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ORIGINAL ARTICLE

Phase I trial of irinotecan and amrubicin with granulocyte colony-stimulating factor support in extensive-stage small-cell lung cancer

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Abstract
Purpose We conducted a phase I trial of irinotecan (CPT-11), a topoisomerase I inhibitor, combined with amrubicin, a topoisomerase II inhibitor, with recombinant human granulocyte colony-stimulating factor (rhG-CSF) support to overcome the neutropenia associated with this particular combination. The aim was to determine the maximum tolerated dose (MTD) of amrubicin combined with a fixed dose of CPT-11 and the dose-limiting toxicities (DLTs) of this combination in extensive-stage small-cell lung cancer (ED-SCLC) patients.
Methods Fifteen patients with ED-SCLC were treated at 3-week intervals with amrubicin on days 1–3 plus 60 mg/m^2 CPT-11 on days 1 and 8. In addition, prophylactic rhG-CSF (50 μg/m^2) was given from day 4 to day 21, except on the day of CPT-11 administration. Amrubicin was started at 30 mg/m^2 and then escalated in 5 mg/m^2 increments until MTD was reached.
Results The MTD of amrubicin was 35 mg/m^2, since 2 of 4 patients experienced DLTs during the first cycle of treatment at the 40 mg/m^2 dose level. Neutropenia, neutropenic fever, ileus, and diarrhea were the DLTs. There were 13 partial responses among the 13 assessable patients, yielding an overall response rate of 100 %. Median progression-free survival and overall survival were 7.4 months and 13.4 months, respectively.
Conclusion The combination of amrubicin and CPT-11 showed high activity against ED-SCLC with acceptable toxicity. Use of rhG-CSF allowed the dose of amrubicin to be raised 40 % above that in the original regimen (60 mg/m^2 CPT-11 and 25 mg/m^2 amrubicin).

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Introduction

Despite the exquisite sensitivity of small-cell lung cancer to chemotherapy, with high response rates, survival is dismal. No major advances have been made in chemotherapy for small-cell lung cancer since the development of platinum and etoposide in the mid 1980s [9, 25]. Therefore, to control small-cell lung cancer more efficiently, new combination regimens are urgently needed.

Amrubicin, a totally synthetic 9-aminoanthracycline [11], is converted to its active metabolite, amrubicinol, through reduction of its C-13 ketone group to a hydroxy group. The in vitro cytotoxic activity of amrubicinol was 18–220 times more potent than that of its parent compound, amrubicin [30]. Despite sharing a similar chemical structure, amrubicin differs from doxorubicin in mode of action. Amrubicin and amrubicinol are inhibitors of DNA topoisomerase II [29]. In preclinical studies, amrubicin showed more potent antitumor activity than doxorubicin in several human tumor xenografts implanted in nude mice. The response rates to amrubicin on days 1–3 in previously untreated patients with stage III or IV non-small-cell lung cancer and extensive-stage small-cell lung cancer (ED-SCLC) were 27.9 and 79 %, respectively [26, 31]. In sensitive and refractory or relapsed small-cell lung cancer, response rates were 50 and 52 %, respectively [24].

Irinotecan (CPT-11) is a water-soluble camptothecin derivative that inhibits topoisomerase I. CPT-11 has shown significant antitumor activity against various animal and human malignancies, including ED-SCLC [2, 6, 15, 20].

DNA topoisomerase I and II are functionally related and act in concert. Therefore, the combined use of topoisomerase I and II inhibitors is theoretically attractive because of the complementary functions of their targets [28]. Indeed, a combination of CPT-11, a topoisomerase I inhibitor, and etoposide, a topoisomerase II inhibitor, is an active treatment for refractory or relapsed SCLC [18, 21]. The high response rate of 71 % and the long median survival time of 271 days may be explained by an additive or even synergistic cytocidal effect with a combination of topoisomerase I and II inhibitors [21]. The development of a new topoisomerase II inhibitor, amrubicin, has led to renewed interest in a combination of topoisomerase I and II inhibitors. Although myelosuppression, especially leukopenia, was one of the major dose-limiting toxicities (DLTs) in our previous phase I and pharmacokinetic trial of a combination of these agents [32], neutropenia associated with this drug combination can be alleviated by the administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) [3].

Based on the different cellular targets of CPT-11 and amrubicin, the single-agent activity of amrubicin or CPT-11 against SCLC, and the results of preclinical studies showing the potentiation of single-agent activity with coadministration of both drugs [27], a phase I trial of this combination supported by administration of rhG-CSF was carried out in patients with ED-SCLC. The objectives of this phase I study were to determine the maximum tolerated dose (MTD) of CPT-11 and amrubicin; to detect and quantify the clinical toxicities of this combination; and to obtain preliminary evidence of the therapeutic activity of this combination in patients with ED-SCLC.

Patients and methods

Patient selection

Patients were enrolled in this study if they met the following criteria: a histologic or cytologic diagnosis of ED-SCLC; a measurable lesion; no prior chemotherapy; a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale; a life expectancy of at least 8 weeks; adequate bone marrow function (leukocyte count $\geq$ 4,000/μl, platelet count $\geq$ 100,000/μl, and hemoglobin $\geq$ 10.0 g/dl); adequate hepatic function (aspartate amino-transferase and alanine amino-transferase levels $\leq$ 100 IU/l, and bilirubin $\leq$ 2.0 mg/dl); adequate renal function (creatinine $\leq$ the upper limit of normal); adequate arterial oxygen partial pressure ($PaO_2 \geq 60$ torr); electrocardiogram findings within the normal range; and between 20 and 74 years of age. Written informed consent was required for participation in the study. Patients were ineligible if they had serious infectious diseases or other severe complications (heart diseases, pulmonary fibrosis/interstitial pneumonia, or uncontrollable diabetes); had watery diarrhea, paralytic ileus, or intestinal obstruction; had massive pleural or pericardial effusion, or ascitic fluid; had symptomatic brain metastases; had active concurrent malignancies; were lactating or pregnant women, or those willing to be pregnant; had a history of a drug allergy; had a history of acute myocardial infarction within the previous 6 months; had superior vena caval syndrome, requiring urgent radiotherapy; or had other medical problems severe enough to prevent compliance with the protocol. The study was approved in advance by the Kitasato University Hospital Ethics Committee.

Drug administration

A 21-day treatment cycle was planned. All agents were obtained from commercial suppliers. CPT-11 (Yakult Honsha Co., Ltd, Tokyo, Japan) was obtained in 5-ml vials containing 100 mg of the drug, which was diluted in 500 ml normal saline for administration. CPT-11 was administered at fixed doses of 60 mg/m^2 as a 90-min intravenous infusion on days 1 and 8. This dose was chosen because it had previously shown high efficacy in combination with cisplatin or etoposide [17–19, 21]. CPT-11 treatment on day 8 was postponed until day 15 if the leukocyte count was less than 3,000/μl, platelet count $<$ 100,000/μl, fever $>$ 38 °C, or grade $\geq$ 1 diarrhea occurred.

Amrubicin was purchased from Nippon Kayaku Co., Ltd. (Tokyo, Japan) as a lyophilized light red powder containing 20 mg of the drug. The appropriate amount of amrubicin was dissolved in 20 ml normal saline and administered intravenously as a 5-minute infusion on days 1–3 just after completion of CPT-11 infusion. Since neutropenia is the overlapping DLT of both CPT-11 and amrubicin, all patients received prophylactic rhG-CSF (filgrastim) at a daily dose of 50 μg/m^2, which was the Japanese recommended dose for chemotherapy-induced neutropenia [13]. Daily subcutaneous injections of rhG-CSF were given from days 4 to 21 of each treatment cycle, except on the day of CPT-11 administration. rhG-CSF treatment was ceased if the leukocyte count was more than 10,000/μl. If the leukocyte count decreased to less than 3,000/μl, rhG-CSF treatment was restarted.

Dosage and dose escalation procedure

Amrubicin was commenced at 30 mg/m^2 intravenously on days 1–3, which was the highest dose evaluated in our

previous phase I study without rhG-CSF support [32]. In the present study, the dose of amrubicin was escalated in increments of 5 mg/m^2 in successive patient cohorts until MTD was reached, while CPT-11 was given at a fixed dose of 60 mg/m^2 intravenously over 90 min on days 1 and 8. The dose of CPT-11 was withheld in instances of leukocyte count $<$ 3,000/μl, platelet count $<$ 100,000/μl, fever $>$ 37.5 °C, or grade $\geq$ 1 diarrhea on the day when the dose was due. DLTs were defined as follows: an absolute neutrophil count (ANC) $<$500/μl or leukocyte count $<$ 1,000/μl for $\geq$4 days; febrile neutropenia (fever $>$ 38.5 °C with ANC $<$ 1,000/μl); platelets $<$ 25,000/μl; and nonhematologic toxicity (except for nausea) $\geq$grade 3 during the first cycle. Toxicity requiring a delay in CPT-11 treatment on day 8 for longer than 7 days and toxicity resulting in a treatment delay $>$14 days in the next cycle were also considered to be DLTs. If DLTs were observed in $\geq$2 of 3 or $\geq$2 of 6 patients, MTD was considered to have been exceeded, and additional patients were recruited at the next lower dose level. The MTD was defined as the highest dose level that could be given to 6 patients with less than 2 patients experiencing DLT. Additional patients were to be treated at the MTD level to gain further experience with the combination and obtain a preliminary assessment of its antitumor activity. No intrapatient dose escalation was allowed in this trial.

Patients showing stabilization or an improvement received at least a second course of treatment. Responding patients were planned to receive 4–6 courses of this treatment. Patients showing clear evidence of disease progression or intolerable toxicity were removed from the study. Before the next course was started, the leukocyte count had to be 3,000/μl or higher, the platelet count 100,000/μl or higher, diarrhea should have recovered completely, and any toxicity other than nausea had to be $\leq$Grade 2. At the time of progression, treatment of combination chemotherapy with etoposide and cisplatin or carboplatin was recommended.

Evaluation

Tumors were staged based on a complete medical history and physical examination, routine chest radiography, bone scintiscanning or positron emission tomography, computed tomography (CT) of the chest and abdomen, whole-brain magnetic resonance imaging or CT scan, bone marrow aspiration or biopsy, and fiberoptic bronchoscopy. Limited disease was defined as that confined to one hemithorax, including the bilateral mediastinal and bilateral supraclavicular nodes; any involvement beyond these confines was defined as extensive disease. Prior to the first course of treatment, a complete blood count (including a differential white cell count and platelet count), biochemistry tests (renal function, hepatic function, and electrolytes), electrocardiography, and a urinalysis were performed. The complete blood count and biochemistry tests were repeated at least once a week after this initial evaluation, while other investigations were repeated at least every 6 weeks to evaluate target lesions. Eligibility, evaluability, and response in each patient were assessed by extramural reviewers. The complete blood count was repeated every day until recovery, when ANC $<$ 500/μl, leukocyte count $\leq$ 1,000/μl, or platelet count 25,000/μl was observed during the first cycle of treatment. Adverse events were recorded and graded using the Common Terminology Criteria for Adverse Events, version 3.0. Tumor response was classified in accordance with the new response evaluation criteria in solid tumors: revised RECIST guidelines (version 1.1) [5]. Time-to-event curves for analysis of overall and progression-free survival were estimated using the Kaplan–Meier method.

UGT1A1 genotyping

From November 2008, a genetic test for *UGT1A1* became commercially available in Japan. Patients were genotyped using a previously validated assay as described by Fujita et al. [7].

Results

Between December 2006 and November 2010, 15 patients were enrolled in the trial. Of these, 13 patients were fully assessed for toxicity and response. Two patients, however, were assessable for toxicity but not response: one patient was removed from the study after developing grade 3 intestinal obstruction during the first course of treatment, and the other patient experienced grade 3 diarrhea during the first course of therapy before becoming assessable for response. A profile of the patient population is given in Table 1. Only one patient was female, and the median age was 63 years (range: 55–74 years), with a median performance status of 1. Dosing information is shown in Table 2. A total of 58 courses of therapy were given. The number of treatment cycles administered per patient ranged from 1 to 6 (3 cycles in 2 patients, 4 in 7, 5 in 2, and 6 in 2). Of 9 patients whose *UGT1A1* polymorphisms were determined, the *UGT1A1* genotype was **1/*1* in 4, **1/*28* in 3, and **1/*6* in 2. No patients were homozygous or double heterozygous for *UGT 1A1* (*28/*28, *6/*6, *28/*6).

Toxicities

DLT

At dose levels 1 and 2 (amrubicin 30 mg/m^2 and 35 mg/m^2, respectively, on days 1–3 and CPT-11 60 mg/m^2 on days 1

Table 1 Patient characteristics

Total no. of patients	15
Sex	
Male	14
Female	1
Age: median (range)	63 years (55–74)
Performance status (ECOG)	
0	3
1	10
2	2
Sites of metastases	
Liver	5
Lung	4
Pleura	4
Bone	3
Adrenal gland	3
Brain	2
Lymph node	1
Parotid gland	1
No. of metastatic sites	
1	9
2	4
3	2
UGT1A1 genotypes	
*1/*1	4
*1/*28	3
*1/*6	2
Not determined	6

and 8), none of the first 3 patients exhibited DLT during the first cycle. At dose level 3 (amrubicin 40 mg/m^2 on days 1–3 and CPT-11 60 mg/m^2 on days 1 and 8), one patient with the **1/*28* genotype experienced grade 4 neutropenia for ≥4 days, grade 3 neutropenic fever and grade 3 ileus, making it necessary to cease CPT-11 on day 8 in the first 3 patients (Table 3). We had intended to expand this dose level to 6 patients. The fourth registered patient, however, who had the wild-type genotype, experienced sustained grade 3 diarrhea, despite maximal antidiarrheal support with high dose loperamide during days 9–13 (Table 3). Therefore, dose level 3 was deemed to exceed the MTD as 2 out of 4 patients developed DLTs at this level. No further attempts at dose intensification were carried out. Among 5 additional patients who were subsequently treated at dose level 2 to confirm its feasibility, one patient with the **1/*28* genotype experienced grade 3 diarrhea after administration of CPT-11 on days 8 and 25. Ultimately, one of 8 patients experienced DLT at dose level 2. Two patients (one at dose level 3 and the other at dose level 2) were removed from the study after the first cycle of chemotherapy due to severe toxicity. Details of the percentage of the scheduled CPT-11 and amrubicin dose actually delivered at each dose level are given in Table 2. The percentage of the scheduled dose actually administered was relatively high at all 3 dose levels.

Hematologic toxicity

Table 4 shows the worst toxicities experienced during the treatment. The most frequent grade 3/4 toxicities were leukopenia and neutropenia. Although only one case of dose-limiting grade 4 neutropenia was observed at dose level 3, short-lived grade 4 neutropenia occurred in 9 of 15 patients (60 %) during the trial (Table 4). Eleven episodes of grade 3/4 neutropenia were reported during this trial. Seven (64 %) of 11 episodes of grade 3/4 neutropenia were asymptomatic, whereas 4 episodes (36 %) were associated with fever and one (9 %) was complicated by grade 3 intestinal obstruction. Four patients experienced grade 3/4 thrombocytopenia and 4 had grade 3/4 anemia.

Nonhematologic toxicity

Another major DLT of this combination regimen was diarrhea (Table 3). Although there was no grade 3/4 diarrhea at dose level 1, the rate of grade 3/4 diarrhea was 20 % at dose level 2 and 25 % at dose level 3. Transient grade 3 nausea was observed in 3 (20 %) of the 15 patients (Table 4).

Grade 2 or 3 interstitial pneumonia was seen in 3 patients (grade 2 in one patient during the third cycle, grade 3 in one patient after the third cycle and in one patient during the fourth cycle). Bilateral pulmonary infiltrates were observed in these patients by chest radiograph or CT.

Table 2 Dose escalation and treatment in patients receiving amrubicin and CPT-11

Dose level	Dose (mg/m^2)		No. of patients	Total no. of courses	Delivered dose/planned dose of CPT-11 & AMR
	CPT-11 (days 1, 8)	Amrubicin (days 1–3)			
1	60	30	3	13	100 and 100 %
2	60	35	8	32	99.1 and 97.4 %
3	60	40	4	13	100 and 89.1 %

Table 3 Dose-limiting toxicities (DLT) during first cycle at different dose levels

	Dose level		
	1	2	3
No. of patients	3	8	4
DLT			
ANC 500/μl for ≥ 4 days	0	0	1*
Febrile neutropenia	0	0	1*
Intestinal obstruction	0	0	1*
Delay in CPT-11 treatment on day 8			
For more than 7 days	0	0	1*
Toxicity resulting in treatment delay			
For more than 14 days	0	0	1*
Diarrhea	0	1	1
No. of patients who experienced DLT	0	1	2

* Occurred in one patient simultaneously

Interstitial pneumonia developed in one patient when their neutrophil count was high. In one patient, interstitial pneumonia developed during G-CSF administration, despite a normal neutrophil count. In the last patient, interstitial pneumonia occurred after the third cycle when their neutrophil count was normal. All 3 patients responded quickly to oral steroids or steroid pulse therapy. No pathogenic microorganisms were detected in repeated examinations in any patient.

Other grade 2 non-hematologic toxicities included anorexia, skin rash, constipation, and alopecia. No cardiotoxicity was observed during this trial.

There were no treatment-related deaths during this trial.

Response and survival

Thirteen patients were assessed for response (Table 5). Objective responses occurred from the first 30-mg/m^2 dose level of amrubicin combined with a fixed dose of 60 mg/m^2 CPT-11. Although no complete response was observed, all 13 patients showed a partial response, with an overall response rate of 100 %. No patient showed stable disease or disease progression. Median progression-free survival was 7.4 months. At the time of progression, 13 patients could receive second-line platinum-based chemotherapy. Of five patients who received cisplatin + etoposide chemotherapy, one patient attained a complete response and another patient had a partial response, for an overall response rate of 40 %. Of eight patients who could receive carboplatin + etoposide treatment, two (25 %) had a partial response.

Table 4 Worst toxicities at different dose levels

	Dose level 1 ($n = 3$)				Dose level 2 ($n = 8$)				Dose level 3 ($n = 4$)			
	Grade				Grade				Grade			
	0–1	2	3	4	0–1	2	3	4	0–1	2	3	4
Leukopenia	0	1	2	0	2	1	4	1	0	1	2	1
Neutropenia	1	0	0	2	2	0	2	4	0	1	0	3
Thrombocytopenia	2	0	1	0	5	1	2	0	3	0	1	0
Anemia	0	2	0	1	3	3	1	1	0	3	1	0
Febrile neutropenia	2	0	1	0	6	0	0	2	3	0	1	0
Abnormal liver function	3	0	0	0	8	0	0	0	4	0	0	0
Abnormal renal function	3	0	0	0	8	0	0	0	4	0	0	0
Nausea	3	0	0	0	4	2	2	0	3	0	1	0
Vomiting	3	0	0	0	8	0	0	0	4	0	0	0
Anorexia	3	0	0	0	4	4	0	0	2	2	0	0
General fatigue	3	0	0	0	6	2	0	0	4	0	0	0
Diarrhea	3	0	0	0	5	1	2	0	3	0	1	0
Rash	2	1	0	0	5	3	0	0	4	0	0	0
Constipation	3	0	0	0	7	1	0	0	3	0	0	0
Dizziness	3	0	0	0	8	0	0	0	4	0	0	0
Interstitial pneumonia	2	0	1	0	7	1	0	0	3	0	1	0
Alopecia	2	1	0	0	8	0	0	0	4	0	0	0
Stomatitis	3	0	0	0	8	0	0	0	4	0	0	0
Abdominal pain	3	0	0	0	8	0	0	0	4	0	0	0
Abdominal obstruction	3	0	0	0	8	0	0	0	3	0	1	0

Table 5 Treatment results in 13 patients by dose level

Dose level	No. of patients	Response					
		CR	PR	SD	PD	NE	CR + PR (%)
1	3	0	3	0	0	0	3 (100)
2	8	0	7	0	0	1	7 (100)
3	4	0	3	0	0	1	3 (100)
Overall	15	0	13	0	0	2	13 (100)

CR complete response, *PR* partial response, *SD* stable disease, *PD* disease progression, *NE* not evaluable

Of the 15 patients, 6 patients (40 %) were still alive as of July 28, 2011. Median survival time in all 15 patients was 13.4 months.

Discussion

This trial demonstrated that the MTD of amrubicin in combination with 60 mg/m^2 CPT-11 with rhG-CSF support was 35 mg/m^2 (Table 3). Neutropenia, neutropenic fever, ileus, and diarrhea were the DLTs. Although use of prophylactic rhG-CSF support did not completely eliminate neutropenia, use of rhG-CSF allowed the dose of amrubicin to be raised 40 % above that in the original regimen (25 mg/m^2 amrubicin and 60 mg/m^2 CPT-11) [32]. The dose of amrubicin was 78 % of that recommended for single-agent administration as an intravenous injection on days 1–3 in patients without prior chemotherapy. The dose of CPT-11 with this schedule was also only 60 % of the recommended single-agent dose as a weekly administration in Japan [22], showing that the combined use of full doses of both agents is not feasible due to overlapping myelotoxicities. However, toxic effects were predictable, reversible, and manageable. The spectrum of toxicities for amrubicin combined with CPT-11 was similar to that of each agent alone [20, 31]. As expected, leukopenia, neutropenia, neutropenic fever, intestinal obstruction, missed CPT-11 treatment on day 8 due to leukopenia, and diarrhea were the principal DLTs of this combination regimen (Table 3). No unexpected toxicity was observed during this trial (Tables 3 and 4). Grade 3/4 leukopenia and neutropenia, typical overlapping toxicities of both drugs [20, 31], occurred in 11 of the 15 patients treated with this regimen, indicating that administration of rhG-CSF cannot completely compensate for the hematologic toxicity of these drugs. However, neutropenia associated with fever was only noted in 4 patients (Table 4). Diarrhea, which could be attributed to CPT-11 [20], was one of DLTs in this trial, with 4 patients showing grade 2 or worse. No incidence of cardiotoxicity, which might have been attributable to amrubicin, was observed, and has never been a reason for treatment discontinuation.

The incidence of pulmonary toxicity observed in this trial was higher than that in our previous trial without G-CSF support (20 % versus 9.1 %, respectively) (Table 4) [32]. Higher age (≥55 years old), poor performance status, smoking, recent non-small-cell lung cancer diagnosis, reduced normal lung on CT scan, preexisting chronic interstitial lung disease, and concurrent cardiac disease are known to be risk factors for interstitial lung disease [14]. Some of these risk factors (higher age, smoking) were observed in the patients experiencing pulmonary toxicity in this trial. However, these risk factors were also observed in the patients in our previous trial. We believe that interstitial pneumonia was probably caused by escalated doses of amrubicin in conjunction with a fixed dose of CPT-11 in this trial, although interstitial pneumonia is a recognized toxicity for both drugs [20, 29]. In addition, interstitial pneumonia related to the use of G-CSF has occasionally reported [1, 12, 23]. It has been postulated that G-CSF exacerbates underlying subclinical pulmonary toxicity induced by chemotherapy by augmenting leukocyte production, pulmonary sequestration, and migration [10]. Therefore, G-CSF may have augmented the pulmonary toxicity of this combination regimen, too.

The response rate of 100 % and median survival time of 13.4 months obtained in this study compare favorably with those previously reported in trials of other combination chemotherapy regimens in patients with ED-SCLC [8, 9, 25]. Recently, evaluation of mRNA levels of excision repair cross-complementation group 1 (ERCC1), an endonuclease responsible for repair of DNA damage, in tumor samples has shown an inverse relationship with either response to platinum-based chemotherapy or survival [4, 16]. In this regard, this non-platinum doublet may offer an alternative not only in patients who cannot undergo cisplatin-containing regimens due to renal or cardiac dysfunction, but also in patients with highly positive for ERCC1.

In conclusion, this study showed that amrubicin can be administered at 78 % of the recommended single-agent dose in combination with CPT-11 (60 mg/m^2). The major DLTs were neutropenia, neutropenic fever, ileus, and diarrhea. In this phase I study of 13 assessable patients with

ED-SCLC, we observed 13 partial responses, yielding an encouraging overall response rate of 100 %. In future phase II trials, the appropriate dosage and schedule in previously untreated patients with ED-SCLC should be 35 mg/m^2 amrubicin (days 1–3) plus 60 mg/m^2 CPT-11 (days 1 and 8) with rhG-CSF support repeated at 3-week intervals. Furthermore, we believe that the results of this study are relevant to the treatment of diseases other than ED-SCLC against which CPT-11 and amrubicin have shown antitumor activity.

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