Irinotecan Hydrochloride for the Treatment of Recurrent and Refractory Non-Hodgkin Lymphoma

A Single Institution Experience

Katsuki Sugiyama, M.D.
Ken Omachi, M.D.
Keiichi Fujiwara, M.D.
Takashi Saotome, M.D.
Nobuyuki Mizunuma, M.D.
Shunji Takahashi, M.D.
Yoshinori Ito, M.D.
Keisuke Aiba, M.D.
Noboru Horikoshi, M.D.

Department of Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan.

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Dr. Sugiyama's current address: Division of Hematology and Oncology, Department of Internal Medicine, Jikei University School Of Medicine, Tokyo, Japan.

Address for reprints: Shunji Takahashi, M.D., Department of Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 1-37-1 Kami-ikebukuro, Toshima-ku, Tokyo, 170-8455 Japan; Fax: (011) 81-3-3918-3716; E-mail: stakahas@jfcr.or.jp

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BACKGROUND. Irinotecan hydrochloride (CPT-11) has a broad range of antitumor activity and has demonstrated little cross-resistance with doxorubicin or vincristine. In the current study, the authors investigated the efficacy and adverse effects of irinotecan in the treatment of recurrent and refractory non-Hodgkin lymphoma, for which current therapies appear to be unsatisfactory.

METHODS. Irinotecan was administered by intravenous infusion at a dose of 40 mg/m^2/day for 3 days, and this regimen was repeated 2–3 times at weekly intervals, followed by 2 weeks off therapy. The subjects were 48 patients with recurrent or refractory non-Hodgkin lymphoma. The histologic classification (Working Formulation) was low grade in 8 patients, intermediate grade in 36 patients, high grade in 1 patient, and other (angiocentric lymphoma, Ki-1 lymphoma, and unidentified) in 3 patients.

RESULTS. Forty-five patients were determined to be evaluable. Therapy resulted in a complete disease remission in 2 patients and a partial remission in 15 patients. The response rate was 37.8%. The median duration of response was 64 days and the median time to disease progression was 77 days. The median survival time was 422 days. Major adverse reactions included myelosuppression and gastrointestinal toxicity. Leukopenia, anemia, and thrombocytopenia of Grade 3 or 4 (according to the National Cancer Institute Common Toxicity Criteria) was observed in 63.0%, 30.4%, and 6.5% of the patients, respectively, and Grade 3 or 4 diarrhea occurred in 30.4% of patients. Treatment was withdrawn because of diarrhea in three patients. Because of myelosuppression and diarrhea, approximately 67% of the patients required changes to the regimen, including dose reduction, prolongation of the interval between treatments, and reducing the number of days of consecutive treatment.

CONCLUSIONS. The results of the current study suggest the activity of irinotecan as salvage therapy for patients with recurrent and refractory non-Hodgkin lymphoma. However, the optimum dosing schedule remains to be determined. ***Cancer* 2002;94:594–600.** *© 2002 American Cancer Society.*
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Irinotecan hydrochloride (CPT-11) is a semisynthetic derivative of camptothecin, a plant alkaloid extracted from a Chinese tree. Unlike the majority of other anticancer agents, its action involves the blocking of nucleic acid synthesis by inhibition of the enzyme topoisomerase I.[1] Irinotecan has a broad range of antitumor activity[1] and already has been shown to be useful for the treatment of non-Hodgkin lymphoma,[2,3] lung carcinoma,[4] uterine cervical carcinoma,[5] ovarian carcinoma,[5] gastric carcinoma,[6] colorectal carcinoma,[7] breast

carcinoma,[8] and squamous cell carcinoma of the skin.[9] Irinotecan demonstrates little cross-resistance with doxorubicin or vincristine,[10] suggesting that it may be of value in the treatment of various malignancies as salvage therapy. In the current study, we administered irinotecan to patients with recurrent or refractory non-Hodgkin lymphoma, and evaluated the response to treatment and adverse reactions.

MATERIALS AND METHODS

Patients

Patients with recurrent or refractory non-Hodgkin lymphoma who had received standard chemotherapeutic regimens were eligible if they met the following criteria: 1) had histologically and/or cytologically confirmed non-Hodgkin lymphoma; 2) had disease that was refractory to standard chemotherapy or that had recurred after the patient attained a complete remission (CR) or demonstrated disease progression after attaining a partial remission (PR); 3) demonstrated the presence of measurable disease; 4) had received no chemotherapy or radiation therapy the previous 2 weeks; 5) had a life expectancy of $\geq$ 2 months; 6) were age $\geq$ 15 years and age $<$ 80 years; 7) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of $\leq$ 3; 8) had adequate bone marrow function (a leukocyte count $\geq$ 3000/μL, neutrophil count $\geq$ 1200/μL, hemoglobin $\geq$ 8.0 g/dL, and platelet count $\geq$ 100,000/μL), adequate hepatic function (bilirubin $\leq$ 2.0 mg/dL and transaminases $\leq$ 2.5 times the upper limits of normal), and adequate renal function (creatinine $\leq$ 1.5 mg/dL and creatinine clearance $\geq$ 50 mL/minute); 9) had no severe complications; 10) had no active double malignancy; and 11) were able to provide informed consent. Exclusion criteria were 1) infections, 2) watery diarrhea, 3) intestinal paralysis or obstruction, 4) interstitial pneumonia or pulmonary fibrosis, and 5) massive pleural effusion or ascites.

Administration and Evaluation

After informed consent was obtained from the eligible patient, irinotecan was administered at a dose of 40 mg/m^2/day by intravenous infusion over a 90-minute period. The drug was given daily for 3 days, and this schedule was repeated 2 or 3 times at weekly intervals followed by a 2-week period off therapy. At the physician's discretion, antiemetics were prescribed as needed.

Response to treatment was defined according to World Health Organization criteria.[11] Adverse reactions were assessed according to the National Cancer Institute Common Toxicity Criteria.

TABLE 1
Patient Characteristics

No. of patients	48
Gender (M/F)	29/19
Median age (yrs) (range)	54 (16–76)
ECOG performance status	
0	28
1	15
2	3
3	2
4	0
Histologic classification (WF)	
Low grade	8
Intermediate grade	36
High grade	1
Others (angiocentric, Ki-1, unidentified)	3
Disease status	
Recurrent disease	30
Refractory disease	18
Prior therapy	
Chemotherapy	48
Radiotherapy	22
Surgery	2
No. of prior chemotherapy regimens	
1	2
2	21
3	14
$>$ 3 (up to 8)	11

M: male; F: female; ECOG: Eastern Cooperative Oncology Group; WF: Working Formulation.

RESULTS

Patient Characteristics

Between December 1995 and January 2000, 48 patients were entered into the current study. Patient characteristics are listed in Table 1. The median age of the patients was 54 years and approximately 60% of the patients were men. All but five patients had a good PS (ECOG score of 0–1). The histologic classification (according to the Working Formulation[12]) was intermediate grade in 75% of patients. Thirty patients had recurrent lymphoma and 18 patients had refractory disease. All patients but 2 had received $\geq$ 2 prior combination chemotherapy treatments, 22 patients had received radiation therapy, and 2 patients had undergone surgery.

The previous chemotherapy regimens are outlined in Table 2. For remission induction, the EPOCH-G regimen[13] (biweekly cyclophosphamide, doxorubicin, vincristine, and prednisolone [CHOP] plus etoposide supported by granulocyte–colony-stimulating factor [G-CSF]) was administered routinely to patients with intermediate-grade and high-grade disease; 29 patients had been treated with this regimen. Another 16 patients had received CHOP alone for remission induction. As second-line chemotherapy, the Salvage 94 regimen[14] (carboplatin, ifosfamide, mitox-

TABLE 2
Prior Chemotherapy

Prior chemotherapy	No. of patients
First-line	
EPOCH-G	29
CHOP	16
VCP	3
C-MOPP	2
Second-line or higher	
Salvage 94	35
Sobuzoxane	15
Etoposide	10
Carboplatin	4
Carboplatin plus etoposide	3
ICE	3
IVAC	3
IVAM	2
ESHAP	2
HD-CT	2
Others	22

EPOCH-G: etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; VCP: vincristine, cyclophosphamide, and prednisolone; C-MOPP: cyclophosphamide, vincristine, procarbazine, and predonisolone; Salvage 94: carboplatin, ifosfamide, mitoxantrone, etoposide, bleomycin, and prednisolone; ICE: ifosfamide, carboplatin, and etoposide; IVAC: ifosfamide, etoposide, and cytarabine; IVAM: ifosfamide, etoposide, cytarabine, and methotrexate; ESHAP: etoposide, methylprednisolone, cytarabine, and cisplatin; HD-CT: high-dose chemotherapy (cyclophosphamide, etoposide, and carboplatin).

antrone, etoposide, bleomycin, and prednisolone) was administered routinely, and 35 patients had received this regimen. Therefore, 21 patients were treated with irinotecan as third-line chemotherapy and 25 patients received the drug as fourth-line or subsequent chemotherapy.

Response to Treatment

Of the 48 patients, 45 were evaluable for response, because 3 patients received irinotecan after the second CR to mobilize peripheral blood stem cells. Thirty-nine patients completed at least the first course. Four patients were withdrawn from treatment during the first cycle because of adverse reactions, and two patients died early in the cycle of disease progression. The overall response rate in the evaluable patients was 37.8% (4.4% in the CR patients and 33.3% in the PR patients) and the response rate in those patients with recurrent and refractory disease was 40.7% (11 of 27 patients) and 33.3% (6 of 18 patients), respectively (Table 3). In evaluable patients, the median duration of response was 64 days (range, 28–579 days), and the median time to disease progression was 77 days (range, 12–1220+ days). The median survival time for all evaluable patients was 422 days; the median survival of those patients with recurrent and refractory disease was 422 days and 325 days, respectively. There was no significant difference in the survival between patients with recurrent disease and those with refractory disease. Figure 1 shows the survival curves for all evaluable cases, recurrent disease cases, and refractory disease cases. Among the responders, the median time and dose required to achieve a PR were 35 days (range, 7–117 days) and 413 mg/m^2 (range, 120–880 mg/m^2), respectively. In the 45 evaluable patients, the median total dose was 600 mg/m^2 (range, 48–3600 mg/m^2) and the median actual dose intensity was 53.0 mg/m^2/week (range, 24–86 mg/m^2/week).

Table 4 shows the response to therapy for the different histologic classifications according to the Working Formulation and the T-cell, B-cell classification. The response rate was 37.5% (3 of 8 patients) for the patients with low-grade lymphoma, 36.4% (12 of 33 patients) for those with intermediate-grade lymphoma, and 0%(no patients) for those with high-grade lymphoma. The response rate was 42.9% (3 of 7 patients) for the patients with T-cell lymphoma and 33.3% (11 of 33 patients) for those with B-cell lymphoma.

Adverse Reactions

Forty-six patients were evaluable for adverse reactions, excluding 2 patients who died early of disease progression (Table 5). Myelosuppression was a frequent, but moderate, reaction. Grade 3 or 4 leukopenia, anemia, and thrombocytopenia were observed in 63.0%, 30.4%, and 6.5% of the patients, respectively. Neutropenic fever developed in eight patients. G-CSF administration, erythrocyte transfusion, and platelet transfusion were required in 28 patients, 11 patients, and 3 patients, respectively. Twenty-nine patients required some changes in regimen (such as dose reduction, prolongation of the interval between courses, or a decrease in the number of days of consecutive treatment) due to delayed myelosuppression.

Gastrointestinal toxicity (including diarrhea, nausea, and emesis) also was frequent. Diarrhea was reported in 73.9% of the patients, and Grade 3 or 4 diarrhea was observed in 30.4% of the patients. Diarrhea persisted for an average of 6 days. It was controlled with no therapy or the administration of loperamide in the majority of patients, but some patients were slow to recover, leading us to remove three patients from therapy. Liver dysfunction was found to be mild and reversible.

DISCUSSION

Patients with aggressive non-Hodgkin lymphoma mainly are treated with chemotherapy, and CHOP is a standard first-line regimen that has been reported to

TABLE 3
Response Rate

	Evaluable cases	Complete cases	CR	PR	NC	PD	% CR + PR: Evaluable cases	% CR + PR: Complete cases
All	45	39	2	15	13	9	37.8	43.6
Recurrent	27	23	2	9	7	5	40.7	47.8
Refractory	18	16	0	6	6	4	33.3	37.5

CR: complete remission; PR: partial remission; NC: no change; PD: progressive disease.

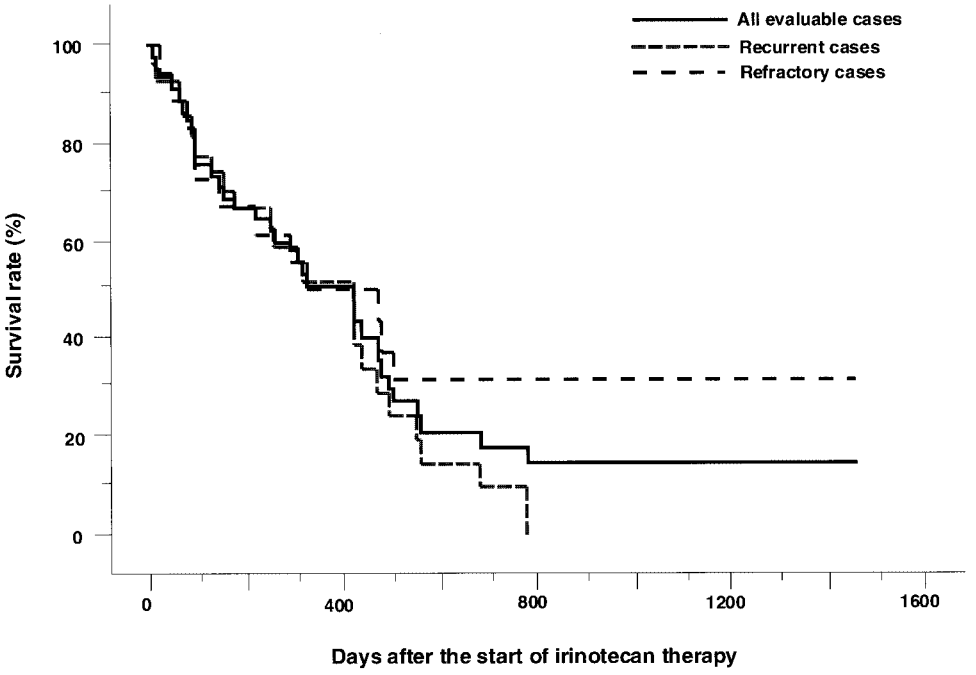

FIGURE 1. Survival curves for all evaluable cases, recurrent cases, and refractory cases. There was no significant difference with regard to survival between patients with recurrent and patients with refractory disease.

achieve a response rate of approximately 80%.[15] However, to our knowledge, no standard therapy is available for recurrent or refractory disease; therefore, there is a real need for the development of new treatment modalities and new antitumor agents. Because of the lack of cross-resistance with doxorubicin and vincristine, irinotecan has been suggested to be a useful agent to use as salvage therapy in patients with recurrent or refractory non-Hodgkin lymphoma.

A previously reported late Phase II study[16] of therapy with irinotecan demonstrated a response rate of 42% (26 of 62 patients) in patients with non-Hodgkin lymphoma that was refractory to standard treatment, a rate comparable to that reported in the current study. The incidence of myelosuppression and gastrointestinal toxicity also was similar to that in the previous study. Single-agent salvage therapy for non-Hodgkin lymphoma using other antitumor agents has achieved response rates of 20–47%(Table 6),[17–23] and a median duration of response of approximately 1–2 months. Thus, the 37.8% response rate and the median duration of response of 64 days reported in the current study when irinotecan was used as third-line therapy appear to indicate the activity of irinotecan as a single agent. Because the response rate for refractory disease was 33.3%, irinotecan appears to be worth exploring as salvage therapy.

Based on the results of an early Phase II study,[24] the following treatment schedule was recommended for patients with non-Hodgkin lymphoma: 40 mg/m^2/day by intravenous infusion for 3 consecutive days, with this regimen being repeated 2–3 times at weekly intervals and followed by at least 2 weeks off therapy. This schedule was employed in a late Phase II study[16] and the current study, but the actual dose intensity was only 53.0 mg/m^2/week in the current study. There was an approximately 10–25% decrease compared with the scheduled dose intensity. The actual dose

TABLE 4
Antitumor Effect Stratified by Histologic Classification

Histologic classification	Evaluable cases	Complete cases	% CR + PR: Evaluable cases	% CR + PR: Complete cases
(Working Formulation)				
Low grade	8	6	37.5	50
Small lymphocytic	2	2	50	50
Follicular, predominantly small cleaved	3	2	0	0
Follicular, mixed, small and large cell	3	2	66.7	100
Intermediate-grade	33	29	36.4	41.4
Follicular, predominantly large cell	2	2	100	100
Diffuse, small cleaved cell	8	6	37.5	50
Diffuse, mixed, small and large cell	1	1	0	0
Diffuse, large cell	22	20	31.8	35.0
High grade	1	1	0	0
Lymphoblastic	1	1	0	0
Others	1			
Angiocentric	1	1	100	100
Ki-1	1	1	100	100
Unidentified	1	1	0	0
(T-cell/B-cell classification)				
T-cell type	7	7	42.9	42.9
B-cell type	33	27	33.3	40.7
Unidentified	5	5	60.0	60.0

CR: complete remission; PR: partial remission.

intensity achieved with the second and subsequent courses of treatment was even lower (45.0 mg/m^2/week) due to frequent dose reduction. The intensive prior chemotherapy given to the patients in the current study appears to have increased the need for frequent alterations of the treatment schedule. However, we observed a response rate with the lower dose intensity that was similar to that of the previous late Phase II study, suggesting the need to reconsider the recommended schedule for irinotecan administration in patients with non-Hodgkin lymphoma. Yamauchi et al.[25] also reported a patient who responded to irinotecan salvage therapy for recurrent non-Hodgkin lymphoma. When a patient was given approximately 67% (40 mg/body/day) of the recommended dose because of advanced age (72 years), the patient tolerated 4 courses of treatment and achieved a CR. The pharmacokinetics of SN-38, the active metabolite of irinotecan, demonstrated that its levels were similar to those obtained in Phase I studies[26,27] and a Phase II study[16]. These findings suggest that a dose of 40 mg/m^2 may be sufficient or even excessive in some patients. Therefore, the regimen for administering this agent needs to be reconsidered, keeping in mind the pharmacokinetic and pharmacodynamic properties of irinotecan, such as time-dependency[1] and the possibility of intensifying its antitumor effect by divided administration.[28]

Because the results of single-agent chemotherapy have not been satisfactory, the development of combination chemotherapy with other cytotoxic agents is essential. To our knowledge, only a few studies have been conducted to date that combine irinotecan with other agents (carboplatin,[29] etoposide,[30] or doxorubicin[31]) in patients with non-Hodgkin lymphoma. Severe toxicity was reported to occur in studies with carboplatin and etoposide, and the initial doses were concluded to be the maximum tolerated doses (MTDs), whereas the response rates were lower than those reported with the use of irinotecan alone. Combination with doxorubicin demonstrated a better response (36% CR rate and 8% PR rate), but 8 of 9 CRs were obtained in patients who developed recurrent disease after achieving a CR with a doxorubicin-containing regimen, and worse results were reported in patients with refractory disease. Therefore, the ideal combination chemotherapy including irinotecan in patients with non-Hodgkin lymphoma remains to be determined.

Preclinical studies have shown that agents such as cisplatin, carboplatin, and cytosine arabinoside have synergistic effects in combination with irinotecan, whereas bleomycin, etoposide, and mitoxantrone have been found to have additive effects.[32–34]

Studies of irinotecan-containing combination chemotherapy in patients with solid tumors also should provide useful information regarding their possible synergism and adverse effects. Moyano et al.[35] administered irinotecan and ifosfamide to patients with solid tumors in a combination Phase I dose-finding trial. Dose escalations did not reach the MTD, even at an ifosfamide dose of 2400 mg/m^2 and an irinotecan dose of 200 mg/m^2 on Day 1 every 3 weeks, and 8 of 25 patients demonstrated stable disease. Results of Phase I/II or Phase II trials combining weekly irinotecan with ifosfamide, cisplatin, or etoposide in patients with lung carcinoma also might be useful.[36–40] In these studies, irinotecan was infused at a dose of 60–70 mg/m^2 on Days 1, 8, and 15. Adverse effects were considered to be acceptable. Among such studies, cisplatin-containing regimens demonstrated response rates of $>$ 50% in patients with previously untreated non-small cell lung carcinoma.[36,37] Masuda et al.[40] also reported combination therapy with irinotecan and etoposide to be effective in patients with recurrent or refractory small cell lung carcinoma, even in those patients who were resistant to etoposide.

TABLE 5
Major Adverse Reactions (n = 46)

Item	Grade 1	Grade 2	Grade 3	Grade 4	Incidence (%)	Incidence of Grade 3 or Grade 4 reactions (%)
WBC ↓	3	10	25	4	91.3	63.0
Hb ↓	6	13	9	5	71.7	30.4
Plt ↓	8	4	2	1	32.6	6.5
GOT ↑	9	6	1	0	34.8	2.2
GPT ↑	10	5	3	0	39.1	6.5
ALP ↑	2	0	1	0	6.5	2.2
T-Bil ↑	—	7	3	0	21.7	6.5
BUN ↑	0	0	0	0	0.0	0.0
Cr ↑	0	0	0	0	0.0	0.0
Diarrhea	11	9	12	2	73.9	30.4
Nausea	16	9	1	0	56.5	2.2
Emesis	13	4	1	0	39.1	2.2

WBC: white blood cell (leukocyte); Hb: hemoglobin; Plt: platelets; GOT: glutamic-oxaloacetic transaminase (aspartate aminotransferase); GPT: glutamic pyruvic transaminase; ALP: alkaline phosphatase; T-Bil: total bilirubin; BUN: blood urea nitrogen; Cr: creatinine.

TABLE 6
Single-Agent Salvage Therapy for Non-Hodgkin Lymphoma

Drug	No. of patients	% CR + PR	Reference
Etoposide	185	30	Radice et al.[17]
Cisplatin	19	26	Cavalli et al.[18]
Ifosfamide	15	47	Rodriguez et al.[19]
Ifosfamide	17	24	Case et al.[20]
Sobuzoxane	27	30	Yamada et al.[21]
Sobuzoxane	33	30	Masaoka et al.[22]
Idarubicin	20	20	Urabe et al.[23]
Irinotecan	45	38	Current study

CR: complete remission; PR: partial remission.

Therefore, combination chemotherapy using irinotecan with ifosfamide, cisplatin, or etoposide, combinations that are used frequently in patients with recurrent or refractory non-Hodgkin lymphoma, should be investigated.

The results of the current study indicate that irinotecan has activity as a single agent for the treatment of patients with recurrent and refractory non-Hodgkin lymphoma. Furthermore, because irinotecan has a unique mechanism of action that is different from that of other currently used antitumor agents for non-Hodgkin lymphoma, it also may be of benefit when added to first-line therapy.

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