 patients were treated after UGT1A1 polymorphism testing (test group) and 66 patients were treated without UGT1A1 polymorphism testing (non-test group). We retrospectively analyzed and compared the adverse events between the test and the non-test groups and observed no reduction in hematological or non-hematological toxicities in the test group compared to that in the non-test group. Of the 9 patients with grade 4 or 5 non-hematological toxicity, 6 patients had febrile neutropenia (FN). All the patients with FN were aged >70 years. The incidence of adverse events was significantly higher among patients aged >70 years compared to that among younger patients. In conclusion, in patients treated with nedaplatin and irinotecan combination chemotherapy, UGT1A1 polymorphism testing prior to the initiation of chemotherapy did not reduce the incidence of adverse events. Therefore, UGT1A1 polymorphism testing alone may not be sufficient to predict the occurrence of severe adverse events and it may be more important to effectively manage adverse events, particularly in elderly patients.

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Key words: lung cancer, UDP glucuronosyltransferase 1 family, polypeptide A1, irinotecan, nedaplatin, diarrhea, neutropenia

Introduction

Irinotecan is currently used as the standard chemotherapeutic agent for lung and colorectal cancer and its efficacy is dependent upon its activation by liver carboxyesterases to form the active metabolite SN-38. SN-38 is eliminated predominantly by a glucuronidation reaction to SN-38G. This glucuronidation reaction is mediated primarily by UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) (1). Irinotecan, SN-38 and SN-38G are all secreted into the bile by hepatocytes, with subsequent excretion into the small intestine (2). Dose-limiting toxicities of irinotecan are diarrhea and neutropenia and reduced enzyme activity and SN-38G formation is closely associated with severe toxicities (3). Genetic polymorphisms of UGT1A1 result in reduced enzyme activity, leading to decreased glucuronidation of SN-38 and, ultimately, in increased toxicity by irinotecan (3).

The association between UGT1A1*28 polymorphism and irinotecan-induced toxicities has been investigated (4). In East Asian populations, including the Japanese, the association between UGT1A1*28 and *6 polymorphisms and irinotecan-induced toxicities was previously investigated (3,5,6). In colorectal cancer, irinotecan-induced grade 3/4 neutropenia occurs more frequently in patients with the homozygous UGT1A1*28 mutation (*28/*28), the homozygous UGT1A1*6 mutation (*6/*6) or the double heterozygous mutation (*1/*28 and *1/*6), compared to patients with the wild-type of UGT1A1*28 and *6 (*1/*1 and *1/*1), the heterozygous UGT1A1*28 mutation (*1/*28) or the heterozygous UGT1A1*6 mutation (*1/*6) (7-9). These findings were similar for Japanese patients (9,10) and individuals with low enzyme activity constitute ~10% of the Japanese population (10,11).

The usefulness of UGT1A1 polymorphism testing prior to the initiation of chemotherapy in patients with lung cancer has not been clearly determined. Therefore, in this study, we aimed to assess the effect of excluding patients with low enzyme activity on the frequency and severity of irinotecan-induced toxicities.

Materials and methods

Study design. We retrospectively analyzed the treatment-related adverse events in patients receiving nedaplatin and irinotecan

combination chemotherapy and compared the incidence of adverse events between two patient groups, according to whether the patients underwent UGT1A1 polymorphism testing prior to treatment. The patients in one group (test group) were those who underwent UGT1A1 polymorphism testing prior to treatment initiation and were found not to have low enzyme activity. Patients with low enzyme activity were excluded from the study. In the second group (non-test group) the patients proceeded to receive treatment without prior UGT1A1 polymorphism testing.

The adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Hematological (leukopenia, neutropenia, thrombocytopenia and anemia) as well as non-hematological toxicities [diarrhea and febrile neutropenia (FN)] were assessed.

Patients. Between November, 2007 and February, 2011, a total of 136 patients with lung cancer were assessed. The patients were all treated with a combination of nedaplatin and irinotecan as initial chemotherapy in the Kanagawa Cancer Center. Patients who received adjuvant chemotherapy were included in this study. No patient developed severe major organ dysfunction. A total of 70 patients were finally included in the test group and 66 patients in the non-test group.

Treatment. All the patients were treated with nedaplatin and irinotecan combination chemotherapy. The regimen consisted

Table I. Results of UGT1A1 polymorphism testing.

	UGT1A1*6		
UGT1A1*28	*1/*1 (wild-type)	*1/*6 (heterozygous)	*6/*6 (homozygous)
*1/*1 (wild-type)	72	27	4
*1/*28 (heterozygous)	26	4	-
*28/*28 (homozygous)	1	-	-

Of the 134 lung cancer patients who were tested for UGT1A1 polymorphisms, 9 (6.7%) exhibited low enzyme activity. UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1.

Table II. Patient characteristics.

Characteristics	Total, no. (%) (n=136)	Test group[a], no. (%) (n=70)	Non-test group[b], no. (%) (n=66)
Age, years median (range)	66 (37-83)	68 (37-80)	64 (39-83)
Gender			
Male	91 (67)	45 (64)	46 (70)
Female	45 (33)	25 (36)	20 (30)
ECOG performance status			
0-1	130 (96)	69 (99)	61 (92)
2	6 (4)	1 (1)	5 (8)
Pathology			
Adenocarcinoma	68 (50)	35 (50)	33 (50)
Squamous cell carcinoma	27 (20)	15 (22)	12 (18)
Small-cell carcinoma	23 (17)	10 (14)	13 (20)
Others	18 (13)	10 (14)	8 (12)
Clinical stage (UICC-7)			
I/II	2 (2)	0 (0)	2 (3)
III	33 (24)	11 (16)	22 (33)
IV	65 (48)	28 (40)	37 (56)
Reccurence	6 (4)	4 (6)	2 (3)
Adjuvant	30 (22)	27 (38)	3 (5)
UGT1A1 polymorphism			
Wild-type	44 (32)	44 (63)	0 (0)
Heterozygous	26 (19)	26 (37)	0 (0)
Non-test	66 (49)	0 (0)	66 (100)

[a]Patients who underwent testing for UGT1A1 polymorphism prior to treatment and were not found to exhibit low enzyme activity. [b]Patients who did not undergo UGT1A1 polymorphism testing. ECOG, Eastern Cooperative Oncology Group; UICC, Union for International Cancer Control; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1.

Table III. Comparison of adverse events between patient groups.

Adverse events	Total, no. (%) (n=136)	Test group, no. (%) (n=70)	Non-test group, no. (%) (n=66)	P-value
Leukopenia				
Grade ≥3	37 (22.1)	19 (27.1)	18 (27.2)	0.99
Grade ≥4	8 (5.9)	7 (10.0)	1 (1.5)	0.037
Neutropenia				
Grade ≥3	78 (57.3)	38 (54.3)	40 (60.6)	0.46
Grade ≥4	27 (19.9)	14 (20.0)	13 (19.7)	0.96
Thrombocytopenia				
Grade ≥3	28 (20.6)	14 (20.0)	14 (21.2)	0.83
Grade ≥4	11 (8.1)	8 (11.4)	3 (4.5)	0.14
Anemia				
Grade ≥3	20 (14.7)	10 (14.3)	10 (15.1)	0.88
Grade ≥4	1 (0.7)	1 (1.4)	0 (0.0)	0.51
Hematological toxicities				
Grade ≥3	83 (61.0)	40 (57.1)	43 (65.2)	0.34
Grade ≥4	28 (20.6)	15 (21.4)	13 (19.6)	0.80
Febrile neutropenia[a]				
Grade ≥3	12 (8.8)	5 (7.1)	7 (10.6)	0.48
Grade ≥4	6 (4.4)	4 (5.7)	2 (3.0)	0.37
Diarrhea				
Grade ≥3	9 (6.6)	6 (8.6)	3 (4.5)	0.28
Grade ≥4	3 (2.2)	2 (2.9)	1 (1.5)	0.52
Non-hematological toxicities				
Grade ≥3	38 (27.9)	24 (34.3)	14 (21.2)	0.089
Grade ≥4	9 (6.6)	7 (10.0)	2 (3.0)	0.097
Treatment-related mortality	4 (2.9)	3 (4.3)	1 (1.5)	0.33

The comparisons between the two groups were performed with the Chi-square test. Adverse events were evaluated with Common Terminology Criteria for Adverse Events, version 4.0. [a]Febrile neutropenia was treated as a non-hematological toxicity.

of four cycles of 50 mg/m^2 nedaplatin on days 1 and 8 and 50 mg/m^2 irinotecan on days 1 and 8, every 4 weeks (12,13). Cisplatin and irinotecan combination chemotherapy is known to be effective for small-cell and non-small-cell lung cancer (14,15). In Japan, cisplatin and irinotecan combination chemotherapy is one of the standard chemotherapy regimens used for the treatment of lung cancer. Nedaplatin is an analogue of cisplatin, with relatively low neurotoxicity and nephrotoxicity and high *in vivo* bioavailability. Three-dimensional analysis models have demonstrated a remarkable synergistic interaction of platinum administration concurrently with irinotecan; this synergistic interaction has also been observed with the combination of nedaplatin and irinotecan (16).

Testing for UGT1A1 polymorphism. UGT1A1 polymorphisms were identified with a modified loop-hybrid mobility shift assay. When loop-hybrids using a Cy5-tagged probe for the *28 and *6 locus were combined and used for mobility shift assay, simultaneous typing of the *28 and *6 variants was achieved in a single lane (17).

Statistical analysis. Differences between groups were assessed with the t-test and the Chi-square test. P<0.05 was considered to indicate statistically significant differences.

Results

UGT1A1 polymorphism. We tested for UGT1A1 polymorphisms in 134 lung cancer patients in the Kanagawa Cancer Center and identified 9 patients (6.7%) with low enzyme activity. The results of the UGT1A1 polymorphism testing are presented in Table I.

Following exclusion of the 9 patients exhibiting low enzyme activity, 70 patients were treated with a combination of nedaplatin and irinotecan as initial chemotherapy after UGT1A1 polymorphism testing. The remaining 64 patients were administered a different therapy or were not treated. A further 66 patients were also treated with a combination of nedaplatin and irinotecan as initial chemotherapy, but without UGT1A1 polymorphism testing prior to treatment initiation.

Patient characteristics. The characteristics of the 136 study patients (test group, n=70; non-test group, n=66) who were

Table IV. Characteristics of 9 patients with severe non-hematological toxicities.

Patient characteristics						Grade of adverse events[a]		
Age (years)	Gender	UGT1A1	PS	Pathology	cStage	FN	Diarrhea	Other severe NH toxicities[b]
73	Female	Non-test	1	SCC	IV	4	-	-
83	Male	Non-test	1	NSCLC	IIIB	5	5	-
56	Male	Wild-type	1	Adenocarcinoma	IV	-	-	5[c]
69	Male	Wild-type	1	SCC	IV	-	-	5[c]
72	Male	Wild-type	1	Adenocarcinoma	IV	5	5	-
73	Male	Wild-type	1	SCC	IV	4	3	-
77	Male	*28 heterozygous	0	Adenocarcinoma	IV	4	4	-
67	Male	*6 heterozygous	1	LCNEC	IV	-	-	4[d]
78	Male	*6 heterozygous	1	SCLC	IV	4	3	-

[a]Adverse events ≥grade 3. [b]Other grade 4 and 5 adverse events. [c]Interstitial pneumonitis. [d]Bowel perforation. LCNEC, large-cell neuroendocrine carcinoma; FN, febrile neutropenia; NH, non-hematological; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1; PS, performance status; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; NSCLC, non-small-cell lung cancer.

Table V. Characteristics of the elderly and non-elderly patients.

Characteristics	Total, no. (%) (n=136)	Elderly, no. (%) (n=46)	Non-elderly, no. (%) (n=90)
Age, years median (range)	66 (37-83)	74 (70-83)	63 (37-69)
Gender			
Male	91 (67)	32 (70)	59 (66)
Female	45 (33)	14 (30)	31 (34)
ECOG performance status			
0-1	130 (96)	44 (96)	86 (96)
2	6 (4)	2 (4)	4 (4)
Pathology			
Adenocarcinoma	68 (50)	26 (57)	42 (47)
Squamous cell carcinoma	27 (20)	8 (17)	19 (21)
Small-cell carcinoma	23 (17)	7 (15)	16 (18)
Others	18 (13)	5 (11)	13 (14)
Clinical stage (UICC-7)			
I/II	2 (2)	2 (4)	0 (0)
III	33 (24)	12 (26)	39 (44)
IV	65 (48)	19 (41)	28 (31)
Recurrence	6 (4)	3 (7)	3 (3)
Adjuvant	30 (22)	10 (22)	20 (22)
UGT1A1 polymorphism			
Wild-type	44 (32)	20 (43)	24 (27)
Heterozygous	26 (19)	10 (22)	16 (18)
Non-test	66 (49)	16 (35)	50 (55)

ECOG, Eastern Cooperative Oncology Group; UICC, Union for International Cancer Control; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1.

treated with a combination of nedaplatin and irinotecan as initial chemotherapy are summarized in Table II. The median age of the total study group was 66 years (range, 37-83 years). The median age of the test group was higher compared to that of the non-test group, but there was no difference in age distribution. The tumors were classified as 68 adenocarcinomas,

Table VI. Comparison of adverse events between elderly (≥70 years) and non-elderly (<70 years) patients.

Adverse events	Total, no. (%) (n=136)	Elderly, no. (%) (n=46)	Non-elderly, no. (%) (n=90)	P-value
Leukopenia				
Grade ≥3	37 (22.1)	15 (32.6)	22 (24.4)	0.31
Grade ≥4	8 (5.9)	8 (17.4)	0 (0.0)	0.001
Neutropenia				
Grade ≥3	78 (57.3)	31 (67.4)	47 (52.2)	0.091
Grade ≥4	27 (19.9)	14 (30.4)	13 (14.4)	0.027
Thrombocytopenia				
Grade ≥3	28 (20.6)	12 (26.1)	16 (17.8)	0.26
Grade ≥4	11 (8.1)	7 (15.2)	4 (4.4)	0.035
Anemia				
Grade ≥3	20 (14.7)	8 (17.4)	12 (13.3)	0.53
Grade ≥4	1 (0.7)	1 (2.2)	0 (0.0)	0.34
Hematological toxicities				
Grade ≥3	83 (61.0)	33 (71.7)	50 (55.6)	0.057
Grade ≥4	28 (20.6)	15 (32.6)	13 (14.4)	0.013
Febrile neutropenia				
Grade ≥3	12 (8.8)	8 (17.4)	4 (4.4)	0.016
Grade ≥4	6 (4.4)	6 (13.0)	0 (0.0)	0.001
Diarrhea				
Grade ≥3	9 (6.6)	6 (13.0)	3 (3.3)	0.040
Grade ≥4	3 (2.2)	3 (6.5)	0 (0.0)	0.037
Non-hematological toxicities				
Grade ≥3	38 (27.9)	18 (39.1)	20 (22.2)	0.037
Grade ≥4	9 (6.6)	6 (13.0)	3 (3.3)	0.040
Treatment-related mortality	4 (2.9)	2 (4.3)	2 (2.2)	0.42

27 squamous cell carcinomas and 23 small-cell carcinomas. A total of 98 patients had clinical stage III-IV disease, according to the criteria of the Union for International Cancer Control, version 7 (18). After surgery, 30 patients received adjuvant chemotherapy. The median number of treatment cycles was 3 (range, 1-4 cycles). Adjuvant chemotherapy was administered to 27 patients (38%) in the test group and to only 3 patients (5%) in the non-test group.

Toxicities. The adverse events are listed in Table III. Of the total study population, grade 4 neutropenia occurred in 27 patients (19.9%), ≥grade 3 diarrhea in 9 patients (6.6%) and ≥grade 3 FN in 12 patients (8.8%). There were 4 treatment-related deaths (2.9%): 2 patients succumbed to FN and diarrhea and 2 patients succumbed to interstitial pneumonitis (IP). In the test group, grade 4 neutropenia occurred in 14 patients (20.0%), ≥grade 3 diarrhea in 6 patients (8.6%) and ≥grade 3 FN in 5 patients (7.1%). In the non-test group, grade 4 neutropenia occurred in 13 patients (19.7%), ≥grade 3 diarrhea in 3 patients (4.5%) and ≥grade 3 FN in 7 patients (10.6%). There was no significant reduction in any of the adverse effects in the test group compared to the non-test group.

We evaluated grade 4 or 5 non-hematological toxicities separately, since, when severe, these toxicities are considered to be the most important in the clinical field. Of the total study population, grade 4 or 5 non-hematological toxicities occurred in 9 patients (6.6%), with 6 patients developing FN and 3 patients developing IP or bowel perforation (Table IV). All 6 patients with FN were elderly (aged ≥70 years) and 5 of these patients developed FN concurrently with ≥grade 3 diarrhea.

Comparison of adverse events between elderly and non-elderly patients. We hypothesized that the incidence of severe toxicities may be higher among elderly patients and we compared the incidence of adverse events between the 46 elderly (≥70 years) and the 90 non-elderly (<70 years) patients (Table V). It should be noted that more patients were tested for UGT1A1 polymorphisms in the non-elderly group. The adverse events are listed in Table VI. In the elderly group, grade 4 neutropenia occurred in 14 patients (30.4%), ≥grade 3 diarrhea in 6 patients (13.0%) and ≥grade 3 FN in 8 patients (17.4%). In the non-elderly group, grade 4 neutropenia occurred in 13 patients (14.4%), ≥grade 3 diarrhea in 3 patients (3.3%) and ≥grade 3 FN in 4 patients (4.4%). These adverse events were significantly more frequent among elderly rather than among non-elderly patients.

Similarly, other hematological and non-hematological toxicities were more frequent among elderly patients. Therefore, elderly patients exhibited a higher risk for toxicities associated with nedaplatin and irinotecan combination chemotherapy.

When the adverse events were compared by other background factors, such as gender, PS, adjuvant chemotherapy and UGT1A1 polymorphisms, no significant differences in incidence were observed between groups.

Discussion

The association between UGT1A1 polymorphism and the risk of irinotecan-induced toxicity is dose-dependent. In 2005, the US Food and Drug Administration recommended testing for UGT1A1*28 polymorphism for dose regulation of irinotecan. As regards colorectal cancer, studies on the optimal dose of irinotecan for the treatment of patients with low enzyme activity have been conducted (19,20). However, the optimal dose of irinotecan for lung cancer patients with low enzyme activity has not been determined and remains a subject of controversy.

In the present study, we observed no reduction in the incidence of adverse events among patients in the test group compared to those in the non-test group, which may be explained as follows: First, since the number of patients exhibiting low enzyme activity was low, the exclusion of such patients exerted a limited effect on the overall incidence of adverse results. In our UGT1A1 polymorphism testing of 134 patients, only 9 patients (6.7%) exhibited low enzyme activity. In the Japanese population, the frequency of individuals with low enzyme activity was reported to be ~10% (11).

Second, the dose of irinotecan in our study was low, which may explain the lack of significant between-group differences in adverse events. A previous meta-analysis demonstrated that the risks of adverse events with low-dose irinotecan (<150 mg/m^2) were similar between patients with UGT1A1 (*1/*1 or *1/*28) (21). However, a later meta-analysis reported that the risk of adverse events was higher, even at low doses of irinotecan (<150 mg/m^2), in patients with UGT1A1*28 (*28/*28) compared to those with UGT1A1*28 (*1/*1 or *1/*28) (22). In the present study, the regimen consisted of four cycles of 50 mg/m^2 nedaplatin on days 1 and 8 and 50 mg/m^2 irinotecan on days 1 and 8, every 4 weeks.

The higher ratio of adverse events in the test group may be attributed to the number of elderly patients in that group. Although there was no between-group difference in age distribution, there were 30 (42%) elderly patients in the test group, but only 16 (24%) in the non-test group. Therefore, elderly patients may be at a higher risk of developing nedaplatin and irinotecan combination chemotherapy-related toxicities compared to non-elderly patients.

Several of the patients with severe toxicities synchronously developed FN and diarrhea. All 9 patients with ≥grade 3 diarrhea had fever. Among the 14 patients with grade 2 diarrhea, 9 patients had fever. Among the 113 patients with grade 0 or 1 diarrhea, 14 patients had fever. Patients with ≥grade 2 diarrhea had fever more frequently compared to patients with grade 0 or 1 diarrhea (P<0.001). Diarrhea may lead to dehydration, which is a risk of severe FN, as is an age of ≥60 years (23,24). Patients with diarrhea are also considered to be at high risk of infection and severe FN.

A meta-analysis demonstrated that the risk of irinotecan-induced diarrhea in patients with UGT1A1 (*28/*28 or *1/*28) was higher compared to that in patients with UGT1A1 (*1/*1) at medium and high doses (25). However, the association between UGT1A1 polymorphism and irinotecan-induced diarrhea has been controversial. In addition to UGT1A1 polymorphisms, an association between irinotecan-induced gastrointestinal toxicity and polymorphisms of the ABCC5, ABCG1 and SLCO1B1 genes has also been reported (26).

The dose-limiting toxicities of irinotecan are diarrhea and neutropenia. Patients with diarrhea are also at a high risk of infection. Therefore, it is important to effectively manage irinotecan-induced diarrhea and neutropenia. High-dose loperamide has been shown to be efficient for managing delayed diarrhea (27,28). Furthermore, the efficacy of oral alkalization for the prevention of irinotecan-induced diarrhea has been reported (29).

Patients with low enzyme activity are at high risk of severe neutropenia. However, with UGT1A1 polymorphism testing alone, it may be difficult to predict the onset of severe adverse events. Regarding the safety and efficacy of irinotecan administration, it is more important to manage adverse events effectively in the clinical field. For elderly patients, in particular, their management while administering irinotecan and nedaplatin combination chemotherapy should be handled with caution. Further investigation on the prevention of irinotecan-induced diarrhea is required.

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