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Phase I study of irinotecan and cisplatin with concurrent split-course radiotherapy in unresectable and locally advanced non-small cell lung cancer

M. Oka [a,b,*], M. Fukuda [a], M. Fukuda [c], A. Kinoshita [d], M. Kuba [e], M. Ichiki [f], T. Rikimaru [f], H. Soda [a], H. Takatani [g], F. Narasaki [h], S. Nagashima [a], Y.-I. Nakamura [a], N. Hayashi [i], S. Kohno [a,b]

[a] *Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan*
[b] *Division of Molecular and Clinical Microbiology, Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Medical Sciences, Nagasaki, Japan*
[c] *Internal Medicine, Japanese Red Cross Nagasaki Atomic Bomb Hospital, Nagasaki, Japan*
[d] *Internal Medicine, Nagasaki-Chuo National Hospital, Nagasaki, Japan*
[e] *Internal Medicine, National Okinawa Hospital, Okinawa, Japan*
[f] *First Department of Internal Medicine, Kurume University School of Medicine, Fukuoka, Japan*
[g] *Internal Medicine, Nagasaki Municipal Hospital, Nagasaki, Japan*
[h] *Internal Medicine, Nagasaki Prefectural Shimabara Onsen Hospital, Nagasaki, Japan*
[i] *Department of Radiology, Nagasaki University School of Medicine, Nagasaki, Japan*

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Abstract

We conducted a phase I study of irinotecan (CPT-11) and cisplatin with concurrent split-course radiotherapy in locally advanced stage III non-small cell lung cancer (NSCLC). This study aimed to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of this therapy. Two chemotherapy cycles of CPT-11 (days 1, 8 and 15) and cisplatin (day 1) were repeated with a 28-day interval. Radiotherapy of 2 Gy/day commenced on day 2 of each chemotherapy cycle, with 24 Gy and 36 Gy administered for the first and second cycle, respectively. 24 eligible patients were enrolled at five dose levels (CPT-11/cisplatin: 40/60, 50/60, 60/60, 60/70 and 60/80 mg/m^2), and 23 patients were evaluated for toxicity and clinical outcome. Only 1 patient experienced a DLT with neutropenia and diarrhoea at 60/60 mg/m^2. Dose escalation was limited to 60/80 mg/m^2 which was the recommended dose for CPT-11/cisplatin alone in NSCLC. Tumour responses included one complete response (CR), 15 partial response (PR), and 7 no change (NC), and the overall response rate was 69.6% (95% confidence interval (CI) 47.1–86.8%). This combined modality is tolerable, and CPT-11/cisplatin of 60/80 mg/m^2 in this modality is recommended for phase II study.

Keywords: Lung cancer; Non-small cell lung cancer; Clinical trial; Chemoradiotherapy; Radiation therapy; Topoisomerase I inhibitor; Cisplatin; Combined modality

1. Introduction

Lung cancer is now the leading cause of cancer-related mortality in most countries. As it is relatively resistant to chemotherapy, new chemotherapeutic options are warranted especially against non-small cell lung cancer (NSCLC). NSCLC represent the majority of lung cancers, most of which are at an advanced stage at diagnosis leading to their overall poor prognosis. Radiotherapy to the primary tumour and regional lymph nodes has been the traditional treatment for locally advanced stage III NSCLC [1]. Recently, a combined modality of chemotherapy and radiotherapy has been recognised as a standard therapy for these

* Corresponding author at: Second Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Tel.: +81-95-849-7274; fax: +81-95-849-7285.

E-mail address: okamikio@net.nagasaki-u.ac.jp (M. Oka).

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patients with good performance scores [1,2]. For the treatment of locally advanced NSCLC, three meta-analyses demonstrated that this modality, especially using cisplatin-based chemotherapy, yielded a modest survival benefit when compared with radiotherapy alone [3–5]. Previous randomised trials, however, comparing chemoradiotherapy with radiotherapy alone, stressed the need for further improvements in systemic and local therapy to improve survival [6–8]. Accordingly, recent phase I and II trials have incorporated concurrent radiation and new active regimens or single-agents such as taxanes and gemcitabine into chemoradiotherapy for locally advanced NSCLC [9–13].

Irinotecan hydrochloride (CPT-11) is a semi-synthetic water-soluble derivative of camptothecin, a plant alkaloid obtained from *Camptotheca acuminata*, which interferes with the breakage-rejoining reaction of DNA topoisomerase I [14,15]. This leads to single-strand DNA breaks, and ultimately to the death of cancer cells [14,15]. Clinical studies of CPT-11 alone have shown a broad spectrum of antitumour activity against various human cancers including NSCLC and small-cell lung cancer (SCLC) [16], and an *in vitro* study showed synergism between the action of cisplatin and an active metabolite of CPT-11, SN-38 [17]. A phase II trial of CPT-11/cisplatin (60/80 mg/m^2) therapy in Japan yielded a 52% (95% CI: 39–64%) response rate for NSCLC [18], and a preclinical study showed an enhancement effect from use of CPT-11 on tumour radiosensitivity [19]. Therefore, we conducted a phase I study of CPT-11/cisplatin with concurrent split-course radiotherapy in unresectable and locally advanced stage III NSCLC. A previous trial of CPT-11/cisplatin with concurrent standard radiotherapy of 60 Gy in 30 fractions failed because of unacceptable toxicities and low radiation therapy completion rate, including persistent leucopenia, neutropenic fever and pneumonitis [20]. Accordingly, the present study incorporated split-course radiotherapy with a rest period between two chemotherapy cycles.

The primary objective of this phase I dose-escalation study was to determine the optimal doses of CPT-11/cisplatin when administered concurrently with split-course thoracic radiation. The secondery goal of this study was to define the toxicity associated with this regimen.

2. Patients and methods

2.1. Patients and evaluation

The study was approved by the Ethics Committee of the Nagasaki University School of Medicine. Patients with previously untreated, unresectable and locally advanced stage III NSCLC were enrolled, but patients with pleural effusion were excluded. Tumour staging was performed on the basis of a complete medical history and physical examination, routine chest radiography, bone scintiscanning, computed tomography (CT) of the chest and abdomen, CT or magnetic resonance imaging (MRI) of the head, and bronchoscopy. Staging was performed according to the tumour, node, metastasis (TNM) system [21]. Eligibility criteria included the following: a histologically confirmed diagnosis of NSCLC; age $\leqslant 75$ years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leqslant 2$; life expectancy >12 weeks; adequate bone marrow function (leucocyte count $\geqslant 4\times10^9$/l platelet count $\geqslant 100\times10^9$/l and haemoglobin $\geqslant 100$ g/l); serum bilirubin $\leqslant 25$ μmol/l; alanine aminotransferase (ALT) and asparate aminotransferase (AST) levels $\leqslant$ double the normal upper limit; serum creatinine $\leqslant 105$ μmol/l and $PaO_2 \geqslant 70$ torr; no medical problems severe enough to prevent compliance with the protocol, and provision of written informed consent.

Prior to the first course of therapy, a complete blood cell count including differential white blood cell count and platelet count, biochemistry tests (renal and hepatic function and electrolytes), and urinalysis were performed. Complete blood cell count and biochemistry were repeated at least once weekly after treatment, while other investigations were repeated as necessary to evaluate various markers. After completion of chemoradiotherapy, each patient was restaged with all tests used during the initial work-up.

2.2. Treatment

Treatment commenced within 1 week of enrolment, and two cycles of CPT-11/cisplatin therapy were repeated after a 28-day interval. On day 1, CPT-11 dissolved in 250 ml of 5% dextrose was infused intravenously (i.v.) over 90 minutes followed 2 hours later by cisplatin, which was infused i.v. over 60 min. The CPT-11 infusion alone was repeated on days 8 and 15. The starting doses of CPT-11 (days 1, 8 and 15) and cisplatin (day 1) were 40 and 60 mg/m^2, respectively, and these were increased in 10 mg/m^2 increments, as shown in Table 1. However, our dose escalation was limited to a level of 60/80 mg/m^2 which was the recommended dose for CPT-11/cisplatin chemotherapy alone in NSCLC [18]. 3

Table 1
Dose escalation schedule[a]

Level	CPT-11 (mg/m^2)	Cisplatin (mg/m^2)
1	40	60
2	50	60
3	60	60
4	60	70
5	60	80

[a] CPT-11 on days 1, 8 and 15; cisplatin on day 1.

patients were enrolled into each dose level. The dose was escalated to the next level if none of three patients experienced a dose-limiting toxicity (DLT) as described below. If 2 of the 3 patients experienced a DLT, the dose level was defined as the maximum-tolerated dose (MTD). If 1 of the 3 patients experienced DLT, 3 more patients were treated at that level. If none of the additional 3 patients experienced a DLT, the dose was escalated to the next level. If 1 or more of the additional 3 patients experienced a DLT, the dose level was then defined as the MTD. The dose level preceding that defined as the MTD was then defined as the recommended dose of this chemoradiotherapy for phase II study.

Thoracic radiation was administered once daily with a split-schedule: 5 days/week with 2 Gy/day from day 2 of each chemotherapy cycle, with a total of 24 and 36 Gy provided at the first and second cycle, respectively. There was a break in the split-course radiation of approximately 12 days. Based on recent chest CT scan, the radiation volumes and fields were individualised for each patient. The radiation fields encompassed areas of the gross primary lesion with a 2 cm margin, and the ipsilateral hilar and mediastinal nodes. If supraclavicular and/or scalene node metastasis was found, the nodes were included in the fields. The area of the lung field included in the radiation field was not greater than half of the area of the ipsilateral lung. Patients received the intended radiotherapy with a total dose of 60 Gy, which was administered with a 10-MeV linear accelerator using two antero-posterior opposed beams.

Blood transfusion was only performed in cases with haemoglobin <75 g/l or platelet count $<20\times10^9$/l. Patients who developed diarrhoea were treated with 2 mg loperamide hydrochloride, which was repeated 6-hourly until the diarrhoea was well controlled.

2.3. Dose modification

2.3.1. Chemotherapy

CPT-11 treatment was omitted on days 8 and 15 if the leucocyte count fell below 3×10^9/L, platelet count $<50\times10^9$/L or any diarrhoea occurred. Leucocytes $\geqslant3\times10^9$/L and platelets $\geqslant75\times10^9$/L were mandatory to commence the second cycle of treatment, and if levels fell below these limits, the second cycle was postponed until the counts recovered. Doses of CPT-11 and cisplatin were reduced to 80% when DLT occurred during the first treatment cycle.

2.3.2. Radiation therapy

If grade 4 haematological toxicity occurred during radiation, radiation was interrupted and restarted after recovery to grade 3 or less. If grade 3 or greater oesophagitis occurred, it was interrupted and restarted after recovery to grade 2 or less. If oesophagitis did not recover, it was discontinued. If PaO_2 fell to 10 torr or a patient had a fever of 38°C or higher, both radiation therapy and chemotherapy were interrupted and restarted as soon as possible after recovery.

2.4. Toxicity and response evaluation

Eligibility, assessability and tumour responses were determined by external reviewers. Tumour response and drug toxicity were classified according to the criteria of the World Health Organization (WHO) [21] except for oesophagitis and pneumonitis. Grading of oesophageal toxicity due to radiation was based on the ECOG criteria [22] and pneumonitis was clinically and radiographically graded according to the Radiation Therapy Oncology Group (RTOG) acute and late lung morbidity scoring criteria [23]. DLT was evaluated during two cycles of treatment at each dose level. DLT was defined as grade 4 leucopenia or neutropenia lasting 4 days or more, grade 4 thrombocytopenia, and grade 3 or greater non-haematological toxicities except nausea and vomiting. Omission of CPT-11 dose on both days 8 and 15 of each chemotherapy cycle was also defined as a DLT.

Tumour response was classified according to the WHO criteria [21]. A complete response (CR) was defined as the disappearance of any evidence of tumours for at least 4 weeks. A partial response (PR) was defined $\geqslant50\%$ reduction in the sum of the products of the greatest perpendicular diameters of all lesions for at least 4 weeks. No change (NC) was defined as $<50\%$ reduction or $<25\%$ increase in the products of the greatest perpendicular diameters of all lesions without any evidence of new lesions. Progressive disease (PD) was defined as an increase of $\geqslant25\%$ or the appearance of new lesions. Response duration was measured from the start of the treatment to disease progression.

3. Results

3.1. Patient characteristics

24 patients from our six institutes were enrolled between April 1996 and August 1998, 23 of whom were eligible for evaluation for toxicity and efficacy. One patient died suddenly of complete right main bronchus obstruction by the tumour on day 1, which was therefore not a treatment-related death. The characteristics of the remaining patients are shown in Table 2. Consequently, no patients with a PS of 2 were enrolled, although they were eligible in this study.

3.2. Dose escalation

3 and 4 patients were treated at dose levels 1 and 2, respectively, and no patients experienced a DLT. One of

Table 2
Patient characteristics ($n = 23$)

Characteristic	n
Age (year)	
Median (range)	62 (35–72)
Sex	
Male	17
Female	6
PS (ECOG)	
0	4
1	19
Stage	
IIIA	7
IIIB	16
Histology	
Adenocarcinoma	8
Squamous cell carcinoma	14
Large cell carcinoma	1

PS, performance status; ECOG, Eastern Cooperative Oncology Group.

3 patients at dose level 3 experienced a DLT of grade 4 diarrhoea, and three more patients were then treated at this level. Only 1 of the 6 patients enrolled into dose level 3 had a DLT, so this study progressed to level 4. At dose levels 4 and 5, no patients experienced a DLT. In an extension study to confirm the safety at dose level 5, no DLT was experienced by an additional 4 patients. Because dose level 5 (CPT-11 60 mg/m^2 and cisplatin 80 mg/m^2) was the recommended dose of CPT-11/cisplatin therapy alone for NSCLC [9], dose escalation was terminated at this level. Finally, level 5 was regarded as the recommended dose of this regimen for phase II study.

3.3. Toxicity

Haematological toxicities during treatment are summarised in Table 3. The principal adverse effects were leucopenia and neutropenia, and 17 (74%) patients experienced these to grade 3–4 severity. Although 4 (17%) and 5 (22%) patients experienced grade 4 leucopenia and neutropenia, respectively, no patients experienced a DLT in all of the treatment cycles. Thrombocytopenia was mild, with only 2 patients experiencing grade 3. Anaemia occurred during the second rather than the first treatment cycle, with 6 (26%) patients experiencing grade 3 anaemia. No patient required a blood transfusion during treatment.

The major non-haematological toxicities were gastrointestinal toxicity, pneumonitis and dermatitis (Table 4). Two patients receiving dose level 5 experienced grade 3 nausea/vomiting. Diarrhoea was observed in 17 (74%) patients, of whom only 1 experienced grade 4 diarrhoea on day 15 of the second cycle. 11 (48%) patients had oesophagitis (none $\geqslant$grade 3). Liver dysfunction was observed in 3 (13%) patients (2 grade 1 and 1 grade 2). Late radiation pneumonitis was observed in 9 (39%) patients (none $\geqslant$grade 3). 2 (9%) patients transiently experienced skin erythema which appeared out of the irradiated field.

3.4. Treatment delivery

A total of 46 chemotherapy cycles were administered in 23 patients at the five dose levels. Thirty-eight (28%) of a planned 138 doses of CPT-11 were omitted, comprising 12 day-8 and 26 day-15 doses. No patients had CPT-11 omitted on both days 8 and 15 of both cycles. The median ratio of actual dose-intensity to planned dose-intensity of CPT-11 through the five dose levels was 0.72 (range 0.67–0.76), and the ratio at the recommended dose level 5 was 0.76. The reasons for CPT-11 omission were leucopenia in 29, diarrhoea in 4, a fall in PS in 3, thrombocytopenia and fever in 2, and liver dysfunction in 1 patient.

Regarding radiation doses, 22 of 23 patients received 50–60 Gy of radiotherapy, and one patient at level 5 refused radiation at 46 Gy due to diarrhoea. Of 6 patients at a recommended dose level 5, 5 received 60 Gy. Compliance with the present protocol was relatively favourable.

Table 3
Haematological toxicities: all dose levels ($n = 23$)

Dose level	No. of patients	WBC[a]			ANC[a]			Platelets			Hgb		
		Grade			Grade			Grade			Grade		
		2	3	4	2	3	4	2	3	4	2	3	4
1	3	0	2	1	0	2	1	0	0	0	1	2	0
2	4	1	3	0	0	3	0	0	0	0	2	1	0
3	6	1	3	2	1	3	2	1	1	0	2	1	0
4	3	0	2	1	1	1	1	1	0	0	2	0	0
5	7	3	3	0	2	3	1	0	1	0	3	2	0

WBC, white blood cells; ANC, absolute neutrophil count; Hgb, haemoglobin.
[a] Leucopenia and neutropenia of grade 4 did not last for the 4 days defined as a dose-limiting toxicity (DLT).

Table 4
Non-haematologic toxicities: all dose levels ($n = 23$)

Dose level	No. of patients	Oesophagitis			Diarrhoea				Pneumonitis			Nausea/vomiting				Skin			Liver		
		Grade			Grade				Grade			Grade				Grade			Grade		
		1	2	⩾3	1	2	3	4	1	2	⩾3	1	2	3	4	1	2	⩾3	1	2	⩾3
1	3	2	0	0	3	0	0	0	0	2	0	2	1	0	0	1	1	0	0	0	0
2	4	1	1	0	2	1	0	0	0	1	0	1	3	0	0	2	1	0	0	0	0
3	6	2	0	0	1	1	0	1	0	0	0	2	4	0	0	1	0	0	1	0	0
4	3	0	1	0	2	1	0	0	1	1	0	1	2	0	0	0	0	0	0	1	0
5	7	2	2	0	3	2	0	0	1	3	0	2	2	2	0	1	1	0	1	0	0

3.5. Response

23 patients were assessed for response, and tumour responses at each dose level are shown in Table 5. 16 (69.6%, (95% CI: 47.1–86.8%)) patients achieved an objective response comprising one CR (4.3% (95% CI 0.1–21.9%)) and 15 PRs (65.2% (95% CI 42.7–83.6%)), and the remaining 7 (30.4%) patients were evaluated as NC.

4. Discussion

This study was designed based on the cytotoxic activity and/or radiosensitising activity of CPT-11, cisplatin and radiation for NSCLC, and for the first time demonstrated that this combination therapy was well tolerated. In the United States, a phase II study of CPT-11/cisplatin therapy for advanced NSCLC recently reported a 28.8% (95% CI 16.5–41.2%) response rate and a 37% 1-year survival, suggesting this therapy is a valid regimen in the treatment of NSCLC [24]. In a randomised trial comparing CPT-11/cisplatin with vindesine/cisplatin for advanced stage IIIB and IV NSCLC, the former regimen yielded a 43.3% overall response rate and a 48.5% 1-year survival rate [25]. The results of CPT-11/cisplatin therapy were superior to those of the latter regimen. Therefore, CPT-11/cisplatin therapy is considered to be one of the most active regimens to date for NSCLC.

Three meta-analysis studies have shown a survival benefit of chemoradiotherapy for locally advanced NSCLC, however, they could not determine which schedule of radiation, concurrent or sequential, was preferable [3–5]. Pritchard and Anthony [5] reported similar treatment effects in trials of concurrent and sequential chemoradiotherapy. The West Japan Lung Cancer Group conducted a phase III trial comparing concurrent and sequential chemoradiotherapy with mitomycin C/vindesine/cisplatin (MVP) for unresectable stage III NSCLC, and recently demonstrated the superiority of concurrent therapy with respect to the response rate and survival [26]. Interestingly, this trial incorporated split-course radiotherapy and full doses of MVP therapy. This early concurrent chemoradiotherapy yielded very promising results with an 84% response rate, median survival of 16.5 months, and 3- and 5- year survival rates of 22.3 and 15.8%, respectively. The Cancer and Leukemia Group B (CALGB)/ECOG conducted a randomised trial comparing concurrent chemoradiotherapy with carboplatin as a radiosensitiser to radiotherapy alone, following induction chemotherapy of vinblastine/cisplatin for 5 weeks [8]. No differences in response rate and survival were demonstrated between the two treatment arms. Therefore, the overall results of these trials suggest that early concurrent chemoradiotherapy using new active agents appears promising for locally advanced NSCLC.

New active single-agents or regimens with platinum-agents for NSCLC, such as vinorelbine, taxanes, gemcitabine and CPT-11, have been incorporated into phase I and II trials of concurrent chemoradiotherapy for several years [9–13,20,27]. All of these agents have been shown to be radiosensitisers *in vitro*. These phase I and II trials using standard radiotherapy of 60–66 Gy have yielded a response rate of 47–80% and/or comparable survival [9,10,12,27], despite administration of lower doses than those used in chemotherapy alone. However, a previous phase I trial of CPT-11/cisplatin concurrently with standard radiotherapy of 60 Gy was discontinued because the dose intensity of CPT-11 and radiation completion rate were restricted due to leucopenia or diarrhoea [20]. Chemoradiotherapy with a single-agent of CPT-11 (60 mg/m^2) was associated with DLTs of oesophagitis and pneumonitis [27]. Similarly, severe adverse effects of haematological toxicities,

Table 5
Tumour responses at each dose level

Dose level	No. of patients	CR	PR	NC
1	3	0	2	1
2	4	0	3	1
3	6	0	4	2
4	3	0	2	1
5	7	1	4	2
Total (%)	23 (100)	1 (4.4)	15 (65.2)	7 (30.4)

CR, complete response; PR, partial response; NC, no change.

oesophagitis and pneumonitis were observed with other new agents [9–13]. This implies that schedules and doses of radiation or new agents should be extensively investigated for each chemoradiotherapy regimen, as toxicities in concurrent chemoradiotherapy appear to be more severe or frequent than those in chemotherapy or radiotherapy alone.

Pneumonitis associated with concurrent chemoradiotherapy using new agents is a frequent serious and fatal toxicity [11,13,27]. The incidence or grade of pneumonitis appears to depend partially on the radiation field size or volume [13,28]. Recently, Yamada and colleagues [28] retrospectively analysed risk factors for pneumonitis following chemoradiotherapy in 60 patients, and found that the frequency of pneumonitis in concurrent radiotherapy with weekly CPT-11 (56.3%) was significantly higher than in those without CPT-11 (13.6%). This analysis concluded that weekly CPT-11 was a significant risk factor for pneumonitis following chemoradiotherapy. However, no patients in our study experienced severe pneumonitis, despite a sufficient radiation field size in each patient. One possible reason for this is the split-course radiation incorporated into our study. None the less, this issue should be investigated in a larger number of patients, and we consider that this pulmonary toxicity is one of the most important endpoints for a phase II study.

This study incorporated a split-course thoracic radiation of 60 Gy, and no patients experienced severe oesophagitis and neutropenia despite full dose administration of CPT-11/cisplatin. In addition, patients exhibited good compliance with the treatment protocol, although the above-mentioned toxicities usually limit administration of full dose chemotherapy concurrently with continuous radiation. In fact, prior chemoradiotherapeutic trials with new agents had to reduce to approximately half or less the doses of chemotherapy alone due to toxicity [9–11,13,27]. Split-course radiation has the potential disadvantage of tumour cell repopulation during the rest period, however, our result showed a comparable overall response rate of 69.6% (95% CI 47.1–86.8%). A possible mechanism for our favourable result is that full dose CPT-11/cisplatin therapy precluded tumour cell repopulation and effectively acted as a radiosensitiser. Similarly, in two trials using a split-course schedule for locally advanced NSCLC, the incidences of severe oesophagitis and pneumonitis were low compared with those for a continuous schedule, although full dose chemotherapy could be administered [26,29]. In addition, the results for tumour response and survival in these trials were similar or better than those for a continuous schedule. Thus, split-course radiation in concurrent chemoradiotherapy may be preferable providing a balance between toxicity and benefit from treatment.

In conclusion, our study demonstrated that concurrent split-course thoracic radiotherapy and CPT-11/cisplatin therapy was well tolerated, and that the recommended doses of CPT-11 and cisplatin were 60 and 80 mg/m^2, respectively. Based on these results, we have already initiated a phase II study using this protocol, with a minor modification for unresectable and locally advanced stage III NSCLC. In addition, because CPT-11/cisplatin therapy has been also shown to be a active regimen for extensive small cell lung cancer (SCLC) [30], this modality could be applicable to the treatment of limited-stage SCLC in the near future.

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