Cancer Chemother Pharmacol (2008) 62:299–304
DOI 10.1007/s00280-007-0607-4

ORIGINAL ARTICLE

Irinotecan plus cisplatin and dexamethasone (ICD) combination chemotherapy for patients with diffuse large B-cell lymphoma previously treated with Rituximab plus CHOP

Hye Jin Kang · Won Seog Kim · Cheolwon Suh · Yeon Hee Park · Bong Seog Kim · Young Jin Yuh · Baek-Yeol Ryoo

Received: 11 July 2007 / Accepted: 14 September 2007 / Published online: 9 October 2007

Abstract
Purpose The therapeutic strategy for relapsed or refractory patients with diffuse large B-cell lymphoma (DLBL) remains challenging yet. Salvage therapy has been tried for these patients according to their clinical status. We studied ICD (irinotecan, cisplatin and dexamethasone) regimen as salvage chemotherapy for DLBL patients previously treated with RCHOP.
Methods Between February 2005 and May 2006, 15 patients were treated prospectively with ICD chemotherapy; irinotecan 65 mg/m^2/day on days 1 and 8, cisplatin 30 mg/m^2/day on days 1 and 8, and dexamethasone 40 mg/day on days 1–2 and 8–9. This schedule was planned to repeat every 3 weeks until disease progression, severe toxicity or stem cell transplantation.
Results Of the 14 patients evaluable for response, 3 patients achieved CR, 7 patients PR, with 1 SD and 3 PD; overall response rate 71% (10/14; 95% confidence interval, 47–95%). The median progression free survival (PFS) and event free survival (EFS) were 113 (range 21–493+) and 77 (range 21–324+) days, respectively. The median overall survival was 267 (range 31–493+) days. Grade 3/4 neutropenia and grade 3 neutropenic fever were observed in 67% (22/33) and 18% (6/33) of cycles, respectively. There were 20% of grade 3/4 nausea and diarrhea observed.
Conclusions The ICD regimen with current schedule showed high response rate for DLBL patients previously treated with RCHOP. But the high incidence of neutropenia led to delay of subsequent cycles causing dose intensity reduced, which seems to be related with short PFS and EFS.

Keywords Diffuse large B-cell lymphoma · Irinotecan · Cisplatin · Salvage chemotherapy

H.J. Kang and W.S. Kim contributed equally to the work.

H. J. Kang · B.-Y. Ryoo (✉)
Division of Hematology–Oncology,
Department of Internal Medicine, Korea Cancer Center Hospital,
215-4, Gongneung-dong, Nowon-gu,
Seoul 139-706, South Korea
e-mail: ryooby@kcch.re.kr

W. S. Kim · Y. H. Park
Division of Hematology–Oncology,
Department of Internal Medicine, Samsung Medical Center,
Sungkyunkwan University School of Medicine,
Seoul, South Korea

C. Suh
Division of Oncology, Department of Internal Medicine,
Asan Medical Center, Ulsan University College of Medicine,
Seoul, South Korea

B. S. Kim
Division of Hematology–Oncology,
Department of Internal Medicine, Seoul Veterans Hospital,
Seoul, South Korea

Y. J. Yuh
Division of Hematology–Oncology,
Department of Internal Medicine,
Inje University Sanggye Paik Hospital, Seoul, South Korea

Introduction

Diffuse large B-cell lymphoma (DLBL) is the most common subtype worldwide comprising about 40% of all non-Hodgkin's lymphomas [1]. The surface antigen CD20 is expressed in more than 90% of all B-cell lymphomas. The chimeric monoclonal antibody Rituximab, targeting CD20, combined with the previous standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen

(RCHOP) has achieved improved disease free and overall survival in elderly and young patients with DLBL [2, 3]. After several important trials, RCHOP has become a standard regimen as a first-line therapy for DLBL.

For the relapsed or refractory DLBL patients, several salvage regimens have been proposed [4–8]. DHAP (high-dose cytarabine, cisplatin and dexamethasone) has been used as a salvage regimen or for intensification or stem cell mobilization for the high-risk patients after achieving complete remission. But the prolonged nephropathy and/or neuropathy caused by high-dose cytarabine and cisplatin, and the inconvenience with 24-h infusion made it difficult to be used widely in practice. And there has been few data of the salvage treatment for the DLBL patients who relapsed or refractory to first-line RCHOP chemotherapy.

Irinotecan hydrochloride (CPT-11), a semisynthetic derivative of camptothecin, is a DNA topoisomerase-I inhibitor and is used widely for the solid tumors. As a monotherapy or combination therapy in some phase I or II clinical trials, it showed 25–62% of response rate for relapsed or refractory aggressive lymphomas [9–12]. But the various histologic subtypes, small study sizes, and the diverse doses and schedules made it difficult to assess the efficacy of irinotecan for these patients.

We planned a pivotal study to evaluate the efficacy and toxicity of salvage ICD (irinotecan, cisplatin and dexamethasone) regimen, which replaced cytarabine with irinotecan in DHAP regimen, for DLBL patients previously treated with RCHOP chemotherapy.

Patients and methods

Patients

The inclusion criteria were as follows: (1) histologically confirmed DLBL; (2) recurrent or refractory to first-line RCHOP chemotherapy; (3) presence of measurable lesion(s); (4) recovered from any toxicity of previous chemotherapy; (5) age between 18 and 70 years; (6) performance status by Eastern Cooperative Oncology Group (ECOG) $\leq$2; (7) adequate renal function (serum creatinine $\leq$1.5 mg/dl or creatinine clearance $\geq$60 ml/min), adequate hepatic function [serum transaminases $\leq 3 \times$ upper normal limit (5 times for patients with hepatic involvement), serum bilirubin <1.5 mg/dl], and adequate bone marrow function (neutrophil count $\geq$1,500/mm^3, hemoglobin level $\geq$8.0 g/dl, and platelets $\geq$100,000/mm^3); (8) life expectancy $\geq$3 months; (9) no chemotherapy or radiation therapy during previous 3 weeks; (10) informed consent provided.

Treatment

After informed consent was obtained from the eligible patient, irinotecan was administered at a dose of 65 mg/m^2/day by intravenous infusion over a 90-min period on days 1 and 8. Cisplatin was infused at a dose of 30 mg/m^2/day by intravenous infusion with proper pre- and post-hydration on days 1 and 8. Dexamethasone was given orally at a dose of 40 mg/day on days 1–2 and 8–9. This schedule was planned to be repeated every 3 weeks until disease progression, severe toxicity or stem cell transplantation, or upto maximum eight cycles.

Evaluation

We planned to evaluate response to treatment after every two cycles. The response to treatment was defined according to International working group recommendations of 1999 [13]. The overall survival (OS) was defined as the time from the date ICD chemotherapy began until death as a result of any cause. The progression-free survival (PFS) was defined as the time from the date ICD chemotherapy began until lymphoma progression or death as a result of any cause. The event-free survival (EFS) was measured from the date ICD chemotherapy began to any treatment failure including disease progression, or discontinuation of treatment for any reason (e.g., disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death). Adverse reactions were assessed by the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Results

Patient characteristics

From February 2005 to May 2006, 15 patients were entered into this trial. Patients' characteristics are listed in Table 1. The median age of the patients was 56 (range 20–67) years and 80% (12/15) of the patients were men. All the patients had a good performance status (ECOG score of 0 or 1). All the patients but one had received only one regimen of RCHOP chemotherapy with or without radiation or surgery before entering this trial. The responses to previous RCHOP were CR (complete remission) in six patients and PR (partial remission) in nine patients by conventional CT scan. The range of duration between the first date of previous RCHOP chemotherapy and that of ICD chemotherapy was 4.3–18.2 (median 7.0) months.

Table 1 Patients' characteristics (%)

No. of patients	15
Sex (male/female)	12/3
Range of age, median (years)	20–67, 56
Performance status (ECOG)	
0	3 (20)
1	12 (80)
Clinical stage	
I or II	8 (53)
III or IV	7 (47)
Serum LDH level	
Normal	4 (27)
Elevated	11 (73)
IPI score	
0–1	6 (40)
2	4 (27)
3	3 (20)
4–5	2 (13)
No. of previous chemotherapy regimen	
1	14 (93)
3	1 (7)
Previous therapy	
Chemotherapy	15 (100)
Radiation	2 (13)
Surgery	1 (7)
Response to previous RCHOP	
Complete remission	6 (40)
Partial remission	9 (60)

ECOG Eastern Cooperative Oncology Group, *IPI* International Prognostic Index, *LDH* lactate dehydrogenase, *RCHOP* Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

Response to ICD chemotherapy

Of the 15 patients, 14 were evaluable for response. For the patients who could not continue the treatment after the first cycle because of other than disease progression, we assessed the response at the end of the study. One patient not evaluable for response was dropped out after one cycle of ICD chemotherapy due to prolonged neutropenia without response evaluation. After 1–4 (median 2) cycles of ICD chemotherapy, three patients achieved CR, seven patients achieved PR, with one stable disease (SD) and three progressive disease (PD). The overall response rate in the evaluable patients was 71% [10/14; 95% confidence interval (CI), 47–95%]. The response rate in those patients who achieved CR and PR with previous RCHOP chemotherapy was 83% (5/6) and 63% (5/8), respectively.

The median PFS for all patients was 113 (range 21–493+) days. The median EFS for all patients was 77 (range 21–324+) days, and the median EFS for 10 responders was 100 (range 63–324+) days. The median OS for all patients was 267 (range 31–493+) days (Fig. 1).

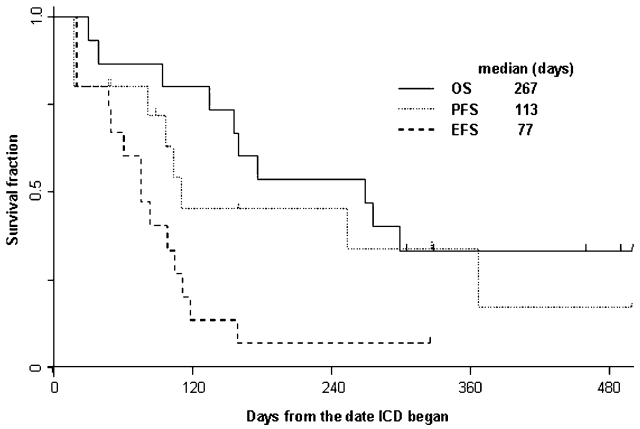

Fig. 1 Survival curves. *OS* overall survival, *PFS* progression free survival, *EFS* event free survival

Total 34 (median 2 for each patient) cycles of ICD chemotherapy were carried out in this trial. The median number of it for responders was 3 (range 1–4) cycles. The reasons for discontinuation of chemotherapy in these responders were prolonged neutropenia more than 3 weeks in four patients, switch to mobilization of peripheral stem cells in one patient, patient preference in one patient, and disease progression in four patients. Of the five responders who dropped out from the study due to prolonged neutropenia or patient preference, three patients received other chemotherapy regimen out of this trial, one patient radiation, and and patient observational follow up.

Study progress and dose intensity

Figure 2 describes the progress according to the number of patients excluded during the study and the reason for exclusion.

The mean relative dose intensity (DI) compared with planned DI after first ICD cycle of all patients was 92% for irinotecan, 93% for cisplatin and dexamethasone. The lower DI even in the first cycle was due to omission or dose reduction of day 8. Of the 15 patients enrolled, only 9 patients received second cycle of chemotherapy. The reasons for dropout after first cycle were prolonged neutropenia more than 3 weeks in three patients and disease progression in three patients. Of nine patients who received second cycle, the number of patients who could start second cycle at planned day, namely 3 weeks after start date, was only four, and one of these four was who had omitted day 8 chemotherapy (relative DI 50%) during first cycle.

The mean relative DI after second cycle for the nine patients was 82% for irinotecan, 86% for cisplatin and dexamethasone. The lower DI after the second cycle was

due to delayed start of second cycle waiting for the recovery of toxicities (mainly neutropenia) or dose reduction for day 8 of second cycle. Actually the number of patients who received the planned 100% DI until second cycle was only 1.

The mean relative DI after third cycle for the six patients was 71% for irinotecan, 77% for cisplatin and dexamethasone. And the mean relative DI after fourth cycle for the four patients was 65% for irinotecan, 75% for cisplatin and dexamethasone.

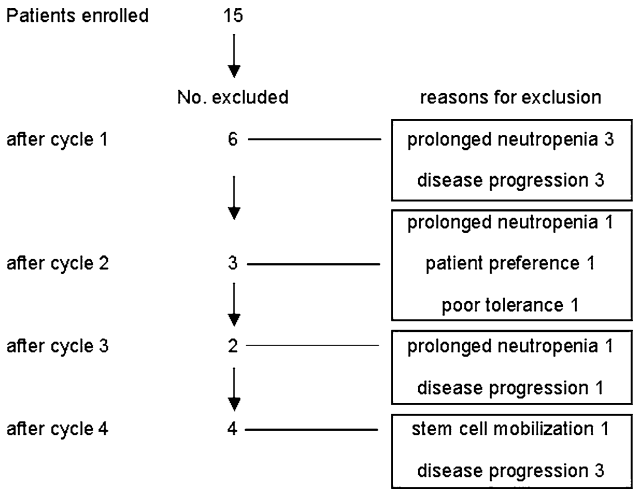

Fig. 2 Study progress according to exclusion of patients after each course of treatment

All 4 patients who received four cycles of chemothearpy discontinued the treatment due to stem cell mobilization in one and disease progression in three patients.

Among 12 patients salvaged with alternate regimen after current trial, 2 patients showed CR and 2 patients PR. One patient who showed CR proceeded to stem cell transplantation.

Adverse reactions

All 15 patients and 33 cycles of chemotherapy were evaluable for adverse reactions (Table 2). Myelosuppression was the most frequent. Grade 3 or 4 neutropenia was observed in 67% (22/33) of cycles conducted and was observed in 80% (12/15) of patients even after the first cycle of ICD chemotherapy. The duration of neutropenia was rather long and five patients were dropped off the study due to prolonged neutropenia 3 weeks or more. Grade 3 neutropenic fever was observed in 18% (6/33), but there was no treatment related death. Nausea and diarrhea were the most frequent non-hematologic toxicities observed.

Discussion

RCHOP regimen is currently standard first-line chemotherapy for DLBL. But there is no salvage treatment acknowledged as standard widely when these patients recurred after or refractory to previous chemotherapy. Irinotecan is

Table 2 Major adverse reactions

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 and 4
Laboratory abnormalities for each cycles					Per 33 cycles
Anemia	10	10	2	1	3%
Leukopenia	2	11	8	8	48%
Neutropenia	2	5	7	15	67%
Thrombocytopenia	9	2	2	0	6%
Neutropenic fever	0	1	6	0	18%
Increased ALT	2	1	0	0	0
Increased AST	2	0	0	0	0
Increased total bilirubin	2	0	0	0	0
Maximum grade for each patient					Per 15 patients
Weight loss	0	2	2	0	13%
Anorexia	1	1	2	0	13%
Nausea	2	1	3	0	20%
Vomiting	1	2	1	0	7%
Stomatitis	1	2	0	0	0
Diarrhea	3	4	3	0	20%
Constipation	2	1	0	0	0
Neuropathy-sensory	1	0	0	0	0
Neuropathy-motor	0	0	0	0	0

ALT alanine aminotransferase, *AST* aspartate aminotransferase

widely used for solid tumors, such as gastrointestinal tumor, lung cancer, breast cancer. The different mechanism of action from other agents used for lymphoma and the lack of cross-resistance with doxorubicin and vincristine make irinotecan worth tried for patients with recurrent or refractory lymphoma [12].

Previous studies with irinotecan monotherapy for recurrent or refractory lymphoma reported response rate of 11–39% and response duration about 2 months [12, 14–16], which indicated activity of irinotecan for lymphoma.

Several agents have been combined with irinotecan. Combination with carboplatin was reported to show lower response rate and maximal tolerated dose less than half the single irinotecan [9]. Combination with mitoxantrone and dexamethasone showed 62% of response rate [11]. But the major barrier was the adverse reactions, especially neutropenia. More than 60% of neutropenia has been reported in single irinotecan or in combination with other agents. The toxicity was thought to be related with high dose of irinotecan. Saotome et al. [17] reported 36% of CR rate with tolerable toxicity when combined with doxorubicin. The reasonable success was considered to be due to lower dose of irinotecan, elimination of irinotecan on days 8–10, 15–17, and the 3-week interval between courses.

Cisplatin is frequently used for recurrent or refractory lymphoma. The combination of irinotecan with cisplatin is commonly used for lung cancer, gastric cancer and cervical cancer with good response and tolerable toxicity. In a randomized phase III clinical trial for small cell lung cancer comparing irinotecan/cisplatin (IP) with etoposide/cisplatin (EP), IP led fewer myelosuppression than EP [18]. The dose and schedule in this trial was cisplatin 30 mg/m^2 IV + irinotecan 65 mg/m^2 IV on days 1 and 8 every 21 days.

We added dexamethasone 40 mg/day PO on days 1, 2 and days 8, 9 to IP of this trial making ICD regimen, the first trial of irinotecan and cisplatin combination for lymphoma patients to our knowledge. To get more valuable information from the study we selected homogeneous DLBL patients previously treated with RCHOP chemotherapy. Although the response rate of 71% seems encouraging, the PFS and EFS is not satisfactory. The short PFS and EFS can be explained by low dose intensity, which is caused mainly by prolonged neutropenia. Actually we could not continue ICD chemotherapy in 5 out of total 15 patients (33%) due to the prolonged neutropenia. The much higher incidence of toxicity in the current trial compared with that of IP regimen in small cell lung cancer study might be explained by whether previous chemotherapy was done or not, the characteristics of disease itself (small cell lung cancer vs. lymphoma), or unknown effect of dexamethasone added in ICD regimen. But, the high response rate gave us the opportunity to use ICD regimen for induction before stem cell transplantation in recurrent or refractory DLBL patients. On the other hand, we can recall the reasonable success of two studies in which irinotecan was combined with mitoxantrone and dexamethasone or doxorubicin [11, 17]. In these two trials, irinotecan was infused at 25 mg/m^2 IV on days 1 and 8 every 21 days. Takagi et al. [19] proposed lower dose of irinotecan, 40 mg/m^2 IV for three consecutive days when used alone for lymphoma. We can assume that much lower dose of irinotecan can be a benefit when combined with other agents by these studies.

In the current study, we experienced activity of ICD regimen by response rate for DLBL previously treated with RCHOP, but there was high incidence of myelosuppression with current dosing and schedule.

Acknowledgments We gratefully acknowledge CJ Corporation, Seoul, Korea, for supplying irinotecan (Campto®) for our study.

References

1. Armitage JO, Weisenburger DD (1998) New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 16:2780–2795
2. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235–242
3. Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Trneny M, Imrie K, Ma D, Gill D, Walewski J, Zinzani PL, Stahel R, Kvaloy S, Shpilberg O, Jaeger U, Hansen M, Lehtinen T, Lopez-Guillermo A, Corrado C, Scheliga A, Milpied N, Mendila M, Rashford M, Kuhnt E, Loeffler M; MabThera International Trial Group (2006) CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 7:379–391
4. Kantarjian H, Barlogie B, Plunkett W, Velasquez W, McLaughlin P, Riggs S, Cabanillas F (1983) High-dose cytosine arabinoside in non-Hodgkin's lymphoma. J Clin Oncol 1:689–694
5. Adelstein DJ, Lazarus HM, Hines JD, Herzig RH (1985) High-dose cytosine arabinoside in previously treated patients with poor-prognosis non-Hodgkin's lymphoma. Cancer 56:1493–1496
6. Velasquez WS, Cabanillas F, Salvador P, McLaughlin P, Fridrik M, Tucker S, Jagannath S, Hagemeister FB, Redman JR, Swan F. Barlogie B (1998) Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 71:117–122
7. Press OW, Livingston R, Mortimer J, Collins C, Appelbaum F (1991) Treatment of relapsed non-Hodgkin's lymphomas with dexamethasone, high-dose cytarabine, and cisplatin before marrow transplantation. J Clin Oncol 9:423–431
8. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, Sonneveld P, Gisselbrecht C, Cahn JY, Harousseau JL (1995) Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 333:1540–1545
9. Tobinai K, Hotta T, Saito H, Ohnishi K, Ohno R, Ogura M, Ariyoshi Y, Takeyama K, Kobayashi T, Ohashi Y, Shirakawa S (1996) Combination phase I/II study of irinotecan hydrochloride

(CPT-11) and carboplatin in relapsed or refractory non-Hodgkin's lymphoma. Jpn J Clin Oncol 26:455–460
10. Tsuda H, Takatsuki K, Ohno R, Masaoka T, Okada K, Shirakawa S, Ohashi Y, Ota K (1994) Treatment of adult T-cell lymphoma with irinotecan hydrochloride (CPT-11). Br J Cancer 70:771–774
11. Niitsu N, Iijima K, Chizuka A (2001) Combination therapy with irinotecan (CPT-11), mitoxantrone, and dexamethasone in relapsed or refractory non-Hodgkin's lymphoma: a pilot study. Ann Hematol 80:411–416
12. Sugiyama K, Omachi K, Fujiwara K, Saotome T, Mizunuma N, Takahashi S, Ito Y, Aiba K, Horikoshi N (2002) Irinotecan hydrochloride for the treatment of recurrent and refractory non-Hodgkin's lymphoma. Cancer 94:594–600
13. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-Lopez A, Hagenbeek A, Cabanillas F, Klippensten D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 17:1244–1253
14. Ota K, Ohno R, Shirakawa S, Masaoka T, Okada K, Ohashi Y, Taguchi T (1994) Late phase II clinical study of irinotecan hydrochloride (CPT-11) in the treatment of malignant lymphoma and acute leukemia. Gan To Kagaku Ryoho 21:1047–1055
15. Ribrag V, Koscielny S, Vantelon JM, Ferme C, Rideller K, Carde P, Bourhis JH, Munck JN (2003) Phase II trial of irinotecan (CPT-11) in relapsed or refractory non-Hodgkin's lymphomas. Leuk Lymphoma 44:1529–1533
16. Sarris AH, Phan A, Goy A, Romaguera J, Hagemeister FB, Rodriguez MA, McLaughlin P, Pro B, Medeiros LJ, Samuels B, Mesina O, Bleyer AW, Cabanillas F (2002) Irinotecan in relapsed or refractory non-Hodgkin's lymphomas. Indications of activity in a phase II trial. Oncology (Williston Park) 16(Suppl 7):27–31
17. Saotome T, Takagi T, Sakai C, Kumagai K, Tamaru J (2000) Combination chemotherapy with irinotecan and adriamycin for refractory and relapsed non-Hodgkin's lymphoma. Ann Oncol 11:115–116
18. Hanna N, Bunn PA, Langer C, Einhorn L, Guthrie T, Beck T, Ansari R, Ellis P, Byrne M, Morrison M, Hariharan S, Wang B, Sandler A (2006) Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 24:2038–2043
19. Takagi T, Saotome T (2001) Chemotherapy with irinotecan (CPT-11), a topoisomerase-I inhibitor, for refractory and relapsed non-Hodgkin's lymphoma. Leuk Lymphoma 42:577–586