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Risk Factors for Severe Adverse Effects and Treatment-related Deaths in Japanese Patients Treated with Irinotecan-based Chemotherapy: A Postmarketing Survey†

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Objectives: This analysis was conducted to clarify risk factors for severe adverse effects and treatment-related deaths reported during a postmarketing survey of irinotecan.
Methods: The survey covered all patients treated with irinotecan in Japan between April 1995 and January 2000. The patient background data and adverse drug reactions were collected through case report forms. Univariate and multivariate logistic regression analyses including 14 explanatory variables were performed to determine the risk factors for grade 3–4 leukopenia, thrombocytopenia and diarrhea for all patients and subgroups with five major cancers. Treatment-related deaths were also analyzed.
Results: Case report forms of 13 935 patients (94.1% of 14 802 patients registered) treated with irinotecan-based chemotherapy were collected. Major grade 3–4 adverse drug reactions were leukopenia (34.8%), thrombocytopenia (12.4%) and diarrhea (10.1%). Multivariate analysis revealed that the risk factors (odds ratio $\geq$1.5) common for all these three adverse drug reactions were performance status ($\geq$3), infection and renal dysfunction before starting irinotecan therapy. Additionally, the risk factors for leukopenia were being female and prior radiotherapy, those for thrombocytopenia were age ($\geq$65 years), while those for diarrhea were pleural effusion and watery stool. The risk factors in each cancer were also identified. The incidence of treatment-related death was 1.3% (176). Myelosuppression-related deaths accounted for 70% and interstitial lung disease for 11% of all treatment-related deaths. Being male, age, performance status $\geq$3, massive ascites and infection and renal dysfunction were identified as risk factors for treatment-related death.
Conclusions: To ensure the safety of irinotecan therapy, it is important to select appropriate patients by considering the risk factors.

Key words: irinotecan – postmarketing survey – risk factor – adverse drug reaction – treatment-related death

INTRODUCTION

Irinotecan is an anticancer drug that inhibits topoisomerase (1). In Japan, it was initially approved for non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), ovarian cancer and cervical cancer in 1994, and it obtained additional approval for gastric cancer, colorectal cancer, malignant lymphoma, breast cancer and squamous cell carcinoma of the skin in 1995. In France and in the USA, irinotecan was first approved for colorectal cancer, and it has been currently used as a key drug for colorectal cancer worldwide.

The major dose-limiting toxicities (DLTs) in irinotecan chemotherapy were revealed to be myelosuppression (neutropenia and leukopenia) and delayed-onset diarrhea from the results of previous clinical trials. It has been reported that adverse drug reactions in some patients are serious, resulting in death (2,3). In Japan, there were widespread media reports of high mortality in clinical trials of irinotecan (2). Accordingly, when Daiichi Sankyo Co., Ltd. and Yakult Honsha Co., Ltd. applied for additional indications of irinotecan in 1995, the Ministry of Health and Welfare (currently the Ministry of Health, Labour and Welfare) directed the two companies to carry out a post-marketing surveillance for 4.5 years from 1995 to 2000 covering all patients treated with irinotecan-based chemotherapy (4).

The postmarketing surveillance was designed to gather safety information from all patients treated with irinotecan-based chemotherapy in order to promote its appropriate use based on the survey results. We have previously reported the results of the postmarketing surveillance demonstrating that the incidence of serious leukopenia, thrombocytopenia and diarrhea were high among patients who received irinotecan therapy (5).

In this article, the risk factors in patient characteristics for severe adverse reactions to irinotecan, such as grade 3–4 leukopenia, thrombocytopenia or diarrhea, were analyzed. In addition, the incidence and the risk factors for mortality in this postmarketing survey of irinotecan therapy are also reported.

This study was conducted under the Pharmaceutical Affairs Act, Good Post-Marketing Surveillance Practice in Japan.

PATIENTS AND METHODS

Design of Collection of Information

A previous article has already reported the practical method of this survey in detail (5). In brief, patients were enrolled by a central registration method before treatment with irinotecan. In order to cover all patients, irinotecan was not supplied to medical institutions until the patients had been enrolled. Information on patients treated with irinotecan was obtained by collecting case report forms (CRFs) from the participating medical institutions.

Each attending doctor filled out the specified checklist and sent it to the data center for reviewing each patient's eligibility. It was checked before registration whether patients met any of the contraindications listed in the package insert focusing on the hematological and other data obtained before the start of irinotecan administration. Detailed hematological data and other clinical data all through the treatment period were collected 1 month after the last administration of irinotecan.

Subjects

About 14 802 patients treated with irinotecan-based chemotherapy at 1204 medical institutions in Japan were registered between April 1995 and January 2000.

Treatment Delivery

While the chemotherapy regimen for each patient was decided by the attending doctor, irinotecan monotherapy was mainly used as follows according to the disease types. All treatment courses were generally repeated until disease progression, severe adverse events or patient's refusal

(1) For lung cancer, breast cancer and squamous cell carcinoma of the skin, treatment schedule contained irinotecan (100 mg/m^2) administered weekly.
(2) For colorectal cancer, gastric cancer, ovarian cancer and cervical cancer, the treatment schedule contained weekly administration of irinotecan (100 mg/m^2) or biweekly administration of irinotecan (150 mg/m^2).
(3) For malignant lymphoma, irinotecan (40 mg/m^2) was administered on three consecutive days a week for 2 or 3 weeks.

Dose and schedule of irinotecan was modified according to patient's age, medical condition and the combination with other anticancer drugs by each attending physician's decision.

Safety Assessment

The severe adverse drug reactions were defined as follows in accordance with the guidelines of the Japan Society of Clinical Oncology (6); grade 3 ($1.0–1.9 \times 10^3/\mu l$) or grade 4 ($<1.0 \times 10^3/\mu l$) leukopenia, grade 3 ($30<$ and $<50 \times 10^3/\mu l$) or grade 4 ($<30 \times 10^3/\mu l$) thrombocytepenia and grade 3 (watery stool $\geq$5 times/day) diarrhea or grade 4 (watery stool with bleeding, dehydration and/or electrolyte abnormalities). Grade 3–4 leukopenia and thrombocytopenia were determined by checking the collected hematologic data or by attending doctors' report.

Treatment-related death (TRD) was defined as death of which relation to irinotecan could not be ruled out by either the attending doctor or the independent investigational committee.

Statistical Analysis for Risk Factors of Adverse Drug Reactions and TRD

To determine predictive factors of grade 3–4 leukopenia, thrombocytopenia and diarrhea as objective variables,

univariate and multivariate (full model with variable selection) logistic regression analyses were carried out. In multivariate analysis, the following 14 explanatory variables were included as explanatory variables: gender, age ($\leq$64 or $\geq$65 years), performance status (PS) ($\leq$2 or $\geq$3), presence or absence of prior chemotherapy, prior radiotherapy, pleural effusion, massive ascites, watery stool, infection, jaundice, ileus, liver dysfunction, renal dysfunction or diabetes at the start of irinotecan therapy. Complications (liver dysfunction, renal dysfunction and diabetes) were diagnosed by attending doctors without any predetermined definitions. Moreover, in order to determine the risk factors for TRD, a multivariable analysis that included stage of tumor (III, IV/I, II), irinotecan therapy (alone or combination), combination therapy with radiation and concurrent diseases at the start of treatment in addition to the 14 explanatory variables was conducted. Furthermore, since the incidence of death is high (67%) in the initial stage of the treatment ($\leq$3 doses), we added the explanatory variable of a total number of doses (1–3/4-).

These analyses were carried out using SAS software (version 6.12 and 9.13, SAS Institute, Cary, NC, USA) for the whole patient population and for each cancer type whose data for all 14 explanatory variables could be collected. For the selection of variables, a stepwise method was used and significance level was set at $P = 0.05$. Probability values (two-sided) were also calculated.

RESULTS

Patient

The analysis included all data from 13 935 patients whose CRFs were collected of a total of 14 802 patients registered. The characteristics of these patients are shown in Table 1. Male patients accounted for 56%, and 66% of patients were 64 years or younger. The primary tumor sites were lung ($n = 6357$, 46%; NSCLC, SCLC), digestive organs ($n = 3510$, 25%; colorectal cancer, gastric cancer) and gynecologic organs ($n = 2787$, 20%; ovarian cancer, cervical cancer). Many of the patients had the disease in stage III or IV (82%) and prior chemotherapy (64%).

Toxicity

Of a total of 13 935 patients, 19 patients had missing values for leukopenia and 19 for thrombocytopenia. Grade 3–4 adverse reactions were observed as follows: leukopenia in 34.8%, thrombocytopenia in 12.4% and diarrhea in 10.1% of all patients included in this survey.

The incidence of myelosuppression such as leukopenia and thrombocytopenia was low in patients with colorectal cancer (18.8 and 4.5%, respectively) and high with ovarian cancer (42.6 and 15.0%) and with SCLC (37.7 and 17.3%).

Risk Factors for Grade 3–4 Adverse Drug Reactions

Total Population

Table 2 shows the results of univariate and multivariate analyses of risk factors for grade 3–4 adverse drug reactions observed in the total population. The numbers of patients for whom all data for the 14 explanatory variables were obtained were 12 023 for grade 3–4 leukopenia, 12 022 for grade 3–4 thrombocytopenia and 11 983 for grade 3–4 diarrhea. Multivariate analysis included those numbers of patients. Multivariate analysis revealed that the risk factors with an odds ratio $\geq$2.0 for thrombocytopenia were PS ($\geq$3) (odds ratio: 2.32) and watery stool for diarrhea (odds ratio: 4.14), while these severe adverse reactions were also significantly associated with many other variables (odds ratios: 1.15–1.99). Significant common risk factors for myelosuppression were gender (female), age ($\geq$65 years), PS ($\geq$3), prior chemotherapy, prior radiotherapy, pleural effusion, infection and hepatic and renal dysfunction (odds ratios: 1.16–1.87), while those for diarrhea were gender (female), age ($\geq$65 years), PS ($\geq$3), prior radiotherapy, pleural effusion, infection and renal dysfunction (odds ratios: 1.15–1.99).

Major Cancers

In lung cancer (NSCLC and SCLC), gender (female), age ($\geq$65 years) and prior radiotherapy (odds ratios: 1.35–1.80) were risk factors for severe leukopenia while pleural effusion (odds ratio: 1.27) was also important in NSCLC. Similarly, PS ($\geq$3) (odds ratio: 2.01) as well as gender (female), age ($\geq$65 years) and pleural effusion (odds ratios: 1.27–1.76) was a risk factor for severe thrombocytopenia while no significant risk factor for thrombocytopenia was found in SCLC. Watery stool (odds ratios: 5.23–6.44) before chemotherapy was a risk factor for severe diarrhea both in NSCLC and SCLC with an odds ratio higher than 5.0.

In ovarian cancer, PS ($\geq$3) (odds ratio: 2.72), prior chemotherapy (odds ratio: 1.28) and prior radiotherapy (odds ratio: 1.73) were risk factors for severe leukopenia while only prior chemotherapy (odds ratio: 2.51) was for severe thrombocytopenia. PS ($\geq$3) (odds ratio: 2.42) and prior chemotherapy (odds ratio: 1.61) were also risk factors for severe diarrhea.

In gastric cancer, jaundice (odds ratios: 2.73, 5.22) and renal dysfunction (odds ratios: 3.56, 2.51) were common risk factors for both severe leukopenia and thrombocytopenia with an odds ratio higher than 2.0, and massive ascites (odds ratios: 1.57, 2.18) was common for severe leukopenia and diarrhea. Being female (odds ratio: 1.68) and age ($\geq$65 years) (odds ratio: 1.74) were significant risk factors for severe leukopenia while PS ($\geq$3) (odds ratio: 2.47) was a risk factor for severe thrombocytopenia.

In colon cancer, PS ($\geq$3) (odds ratios: 2.21, 6.22) and renal dysfunction (odds ratios: 3.22, 2.58) were common risk factors for severe leukopenia and thrombocytopenia while watery stool (odds ratio: 9.38) was a strong risk factor for

Table 1. Patient characteristics

	Patients ($n = 13\,935$)	
	n	%
Gender		
Male	7791	55.9
Female	6143	44.1
Unknown	1	0.0
Age (years)		
≤64	9171	65.8
≥65	4760	34.2
Unknown	4	0.0
Performance status		
0–2	13 181	94.6
3–4	505	3.6
Unknown	249	1.8
Tumor type		
NSCLC	4415	31.7
Colorectal	2259	16.2
SCLC	1942	13.9
Gastric	1251	9.0
Malignant lymphoma	539	3.9
Ovarian	2136	15.3
Cervical	651	4.7
SCC of the skin	18	0.1
Breast	288	2.1
Others	436	3.1
Tumor stage		
I, II	1493	10.7
III, IV	11 472	82.3
Unknown	970	7.0
Prior chemotherapy		
No	4872	35.0
Yes	8950	64.2
Unknown	113	0.8
Prior radiotherapy		
No	10 743	77.1
Yes	3027	21.7
Unknown	165	1.2
Pleural effusion[a]		
No	12 250	87.9
Yes	1095	7.9
Unknown	590	4.2
Massive ascites[a]		
No	12 699	91.1
Yes	642	4.6
Unknown	594	4.3
Watery stool[a]		
No	13 375	96.0
Yes	96	0.7
Unknown	464	3.3
Infection[a]		
No	13 192	94.7
Yes	196	1.4
Unknown	547	3.9
Jaundice[a]		
No	12 713	91.2
Yes	76	0.5
Unknown	1146	8.2
Ileus[a]		
No	13 641	97.9
Yes	39	0.3
Unknown	255	1.8
Concurrent diseases at the start of treatment		
No	9927	71.2
Yes	3844	27.6
Hepatic dysfunction[b]	601	
Renal dysfunction	357	
Diabetes mellitus	919	
Heart disease	489	
Unknown	164	1.2
Total no. of doses		
1–3	5387	38.7
4–6	4395	31.5
7–9	1947	14.0
10–12	1027	7.4
13–15	466	3.3
16–	708	5.1
Unknown	5	0.0

NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; SCC, squamous-cell carcinoma.
[a]At the beginning of irinotecan treatment.
[b]Main concurrent diseases.

severe diarrhea with an odds ratio higher than 9.0. Additionally, significant risk factors for severe leukopenia were being female (odds ratio: 1.88), age (≥65 years) (odds ratio: 1.48), prior radiotherapy (odds ratio: 1.83), ascites

Table 2. Risk factors for grade 3–4 leukopenia, thrombocytopenia and diarrhea in patients receiving irinotecan therapy

Variable	G3–4 leukopenia					G3–4 thrombocytopenia					G3–4 diarrhea				
	n[a]	Univariate		Multivariate ($n = 12\,023$)		n[a]	Univariate		Multivariate ($n = 12\,022$)		n[a]	Univariate		Multivariate ($n = 11\,983$)	
		Odds (95% CI)	P value[c]	Odds (95% CI)	P value[c]		Odds (95% CI)	P value[c]	Odds (95% CI)	P value[c]		Odds (95% CI)	P value[c]	Odds (95% CI)	P value[c]
Gender (female/male)	13 915	1.48 (1.38–1.58)	0.0001	1.62 (1.50–1.75)	0.0001	13 915	1.08 (0.98–1.20)	0.1307	1.16 (1.03–1.29)	0.0120	13 861	1.05 (0.94–1.17)	0.4237	1.15 (1.02–1.30)	0.0271
Age ($\geq$65/$\leq$64 years)	13 912	1.20 (1.12–1.30)	0.0001	1.41 (1.30–1.53)	0.0001	13 912	1.37 (1.24–1.52)	0.0001	1.50 (1.34–1.68)	0.0001	13 858	1.34 (1.20–1.50)	0.0001	1.39 (1.22–1.57)	0.0001
PS ($\geq$3/$\leq$2)	13 670	2.05 (1.71–2.45)	0.0001	1.66 (1.36–2.03)	0.0001	13 669	2.79 (2.28–3.42)	0.0001	2.32 (1.85–2.91)	0.0001	13 624	2.01 (1.58–2.54)	0.0001	1.70 (1.31–2.21)	0.0001
Prior chemotherapy	13 804	1.23 (1.14–1.33)	0.0001			13 803	1.56 (1.40–1.75)	0.0001	1.43 (1.26–1.62)	0.0001	13 749	1.01 (0.90–1.14)	0.8347		
Prior radiotherapy	13 752	1.63 (1.50–1.77)	0.0001	1.73 (1.58–1.90)	0.0001	13 751	1.37 (1.22–1.54)	0.0001	1.22 (1.07–1.39)	0.0023	13 697	1.21 (1.07–1.38)	0.0035	1.20 (1.05–1.38)	0.0098
Pleural effusion[b]	13 328	1.31 (1.15–1.48)	0.0001	1.25 (1.09–1.43)	0.0013	13 327	1.34 (1.13–1.59)	0.0009	1.26 (1.05–1.52)	0.0121	13 283	1.82 (1.53–2.16)	0.0001	1.66 (1.38–2.00)	0.0001
Massive ascites[b]	13 324	1.56 (1.33–1.83)	0.0001	1.41 (1.19–1.68)	0.0001	13 323	1.24 (0.99–1.56)	0.0559			13 279	1.39 (1.10–1.76)	0.0061		
Watery stool[b]	13 453	1.52 (1.01–2.27)	0.0426			13 453	0.73 (0.37–1.45)	0.3617			13 407	4.03 (2.59–6.26)	0.0001	4.14 (2.50–6.85)	0.0001
Infection[b]	13 370	1.83 (1.38–2.43)	0.0001	1.70 (1.24–2.31)	0.0009	13 370	2.28 (1.64–3.18)	0.0001	1.87 (1.30–2.68)	0.0007	13 326	2.64 (1.88–3.72)	0.0001	1.99 (1.37–2.90)	0.0003
Jaundice[b]	12 771	2.01 (1.27–3.16)	0.0027			12 771	2.96 (1.80–4.88)	0.0001			12 725	0.89 (0.41–1.93)	0.7585		
Ileus[b]	13 662	2.20 (1.17–4.13)	0.0145			13.662	2.46 (1.20–5.05)	0.0145			13 615	1.02 (0.36–2.86)	0.9764		
Hepatic dysfunction[b]	13 754	1.45 (1.23–1.71)	0.0001	1.41 (1.18–1.69)	0.0002	13 752	1.51 (1.21–1.88)	0.0002	1.35 (1.07–1.71)	0.0125	13 699	1.30 (1.02–1.67)	0.0366		
Renal dysfunction[b]	13 754	2.03 (1.65–2.51)	0.0001	1.76 (1.39–2.22)	0.0001	13 752	2.24 (1.75–2.88)	0.0001	1.82 (1.38–2.40)	0.0001	13 699	1.81 (1.36–2.41)	0.0001	1.62 (1.19–2.21)	0.0022
Diabetes[b]	13 754	0.75 (0.64–0.86)	0.0001	0.73 (0.62–0.86)	0.0001	13 752	0.98 (0.80–1.20)	0.8385			13 699	1.16 (0.93–1.43)	0.1843		

[a]No. of patients for univariate analysis.
[b]At the beginning of irinotecan treatment.
[c]Wald chi-square test.

Table 3. Patient characteristics of treatment-related death

	Treatment-related death ($n = 176$)	
	n	Mortality (%)
Gender		
Male	115	1.5
Female	61	1.0
Age (years)		
≤64	89	1.0
≥65	87	1.8
Performance status		
0–2	150	1.1
3–4	26	5.2
Tumor type		
NSCLC	48	1.1
Colorectal	30	1.3
SCLC	29	1.5
Gastric	28	2.2
Malignant lymphoma	14	2.6
Ovarian	16	0.7
Cervical	7	1.1
SCC of the skin	2	11.1
Breast	0	0
Others	2	0.5
Tumor stage		
I, II	13	0.9
III, IV	150	1.3
Unknown	13	1.3
Prior chemotherapy		
No	53	1.1
Yes	123	1.4
Prior radiotherapy		
No	133	1.2
Yes	42	1.4
Unknown	1	0.6
Pleural effusion[a]		
No	148	1.2
Yes	24	2.2
Unknown	4	0.7
Massive ascites[a]		
No	152	1.2
Yes	20	3.1
Unknown	4	0.7
Watery stool[a]		
No	172	1.3
Yes	1	1.0
Unknown	3	0.6
Infection[a]		
No	164	1.2
Yes	9	4.6
Unknown	3	0.5
Jaundice[a]		
No	162	1.3
Yes	3	3.9
Unknown	11	1.0
Ileus[a]		
No	173	1.3
Yes	2	5.1
Unknown	1	0.4
Concurrent diseases at the start of treatment		
No	102	1.0
Yes	73	1.9
Hepatic dysfunction[b]	14	
Renal dysfunction	20	
Diabetes mellitus	4	
Heart disease	13	
Unknown	1	0.6
Chemotherapy		
Irinotecan alone	53	1.6
Combination	123	1.2
Combination therapy with radiation		
No	161	1.2
Yes	15	1.6
Total no. of doses		
1–3	118	2.2
4–	58	0.7
1	48	
2	57	
3	13	

[a]At the beginning of irinotecan treatment.
[b]Main concurrent diseases.

(odds ratio: 2.02), watery stool (odds ratio: 3.27) and hepatic dysfunction (odds ratio: 2.80), while prior radiotherapy (odds ratios: 1.83, 2.44) was a common risk factor for severe leukopenia and diarrhea. For severe thrombocytopenia, prior chemotherapy (odds ratio: 2.23) was a significant risk factor.

Table 4. Risk factors for treatment-related death in patients receiving irinotecan therapy

Variable	n[a]	Treatment-related death					
		Univariate			Multivariate ($n = 11\,249$)		
		Odds	(95% CI)	P value[c]	Odds	(95% CI)	P value[c]
Gender (female/male)	13 934	0.67	(0.49–0.91)	0.0118	0.59	(0.41–0.86)	0.0054
Age (≥65/≤64 years)	13 931	1.90	(1.41–2.56)	0.0001	1.91	(1.37–2.68)	0.0002
PS (≥3/≤2)	13 686	4.72	(3.08–7.22)	0.0001	3.03	(1.84–5.00)	0.0001
Tumor stage (I, II/III, IV)	12 965	1.51	(0.85–2.67)	0.1571			
Prior chemotherapy	13 822	1.27	(0.92–1.75)	0.1523			
Prior radiotherapy	13 770	1.12	(0.79–1.59)	0.5168			
Pleural effision[b]	13 345	1.83	(1.19–2.83)	0.0064			
Massive ascites[b]	13 341	2.65	(1.65–4.26)	0.0001	2.11	(1.20–3.71)	0.0098
Watery stool[b]	13 471	0.81	(0.11–5.83)	0.8327			
Infection[b]	13 388	3.82	(1.93–7.60)	0.0001	2.25	(1.04–4.89)	0.0405
Jaundice[b]	12 789	3.18	(0.99–10.21)	0.0513			
Ileus[b]	13 680	4.21	(1.00–17.60)	0.049			
Concurrent disease at the start of treatment	13 771	1.87	(1.38–2.52)	0.0001			
Hepatic dysfunction[b]	13 771	1.93	(1.11–3.35)	0.0199			
Renal dysfunction[b]	13 771	5.08	(3.15–8.20)	0.0001	4.82	(2.87–8.10)	0.0001
Diabetes[b]	13 680	0.32	(0.12–0.88)	0.0263			
Chemotherapy (mono/combined)	13 935	0.75	(0.54–1.04)	0.0834			
Combination therapy with radiation	13 935	1.30	(0.76–2.21)	0.3423			
Total no. of doses (1–3/4–)	13 930	0.31	(0.22–0.42)	0.0001	0.344	(0.24–0.49)	0.0001

PS, performance status.
[a]No. of patients for univariate analysis.
[b]At the beginning of irinotecan treatment.
[c]Wald chi-square test.

Treatment-related Death

The number of deaths from severe adverse drug reactions whose causal relationship with irinotecan could not be ruled out was 176 (1.3%) of the 13 935 patients. Of the 176 TRDs, 103 (59%) were caused by myelosuppression, 19 (11%) by myelosuppression accompanied by diarrhea, 6 (3%) by myelosuppression with ileus, 20 (11%) by interstitial lung disease, 8 (5%) by renal failure, 1 by diarrhea and 19 (11%) by other causes, including heart failure (2), hepatic failure (1), tumor necrosis with massive hemorrhage (1) and intestinal perforation (1). Of all TRDs, 73% were associated with myelosuppression, or concurrent incidence of myelosuppression, ileus and diarrhea. Their patient characteristics are shown in Table 3. Moreover, risk factors for TRD are summarized in Table 4. Multivariate analysis revealed that gender (male), age (≥65 years) (odds ratio: 1.91), PS (≥3) (odds ratio: 3.03), ascites (odds ratio: 2.11), infection (odds ratio: 2.25) and renal dysfunction (odds ratio: 4.82) were risk factors for TRD, and that risk of TRD was higher in patients receiving total number of doses 1–3 compared with those receiving ≥4 doses.

DISCUSSION

To identify the risk factors for severe adverse drug reactions associated with irinotecan, we carried out a multivariate analysis using patient characteristics for all patients and for five types of major cancers (SCLC, NSCLC, ovarian cancer, gastric cancer and colorectal cancer). From the multivariate analysis, we identified the risk factors for severe adverse drug reactions in relation to patient characteristics and cancer types.

Risk factors with odds ratio ≥1.5 common for the three major severe adverse drug reactions (leukopenia, thrombocytopenia and diarrhea) were PS ≥3, infection and renal dysfunction. Risk factors identified for each severe adverse

effect were gender and prior radiotherapy for leukopenia, age for thrombocytopenia and pleural effusion and watery stool for diarrhea. Although watery stool observed during treatment is difficult to distinguish from diarrhea after chemotherapy, attention should be paid to this as a risk factor indicative of worsening.

It was shown that the risk factors vary depending on the type of cancer. Symptoms that appear in association with cancer progress such as pleural effusion (NSCLC), massive ascites (gastric and colorectal cancer) and hepatic dysfunction (colorectal cancer) were the risk factors for severe leukopenia, while jaundice (gastric cancer) was a risk factor for severe leukopenia and thrombocytopenia. Moreover, prior radiotherapy for lung cancer and ovarian cancer were risk factors for severe leukopenia, and this should be noted when initiating treatment with irinotecan.

In this survey, cisplatin was most frequently used in combination with irinotecan in patients with lung cancer and gastric cancer (43%). In patients with ovarian cancer, mitomycin C, which is effective for clear-cell carcinoma, was concomitantly used in 30% of patients. On the other hand, in patients with colorectal cancer, of whom 51% received irinotecan monotherapy, the incidence of severe adverse drug reactions was lower than that of patients with lung cancer and ovarian cancer (5). Therefore, it was suggested that predictive factors of adverse drug reactions of irinotecan may depend on the dose and regimen as well as concomitant anticancer drug used.

The DLTs of irinotecan are neutropenia and diarrhea (3). Clinical studies have also suggested that high bilirubin, low hemoglobin and a number of dysfunctional organs are risk factors for severe neutropenia, while poor PS, high creatinine and low white blood cell count during irinotecan therapy, and prior radiotherapy to the pelvic cavity are for severe diarrhea (7). Thus, in the package insert for irinotecan in the USA and Japan, the drug is contraindicated for use in patients with myelosuppression, infection, diarrhea, intestinal paralysis, intestinal obstruction and massive ascites or pleural effusion (8,9). The present survey confirmed the risk factors for severe adverse drug reactions of irinotecan-based chemotherapy.

Interestingly, this multivariate analysis showed that the risk of adverse drug reactions was higher among female patients than male patients. In a previous report, the incidence of grade 3–4 leukopenia in the regimens including irinotecan was significantly higher in females (10). Meta-analysis demonstrated that toxicity of fluorouracil was also more severe among female patients, suggesting a gender difference in tolerability to irinotecan (11,12). However, while some reports showed that the area under the curve of SN-38, the active metabolite of irinotecan, was significantly higher in females (13), the reasons for this gender difference remain unclear.

It has been reported that concomitant occurrence of neutropenia and diarrhea is likely to cause TRD (14,15). While TRDs occurred in 55 (4.4%) out of a total 1245 patients in Japanese clinical trials (2), this survey showed the incidence of TRD was as low as 1.3%. It seemed that the experience in clinical trials could have provided information on supportive therapy such as granulocyte-colony stimulating factor for myelosuppression and loperamide for diarrhea. However, TRD was significantly correlated among patients with a poor PS and those who had infection, renal dysfunction or other complications in this study, careful attention should be paid to these risk factors for severe myelosuppression and diarrhea before irinotecan-based chemotherapy.

Furthermore, because early deaths within three doses of irinotecan accounted for 66% of all TRDs, it is necessary to monitor adverse drug reactions carefully during the early stage of administration.

The relationship between severe neutropenia and diarrhea caused by irinotecan and *UGT1A1* polymorphism has been investigated in recent years. It has been shown that *UGT1A1*28* and *UGT1A1*6* polymorphism are predictive factors for severe neutropenia (4,16–18). Since 2005, the US package insert has noted that the risk of severe neutropenia is high for patients with *UGT1A1*28* polymorphism (9). However, there are racial differences in incidence of *UGT1A1*6* polymorphism (17,18). Since 2008, the Japanese package insert has also noted that the risk of severe neutropenia is high for patients with *UGT1A1*28* polymorphism and patients who are homozygous for the *UGT1A1*6* allele or are combined heterozygotes for the *UGT1A1*28* and *UGT1A1*6* alleles (8). A UGT1A1 kit that is useful for examining these polymorphisms has been launched in both the USA and Japan, and polymorphisms have been used in clinical practice as predictors of severe adverse drug reactions to irinotecan. While during the period of this survey, the UGT1A1 kit was not available in Japan, it is considered that the risk of irinotecan has been reduced through examining the polymorphism recently in Japan.

Of the 176 deaths for which a causal relationship with irinotecan could not be ruled out, 20 were due to interstitial lung disease. It has only been reported that irinotecan causes interstitial lung disease in some patients (19,20). Yoshii et al. (21) examined the image analysis of 18 patients with irinotecan-induced interstitial lung disease. They reported that although the clinical form and image findings specific to irinotecan were not seen, diffuse alveolar damage pattern was found in six patients, four of whom died. Interstitial lung disease should also be noted as an adverse drug reaction that can cause death.

Although the present survey was a large-scale review of actual clinical practice and may contain some missing data and bias, this information on adverse drug reactions of irinotecan over a certain period is considered to contribute significantly to its safe and effective use for treatment of cancer. The risk factors shown in the present analysis have been noted in the package inserts in the USA and Japan (8,9). To ensure the safety of irinotecan therapy and maximize its efficacy, it is important to select appropriate patients, monitor patients carefully and treat adverse drug reactions promptly.

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Conflict of interest statement

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