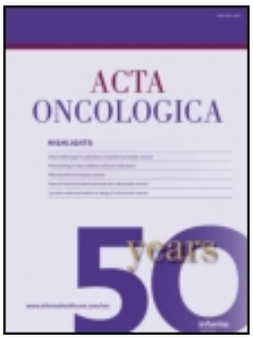

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ORIGINAL ARTICLE

Phase II study of irinotecan and amrubicin in patients with relapsed non-small cell lung cancer: Okayama Lung Cancer Study Group Trial 0402

NAOYUKI NOGAMI[1], KATSUYUKI HOTTA[2], YOSHIHIKO SEGAWA[1], NAGIO TAKIGAWA[2,7], SHINOBU HOSOKAWA[3], ISAO OZE[1], MASANORI FUJII[1], EIKI ICHIHARA[2], TAKUO SHIBAYAMA[4], ATSUHIKO TADA[4], NOBORU HAMADA[4], MASATOSHI UNO[5], AKIHIKO TAMAOKI[3], SHOICHI KUYAMA[6], GENYO IKEDA[2], MASAHIRO OSAWA[2], SABURO TAKATA[2], MASAHIRO TABATA[2], MITSUNE TANIMOTO[2] & KATSUYUKI KIURA[2]

[1]*Department of Respiratory Medicine, NHO Shikoku Cancer Center, Matsuyama, Japan,* [2]*Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan,* [3]*Department of Respiratory Medicine, Okayama Red Cross Hospital, Okayama, Japan,* [4]*Department of Respiratory Medicine, NHO Minami-Okayama Medical Center, Okayama, Japan,* [5]*Department of Medicine, Kaneda Hospital, Maniwa, Japan,* [6]*Department of Medicine, Chugoku Central Hospital, Fukuyama, Japan, and* [7]*Department of General Internal Medicine 4, Kawasaki Medical School, Okayama, Japan*

Abstract

Background. The survival advantage achieved by existing anti-cancer agents as second-line therapy for relapsed non-small cell lung cancer (NSCLC) is modest and further improvement of treatment outcome is desired. Combination chemotherapy with irinotecan and amrubicin for advanced NSCLC has not been fully evaluated. *Methods*. The primary endpoint of this phase II clinical trial was objective response. Patients with NSCLC who had been treated previously with one or two chemotherapy agents were enrolled. Irinotecan and amrubicin were both administered on Days 1 and 8 of a 21-day cycle, at doses of 100 mg/m^2 and 40 mg/m^2, respectively. *Results*. Between 2004 and 2006, 31 patients received a total of 101 courses; the median number of courses administered was three (range, one to six). Objective response was obtained in nine of the 31 patients (29.0% response rate; 95% confidence interval (CI), 12.1–46.0%). With a median follow-up time of 43.9 months, median survival time and the median progression-free survival time were 14.2 and 4.0 months, respectively. Myelosuppression was the most frequently observed adverse event, with grade 3/4 neutropenia in 51% of patients. Febrile neutropenia developed after nine courses (9%) and resulted in one treatment-related death. Cardiac toxicity and diarrhea, possibly specific for both agents, were infrequent and manageable. *Conclusion*. Combination chemotherapy with irinotecan and amrubicin is effective in patients with NSCLC but showed moderate toxicities in second- or third-line settings.

The standard treatment for relapsed non-small cell lung cancer (NSCLC) has historically been docetaxel monotherapy [1]. Thereafter, treatment with pemetrexed and the epidermal growth factor receptors-tyrosine kinase inhibitors (EGFR-TKI) gefitinib and erlotinib has shown efficacy similar to that of docetaxel in several phase III clinical trials [2–4]. However, the increase in survival achieved by these chemotherapy regimens was very modest and further improvement in treatment outcome is desired. Additionally, several agents with unique mechanisms are now available and have been shown to be highly effective in treating NSCLC [5]. Irinotecan is a semi-synthetic, water-soluble derivative of camptothecin, which inhibits topoisomerase I, an enzyme that relaxes DNA by inducing single-strand DNA breaks [6]. This compound is also active for NSCLC, both as a single agent and in combination with cisplatin (CDDP) [7–9]. Amrubicin, a totally synthetic anthracycline derivative characterized by

Correspondence: K. Hotta, Department of Respiratory Medicine, Okayama University Hospital, 2-5-1, Shikata-cho, Kitaku, Okayama, 700-8558, Japan. Tel: +81 86 2357227. Fax: +81 86 2328226. E-mail: khotta@md.okayama-u.ac.jp

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a 9-amino group and a simple sugar moiety, is converted in the body to amrubicinol by reduction of the 13-position ketone, leading to higher anti-tumor activity (25% response rate) [10]. Although classified as anthracycline agents, amrubicin and amrubicinol exert cytotoxic effects as DNA topoisomerase II inhibitors, not only as DNA intercalators. The combined use of topoisomerase I and II inhibitors has been demonstrated to be complementary in preclinical studies [11,12], and in vitro simultaneous administration of both agents has an advantage for cytokilling [13].

On the basis of these results, we conducted a phase I clinical trial assessing the combination of irinotecan and amrubicin in patients with advanced NSCLC [14]. This regimen was well tolerated, and the recommended doses for phase II studies were 40 mg/m^2 amrubicin, followed by 100 mg/m^2 irinotecan, given on Days 1 and 8 of a 21-day cycle. In the phase I clinical trial, an objective response was observed in the relapsed patients but not in the chemo-naïve patients, but no definitive reason for this difference was found.

Here, we report the results of a phase II clinical trial using this combination chemotherapy in patients with relapsed NSCLC. The primary objective was to determine the response rate for this combination. Secondary objectives included overall survival time (OS), progression-free survival (PFS) times, and safety in the second- or third-line setting.

Patients and methods

Eligibility criteria

To be enrolled in the trial, patients had to meet the following eligibility criteria: pathologically proven, advanced, and inoperable NSCLC; measurable lesions; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; age ≤ 75 years; adequate reserves of hematologic function [white blood cell (WBC) count $> 4000/\mu l$, neutrophil count $> 2000/\mu l$, hemoglobin level > 9.5 g/dl, platelet count $> 10 \times 10^4/\mu l$], renal function (serum creatinine < 1.5 mg/dl), hepatic function (total bilirubin < 1.5 mg/dl, serum transaminases $< 2.5 \times$ upper limit of normal range) and pulmonary function ($PaO_2 \geq 60$ Torr); and provision of written informed consent. Patients who had undergone one or two previous chemotherapy regimens, but had no prior use of irinotecan and/or amrubicin, were eligible. Patients with symptomatic brain metastasis were excluded from the study. Baseline pretreatment evaluations included a complete history, physical examination, laboratory tests, chest radiograph, electrocardiogram, computed tomography (CT)-scans of the chest and abdomen, magnetic resonance imaging (MRI) of the brain, and a radionuclide bone scan. Positron emission tomography (PET)/CT was also used for staging in some cases. Staging was assessed according to the tumor, node, and metastasis [15]. The protocol was approved by the institutional review board of each participating institute and performed in accordance with the Declaration of Helsinki (1964, amended in 2000) of the World Medical Association.

Treatment schedules

Based on the phase I study results [14], 40 mg/m^2 of amrubicin diluted in 20 ml of physiological saline was initially administered intravenously over a 5-min period on Days 1 and 8. Soon thereafter, 100 mg/m^2 of irinotecan diluted in 250 ml of physiological saline was administered intravenously over a 1-h period on the same day. Treatment was repeated every 3 weeks. Each patient was premedicated with an intravenous administration of dexamethasone (8 mg) and granisetron (3 mg) 30 min before the bolus infusion of amrubicin. Treatment was repeated basically for four cycles.

The administration of irinotecan and amrubicin on Day 8 was delayed until Day 15 if hematological toxicity $\geq$ grade 3, non-hematological toxicity $\geq$ grade 2, or diarrhea was observed on the day of administration. If these toxicities did not improve by Day 15, therapy administration was cancelled during that course. The initiation of the next course of chemotherapy was delayed until the recovery of WBC count to $\geq 3000/\mu l$, neutrophil count to $\geq 1500/\mu l$, platelet count to $\geq 10 \times 10^4/\mu l$, and the resolution of non-hematological toxicities to $\leq$ grade 1. The use of granulocyte colony-stimulating factor (G-CSF) was permitted when grade 4 leukopenia, grade 4 neutropenia, or febrile neutropenia was noted.

Assessment of efficacy, toxicity, and anti-tumor activity

The Response Evaluation Criteria in Solid Tumors (RECIST; ver. 1.0) guideline was applied to evaluate responses. The best overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence. Complete and partial responses were confirmed by two observations not less than 4 weeks apart. A determination of stable disease required disease stabilization for at least 6 weeks. All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (ver. 3.0).

Statistical considerations

Assuming that a response rate of 20% in eligible patients would indicate potential usefulness, whereas a rate of 5% would be the lower limit of interest, with $\alpha = 0.05$ and $ß = 0.20$, the estimated accrual number was 27 patients. This regimen would be rejected when only one of the first 13 patients had an objective response at the interim analysis. With an assumed dropout rate of 10%, 30 patients were required. OS was defined as the interval between the date of enrollment in this study and the date of death or the last follow-up visit. PFS was defined as the interval between the date of enrollment and the date of the first observation of disease progression or death from any cause. The survival distribution was estimated using the Kaplan-Meier method [16].

Results

Patient characteristics

A total of 31 patients with recurrent NSCLC were enrolled between November 2004 and June 2006 at six institutes. The baseline patient characteristics are shown in Table I. Most patients were male and non-smokers, with a good PS and adenocarcinoma histological findings. The most dominant prior chemotherapy regimens were cisplatin-based chemotherapy as a first-line treatment and EGFR-TKI as a second-line therapy. The maximal responses to the prior chemotherapies were as followed: complete response 1, partial response 13, stable disease 3 and inevaluable 1, and the corresponding median PFS was 2.2 months. All patients and courses were assessable for safety and efficacy.

Table I. Patient characteristics.

Number of patients		31
Age (years)	Median (range)	66 (29–75)
Gender	Male	21
	Female	10
Smoking status	Current/former/never	3/18/10
Performance status	0/1	19/12
Histology	Adenocarcinoma	21
	Squamous cell carcinoma	5
	Unclassified	5
Stage	IIIB	6
	IV	21
	Post-operative recurrence	4
No. of prior chemotherapy regimens	1/2	13/18
Prior regimens		
First-line regimens	CDDP-based chemoradiotherapy	9
	CDDP-based chemotherapy	16
	CBDCA-based chemotherapy	4
	Non-platinum based chemotherapy	1
	EGFR-TKI	1
Second-line regimens	EGFR-TKI	11
	CBDCA based chemotherapy	4
	Single new agent	3

CBDCA, carboplatin; CDDP, cisplatin; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

Treatment delivery

In total, 101 treatment courses were administered. The median number of treatment courses was three, with a range of one to six courses. Dose and schedule modifications were necessary in 27 (27%) courses; dose reduction was required in 23 courses, administration was delayed in two courses, and chemotherapy was skipped on Day 8 in two courses.

Objective tumor response and overall survival

Tumor response was observed in nine patients, leading to an objective response rate of 29.0% [95% confidence interval (CI) 12.1–46.0%]. Among these nine patients, three were treated in the second-line setting (three of 13 patients, response rate: 23.1%) while the remaining six were treated in the third-line setting (six of 18 patients, response rate: 33.3%). Eighteen (58.1%) patients achieved disease stability, whereas nine (9.7%) developed disease progression. The OS periods of all treated patients are shown in Figure 1. At the time of survival analysis, progression event was observed in all 31 patients while 28 of the 31 patients had died. The median follow-up time for surviving patients (censored patients) was 28.6 months (range, 27.7–33.9 months), the median survival time of the 31 treated patients was 14.2 months, and the 1-year survival rate was 64.5%. The median PFS time and 6-month PFS rate were 4.0 months and 22.6%, respectively (Figure 1).

Adverse events

Neutropenia was the principal hematological toxicity observed; half of all patients developed grade 3 or 4 neutropenia (Table II). G-CSF was administered in 17 (17%) of the 101 courses. Grade 3 or 4 anemia and thrombocytopenia were less common, and transfusions to address these conditions were required in only two courses each.

The non-hematological toxicities were moderate: grade 3 or 4 febrile neutropenia occurred in seven patients (23%) with nine (9%) courses. Diarrhea was almost manageable, manifesting as grades 3–4 in four patients with four cycles; however, one patient

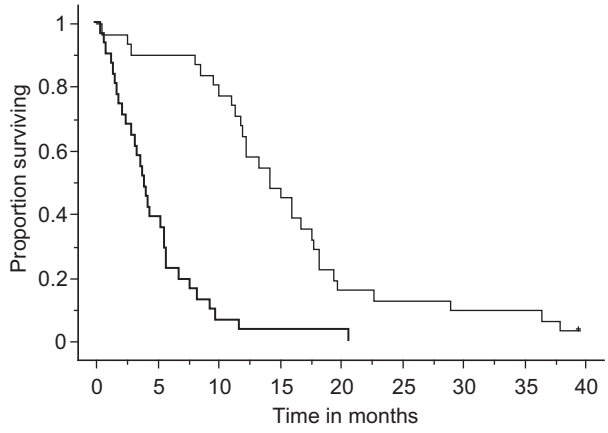

Figure 1. Survival curves: Bold and thin lines indicate progression-free and overall survival, respectively. The median survival time and 1-year survival rate were 14.2 months and 64.5%, respectively, while the median progression-free survival time and 6-month progression-free survival rate were 4.0 months and 22.6%, respectively.

who developed fatal diarrhea with febrile neutropenia died. Cardiac ischemia (vasospastic angina) developed in one patient with one course, but was reversible. Severe hepatic and pulmonary toxicities were rarely observed, and all of these toxicities were reversible with appropriate supportive care.

Discussion

Here, we have demonstrated that the combination of irinotecan and amrubicin using a fractionated administration schedule produced therapeutically relevant effects as a second- or third-line treatment option (29.0% response rate; 95% CI 12.1–46.0%). Additionally, this regimen was moderately tolerated; the principal toxicity observed was myelosuppression. Diarrhea and cardiac toxicity were also observed during several treatment courses, and one patient died.

The combination of irinotecan and amrubicin produced a high response rate and favorable survival in our study. The existing efficacy data for the standard regimen revealed a lower ($<10\%$) objective response rate and a median PFS time of <3 months [1–4]. The high response rate might be partly attributable to possible compensatory roles of both topoisomerase I and II enzymes: development of cellular resistance to topoisomerase II inhibitors conferred an increased sensitivity to topoisomerase I inhibitors [11]. The reverse effect, in which resistance to a topoisomerase I inhibitor enhances the sensitivity to topoisomerase II inhibitors, has also been reported [12]. Indeed, when administered simultaneously, some reports have indicated synergistic or additive cytotoxic effects in various tumor cell lines [13]. A potential role by each topoisomerase enzyme in overcoming a shortage in the other would enhance sensitivity.

Another hypothesis for the favorable efficacy data is that neither irinotecan nor amrubicin was cross-resistant to the prior chemotherapy regimens, especially those using platinum, a key chemotherapeutic drug [17–19] that had frequently been used in the first-line setting in our cohort (Table I). In an in vitro study, both agents remained sensitive to cancer cells that were resistant to platinum [20,21]. Therefore, their non-cross-resistant activity led to favorable OS results. Additionally, assuming the discordant time interval between OS and PFS, it should be taken into consideration that the effects of post-study treatments and/or patient selection may have favorably affected patient survival. However, we have no available data regarding post-study treatments, which is one of the major limitations in this study.

Table II. Adverse events in the 31 patients with 101 courses.

	Grades			
	Number of patients		Number of cycles	
	3	4	3	4
Leucopenia	14 (45%)	6 (19%)	27 (27%)	9 (9%)
Neutropenia	10 (32%)	14 (45%)	32 (32%)	20 (20%)
Hemoglobin	5 (16%)	2 (7%)	9 (9%)	3 (3%)
Thrombocytopenia	4 (13%)	1 (3%)	4 (4%)	1 (1%)
Febrile neutropenia	4 (13%)	3 (10%)	6 (6%)	3 (3%)
Infection	1 (3%)	1 (3%)	2 (2%)	3 (3%)
Nausea/vomiting	2 (7%)	0	3 (3%)	0
Diarrhea	2 (7%)	2 (7%)	2 (2%)	2 (2%)
Hepatotoxicity	1 (3%)	1 (3%)	1 (1%)	1 (1%)
Pneumonitis	1 (3%)	0	1 (1%)	0
Cardiac ischemia	1 (3%)	0	1 (1%)	0

Amrubicin is commonly administered intravenously for three consecutive days [22,23]. However, this approved dosing schedule is too toxic in relapsed patients; in a previous study, the use of amrubicin as a single agent led to febrile neutropenia in 35% of patients and one case of treatment-related pneumonia [24]. For this reason, we considered the fractionated schedule of the two drugs to be less toxic and more manageable, and conducted the initial phase I clinical trial using separate administration [14]. Another group also investigated the same combination but used a consecutive three-day administration of amrubicin [25]. This led to unexpected severe toxicities, including myelosuppression, followed by infection, diarrhea, and pneumonitis. The doses of both agents could not be increased, and the maximum tolerated dose and the recommended dose could not be determined. The difference between these results and ours might be partly due to the difference in the treatment schedule, although other known and unknown confounding issues, including differences in patient selection and supportive care, may also have contributed.

As observed in our phase I clinical trial, myelosuppression was the major toxicity. However, the toxicity profiles of this regimen seemed moderate due to the relatively high proportion of febrile neutropenia and the single toxic death. Genetic variants in the uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1) gene were associated with the risk of severe neutropenia caused by irinotecan [26], and the UGT1A1*6 or *28 allele was observed in 13–17% of the Japanese population [27]. This patient might have possessed the homozygous genotypes for UGT1A1*6 or *28, although we did not investigate the UGT1A1 gene status. Therefore, UGT1A1 gene status may need to be assessed during patient selection, prior to the administration of irinotecan, although such assessment is not currently required by the Japanese government prior to the administration of irinotecan.

One of the major toxicities associated with anthracyclines is cardiotoxicity [28]. However, in a preclinical study using dogs, amrubicin had neither cardiotoxicity nor deteriorating effects on pre-existing cardiomyopathy [29]. Also, previous clinical trials involving 74 patients with small cell lung cancer demonstrated that amrubicin had no cardiotoxicity [30,31]. In our trial, reversible vasospastic angina was observed in one patient and may have been treatment-related. Further assessment of this issue is required in a larger cohort.

In conclusion, a fractionated administration of irinotecan and amrubicin seemed highly effective for advanced NSCLC that had relapsed after first- or second-line treatment with platinum-based regimens, but was associated with moderate toxicities and one treatment-related death occurred. It might be useful in selected relapsed patients, especially who have already received docetaxel or pemetrexed, standard salvage chemotherapy regimen, in the earlier line setting, and who have adequate reserves of hematologic function. The development of appropriate tools for the selection of patients who would benefit most from this treatment regimen, and further improvement of the regimen's efficacy and toxicity profiles, are warranted.

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