Study on the Optimal Dose of Irinotecan for Patients with Heterozygous Uridine Diphosphate-Glucuronosyltransferase 1A1 (UGT1A1)

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Irinotecan, a platykinase, is one of the highly effective anticancer drugs used clinically, and its main adverse effects include myelosuppression, severe diarrhea, nausea, and vomiting. It is a prodrug, and then partly transferred to the systemic circulation via the enterohepatic circulation. 5,6) However, there are two genetic polymorphisms (UGT1A1*6 and UGT1A1*28). In UGT1A1 homozygous or heterozygous patients, metabolism is delayed and the risk of developing adverse effects is increased, and therefore, dose reduction of irinotecan is considered. However, the specific dose reduction rate of irinotecan for heterozygous patients is uncertain. We studied the necessity of irinotecan dose reduction and its optimal dose in UGT1A1 heterozygous patients with lung cancer. Patients with lung cancer treated with irinotecan in the Tokushima University Hospital or Tokushima Municipal Hospital were included in this study. The dose of irinotecan was evaluated based on the relative dose intensity (RDI). The time to treatment failure (TTF) was defined as the period until treatment change, death, or progressive disease based on response evaluation criteria of solid tumors. We targeted 31 patients treated with irinotecan: 12 wild types (WT), 14 heterozygotes, and 1 complex heterozygote and 4 homozygotes. There was no significant difference in the TTF, but the mean RDI during the entire treatment period was significantly different in the wild type (79%), heterozygous (62%), and complex heterozygous and homozygous groups (46%). In addition, the proportion of patients who completed treatment without dose reduction in the WT group tended to be higher than that in the other groups. For lung cancer patients with UGT1A1 heterozygote types who start irinotecan therapy, reducing the initial dose by approximately 20% might be a safer chemotherapy without decreasing the therapeutic effect.

Key words irinotecan; optimal dose; polymorphism; uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1)

INTRODUCTION

Irinotecan is one of the drugs used to treat various cancers, such as lung cancer, gynecological cancer, stomach cancer, colon cancer, breast cancer, malignant lymphoma, pediatric malignant solid tumor, and pancreatic cancer. Currently, irinotecan is one of the highly effective anticancer drugs used clinically, and its main adverse effects include myelosuppression, severe diarrhea, nausea, and vomiting. It is a prodrug, which is mainly hydrolyzed by carboxylesterase in the liver and converted to an active metabolite (SN-38).1,2) Subsequently, SN-38 is inactivated via glucuronidation by liver uridine diphosphate-glucuronosyltransferase (UGT) and excreted into the intestinal tract mainly via bile as SN-38 glucuronide conjugate (SN-38G).3,4) SN-38G in the intestinal tract is unconjugated to SN-38 by intestinal bacterial β-glucuronidase, and then partly transferred to the systemic circulation via the enterohepatic circulation.5,6) However, there are two genetic polymorphisms of UGT1A1: UGT1A1*6 and UGT1A1*28. Patients with either homozygous or heterozygous UGT1A1 (complex heterozygotes) have lower SN-38G production capacity than those without gene polymorphism, and the metabolism of SN-38 is delayed. Therefore, it has been reported that patients with UGT1A1 gene polymorphism develop adverse effects, such as severe neutropenia.7,8) There are not a few reports of deaths related to these adverse events.9) In the United States, in the package insert of irinotecan, patients with homozygous UGT1A1*28 are recommended to be administered with irinotecan by one-step dose reduction. As the area under the curve ratio (SN-38G/SN-38) has a difference of 2.4 times between high-risk and non-high-risk groups, Minami et al. suggested that irinotecan should be administered half of the standard dose to the high-risk group.10) However, there has been no study on the effectiveness and safety of administration of irinotecan at half of the standard dose to the high-risk group. Moreover, the influence of race cannot be ignored, because the allele frequency of UGT1A1*6 and UGT1A1*28 in Japanese has been reported to be 13.0–17.7% and 8.6–13.0%, respectively.11–13) Evidence regarding the optimal dose of irinotecan and dose reduction for patients with Japanese UGT gene polymorphism is still insufficient, and there is a need to accumulate prospective research data to confirm these.

Therefore, we examined the necessity of dose reduction and optimal dose for patients with heterozygous polymorphism, based on the dose and therapeutic effects in patients who received irinotecan in the Tokushima University Hospital and Tokushima Municipal Hospital.

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MATERIALS AND METHODS

Study Design, Setting, and Patient Population In the present study, eligible participants were patients aged <75 years, who received irinotecan mono chemotherapy as the treatment for lung cancer in the Tokushima University Hospital (Tokushima, Japan) and Tokushima Municipal Hospital (Tokushima, Japan) (April 2010 to April 2017). Patients were excluded if they had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of >2 or whose genotype was not known. The protocol of this study was approved by the ethics committee of the Tokushima University Hospital (approval no. 1404), and that of the Tokushima Municipal Hospital. The study was conducted in accordance with the Declaration of Helsinki.

Schedule of Administration Intronotecan monotherapy for lung cancer in the two institutions was according to the following three treatment methods. Patients received irinotecan on days 1, 8, and 15 every four weeks and the drug is withdrawn for one week (weekly regimen); on days 1 and 15 every four weeks (biweekly regimen); and on days 1 and 8 every three weeks (triweekly regimen) as intravenous infusion at a dose of 100 mg/m² (Fig. 1).

Data Collection and Assessment All data, including the results of blood test, UGT1A1 gene polymorphism, histological type of lung cancer, sex, adverse events, and drug dose, were collected retrospectively from the electronic medical record system. All adverse reactions, such as cytopenia and diarrhea, which occurred during the study period, were evaluated according to the Adverse Event Common Term Criterion (CTCAE) ver.3.0. The dose intensity was evaluated using relative dose intensity (RDI) taking into account effects such as treatment postponement and dose reduction. The RDI is one of the better clinical methods of dose evaluation in chemotherapy. The RDI was calculated using the following equation: RDI (%) = actual total dose per week (mg/m²/week)/standard planned total dose per week (mg/m²/week). The standard planned total dose was as follows: 100 mg/m² irinotecan on days 1, 8, and 15 every four weeks per course (75 mg/m²/week). In patients who opted for the biweekly regimen, even if they were administered 100 mg/m² irinotecan according to the administration schedule, the RDI was calculated as the treatment intensity of 66.7% (50 mg/m²/week). In addition, the RDI reflects the postponement of treatment or dose reduction of irinotecan.

Treatment effect was evaluated using the time to treatment...
failure (TTF). The TTF in this study was defined as the period until a patient died, was determined to have progressive disease (PD) based on the Response Evaluation Criteria in Solid Tumors, or was judged that treatment cannot be continued. Then, they were retrospectively investigated from the electronic medical record system.

**Statistical Analyses** Statistical analyses were performed using Bell Curve for Excel. The log rank test and Kaplan–Meier analysis were used to determine significant difference in treatment success period by genetic polymorphism. Mann–Whitney $U$ test was used to test whether there was a significant difference in the RDI throughout the treatment period among the wild type, heterozygous, and complex heterozygous and homozygous groups. Another significant difference test used was Fisher’s exact test. In all the tests, the standard of significant difference was set as $p < 0.05$.

**RESULTS**

**Patient Baseline Clinical Characteristics** There were 64 patients with lung cancer who received irinotecan alone during the treatment period, among them 31 patients fulfilled the selection criteria of this study (Fig. 2). The main reason for excluding patients was that their ECOG-PS score was 2 or higher. There was no significant difference in their clinical features at the start of treatment in the subjects (Table 1).

**Therapeutic Effect** The treatment period was compared using the TTF as described above. The median value of TTF was 61, 103, and 69 d in the wild type, heterozygous, and complex heterozygous and homozygous groups, respectively. There was no significant difference in the TTF, as an index of therapeutic effect, among the three groups (Fig. 3).

**Reason and Time of Dose Reduction** The proportion of patients requiring dose reduction during the treatment period was 25, 43, and 40% in the wild type, heterozygous, and complex heterozygous and homozygous groups, respectively (Fig. 4). One patient reduced dose due to both diarrhea and neutropenia in the wild type group. One patient reduced dose due to diarrhea and nausea, and one due to diarrhea and neutropenia in the heterozygous type. There was no significant difference in the ratio. The reasons for dose reduction in each group were also extracted from the electronic medical record system, most of which included myelosuppression and diarrhea. There was no significant difference in the occurrence of grade 3 or more

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**Table 1. Characteristics, Genotype, and Irinotecan Chemotherapy of Patients**

| UGT1A1 Polymorphism | Wild (−/−) | *6 | *28 | Complex hetero (*6/*28) |
|----------------------|------------|----|-----|-----------------------|
| Age (years)          | 65         | 64 | 67  | 71                    |
| Median (range)       | (54–74)    | (44–72) | (59–74) | (68–72)         |
| Sex                  | Male       | 8  | 7   | 1                     |
|                     | Female     | 4  | 2   | 0                     |
| BSA (m²)             | 1.53 (1.18–1.86) | 1.69 (1.47–1.79) | 1.81 | 1.56 (1.44–1.85) | 1.60 (1.50–1.68) | 1.57 |
| Primary disease      | Small cell carcinoma | 8 | 2 | 1 | 2 | 1 |
|                     | Adenocarcinoma    | 1 | 4 | 0 | 1 | 1 |
|                     | Squamous cell carcinoma | 3 | 3 | 0 | 2 | 1 |
| Baseline T-Bil; median (range) | 0.5 | 0.6 | 1 | 0.6 | 1.0 | 0.9 |
| Prior chemotherapy   | 1           | 7  | 2   | 0 | 1 | 1 |
|                     | 2–4         | 3  | 3   | 1 | 3 | 1 |
|                     | 5 ≤         | 2  | 4   | 0 | 1 | 1 |
| Schedule of administration | Weekly | 11 | 7  | 0 | 4 | 2 |
|                      | Bi-weekly   | 0  | 0   | 1 | 1 | 0 |
|                      | Tri-weekly  | 1  | 2   | 0 | 0 | 1 |
| Initial administration RDI (%) median (range) | 90 | 66 | 42 | 66 | 56 | 34 |

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**Fig. 3. TTF for Each UGT1A1 Polymorphism**

It shows the transition of treatment continuation proportion until the completion of treatment for all patients. The median value of TTF was 61, 103, and 69 d in the wild type, heterozygous, and complex heterozygous and homozygous groups, respectively. There was no significant difference among the groups.
adverse effects, which are serious adverse effects, in each group of UGT1A1 gene polymorphism. Moreover, the day on which the dose was most frequently reduced was day 1 of the second course, followed by day 8 of the first course (Fig. 5). It turned out that dose reduction was implemented early.

Relative Dose Intensity The RDI during the entire treatment period was 79, 62, and 46% in the wild type, heterozygous, and complex heterozygous and homozygous groups, respectively. These results revealed that the RDI of patients with genetic polymorphisms was significantly lower than that of patients with wild type (Fig. 6). Compared with that of patients with wild type, patients with heterogeneous polymorphisms had RDI of approximately 80% and those with complex heterozygous and homozygous polymorphisms had RDI of approximately 60%. The reason for discontinuation of treatment was PD in the wild type group, whereas that in the heterozygous type group included various reasons, other than PD. In addition, the percent of serious discontinuation reasons, such as death, tended to be higher in complex heterozygous and homozygous group than that in the other groups (Fig. 7).

Incidence of Adverse Events Depending on the Translocation Positions *6 and *28 Sixteen patients had serious adverse reactions of grade 3 or higher throughout the treatment period. The incidence of grade 3 neutropenia was observed in 7 patients, grade 3 anemia in 3 patients, grade 4 diarrhea in 1 patient, grade 3 diarrhea in 3 patients, grade 3 anorexia in 1 patient, and grade 3 oral mucositis in 1 patient. Although the incidence of adverse events was 55.5% with translocation position *6, it was 20% with translocation position *28 (Fig. 8). With respect to serious adverse events of grade 3 or higher, the incidence was 44.4 and 0% with translocation positions *6 and *28, respectively (Fig. 8). Regarding the incidence of adverse events, there was no significant difference depending on the location of translocation position. However, for all adverse event incidences including serious adverse events, patients with heterozygote *6 tended to be higher.
DISCUSSION

The incidence of adverse events of irinotecan is high in patients with UGT1A1 heterozygous polymorphisms, but its optimal dose and necessity for dose reduction are unclear. The results of this study showed the need for dose reduction of irinotecan and the optimal dose of approximately 80% for patients with heterozygous polymorphisms compared to the full dose in wild type. The UGT1A1 gene test has been commonly carried out even in Japan after it was reported that in patients with UGT1A1 gene polymorphism, the metabolism of irinotecan is delayed and that it might lead to serious adverse effects.7,10,20 Furthermore, as the UGT1A1 gene test has been applied for insurance in Japan since 2008, it has been carried out for almost all patients scheduled to receive irinotecan in several hospitals.

In the Tokushima University Hospital and Tokushima Municipal Hospital, the UGT1A1 gene test has been carried out in almost all patients who are administered irinotecan regardless of the cancer type as a matter of principal since 2008. However, evaluation of the UGT1A1 gene test results and their application to the clinical site vary depending on the physicians and pharmacists in charge. Although the cause varies, one of the main reasons is that there are only a few entrenched reports on the need or clear proportion according to dose reduction for each genetic polymorphism and that reports abroad cannot be applied to Japanese due to the difference in race.11,12,21 There is a need to accumulate evidence on the relationship between UGT1A1 gene polymorphism and dose of irinotecan in Japan.

In this study, we classified patients as wild type, heterozygous, and complex heterozygous and homozygous based on the test result of UGT1A1 gene polymorphism. Moreover, the purpose was to calculate the recommended dose from the RDI of each genetic polymorphism group in which noninferiority of TTF was confirmed. There was no significant difference in the patient background (Table 1). We compared the TTF using Kaplan–Meier estimator, but no significant difference was found among the three groups (Fig. 3). This shows non-inferiority of therapeutic effect determined by the RDI of each group during the entire treatment period. Regarding the reasons for the discontinuation of treatment, the heterozygous group tended to have more varied reasons, other than PD, than the wild type group, and the complex heterozygous and homozygous group presented even higher proportion (Fig. 4). Among cases requiring dose reduction, the number of patients in whom dose was reduced on day 1 of the second course was the highest, and in most cases, dose reduction was performed by day 1 of the second course (Fig. 5). Furthermore, in most cases of dose reduction, it was done only once. This implies how optimal dose reduction of irinotecan from the first time will lead to safer treatment, thus reducing burden on patients with lung cancer. In complex heterozygous and homozygous group, the reasons for discontinuation of treatment were serious, including interstitial pneumonia and death (Fig. 7). Patients whose treatment was discontinued due to death had small-cell lung cancer with early disease progression, and their death was considered to be due to disease progression. This also indicates that proper dose reduction from initial treatment could avoid serious adverse effects and might lead to safer and more effective chemotherapy in patients with genetic polymorphisms.16}

The average RDI during the entire treatment period was
79, 62, and 46% in the wild type, heterozygous, and complex heterozygous and homozygous groups, respectively (Fig. 6). Compared with that of the wild type group, the RDI of the group having genetic polymorphism was significantly low. Because the metabolism of irinotecan is delayed in patients with polymorphisms, it is thought that even at low doses (79%), blood levels in heterozygous polymorphisms are similar to those of wild type and similar anti-tumor effects are achieved. This is consistent with the result that even if there was a significant difference in the RDI, there was no significant difference in the incidence of adverse effects between the patient group with genetic polymorphism and wild type. Although adverse event incidences including serious adverse events tended to be higher in patients with heterozygote *6, there was no significant difference depending on the translocation positions *6 and *28 (Fig. 8). It might be influenced by patient baseline clinical characteristics. These results suggest that safer and more effective chemotherapy can be provided to patients with heterozygous polymorphisms by administering approximately 80% dose (by one-step dose reduction) compared to the full dose in wild type. Although the number of cases was low, it was shown that for patients with complex heterozygous and homozygous polymorphisms, it might be adequate to administer approximately 60% dose (by two-step dose reduction) compared to the full dose in wild type.

The study had some limitations. Although this study was a multicenter study, the total number of patients was small, and both small cell carcinoma and non-small cell cancer were considered as “lung cancer.” As this study focuses on the RDI and adverse events related to irinotecan administration, differences in histologic type are considered to have negligible effect, but it is necessary to accumulate more data. Furthermore, in this study, we examined patients treated with irinotecan mono chemotherapy to avoid the influence of other drugs, but in clinical practice, a combination regimen with other drugs has been used in several cases. Therefore, further studies are necessary in terms of feedback to actual clinical practice. As the dose of irinotecan varies depending on cancer type, it is necessary to consider the influence of differences in applied dose of irinotecan, as it is 100 mg/m² for lung cancer and 150 mg/m² for colon cancer. It is predicted that risk of treatment discontinuation or severe adverse event development will be higher with higher dose of irinotecan. Although the findings obtained from this study cannot be extrapolated directly, they may help determine the dose of combination chemotherapy including irinotecan for UGT1A1 heterozygous polymorphism patients. The proposal of optimal dose in patients with UGT1A1 heterogeneous polymorphism leads to safer and more effective chemotherapy in cancer other than lung cancer.

In conclusion, the UGT1A1 gene test is performed in almost all patients who are scheduled to receive irinotecan in Japan, but the clinical application of the results is inadequate. According to the results of this study, when irinotecan mono-therapy is started for patients with lung cancer, one-step dose reduction (80 mg/m²) is suggested for patients with UGT1A1 heterogeneous polymorphism from the first dose. Thus, effective chemotherapy without serious adverse events can be performed.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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