Phase I trial of weekly irinotecan and paclitaxel combined with carboplatin in patients with advanced cancer: a Hellenic Cooperative Oncology Group Study

Evangelos Briasoulis[a], Vassilis Golfinopoulos[a], Maria Karina[b], Pavlos Papakostas[c], Nicholas Pavlidis[a] and George Fountzilas[b]

This trial aimed to define a recommended safe dose (RSD) of weekly paclitaxel and irinotecan combined with carboplatin in patients with advanced cancer. Patients with advanced cancer were eligible for this trial. Dose-limiting toxicity (DLT) was considered to be any grade greater than or equal to 3 (G ≥ 3) nonhematological toxicity except nausea/vomiting, G4 hematological toxicity of more than 4 days without recombinant human granulocyte colony-stimulating factor support, concurrent diarrhea G ≥ 2 and neutropenia G ≥ 3, and a treatment delay for more than 14 days because of toxicity. Patients were given carboplatin area under the curve (AUC) 5 mg*min/ml on day 1 combined with irinotecan and paclitaxel on days 1 and 8, every 3 weeks. The starting dose of both irinotecan and paclitaxel was 50 mg/m^2 and a toxicity-guided escalation/de-escalation was planned by 10 mg/m^2 steps. Sixteen patients were enrolled. DLTs occurred in three of the four patients treated at the starting dose level, which defined that dose as the maximum tolerated dose. Accrual continued with irinotecan and paclitaxel doses, which were de-escalated by one step. At this dose level, two of the 12 patients developed DLT, which defined that dose as the RSD. We concluded that the maximum tolerated dose of weekly irinotecan and paclitaxel when given in combination with carboplatin AUC 5 mg*min/ml was 50 mg/m^2 and the RSD 40 mg/m^2. DLTs were febrile neutropenia, concurrent neutropenia (G3) and diarrhea (G3), and prolonged treatment delay because of toxicity. The most common non-DLT G3/G4 toxicity was leukopenia and neutropenia (18%), and thrombocytopenia and diarrhea (6%). A patient with metastatic endometrial carcinoma treated at the RSD had a compete response of retroperitoneal lymph node metastases, lasting for more than 3 years. Two other patients had their minimal tumor shrinkage documented. Paclitaxel (40 mg/m^2) and irinotecan (40 mg/m^2) can safely be administered on days 1 and 8 in combination with carboplatin AUC 5 mg*min/ml given on day 1. At the recommended doses this is a well-tolerated regimen with noticeable antitumor activity and warrants further investigation in phase II studies. *Anti-Cancer Drugs* **21:785–789 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2010, **21**:785–789

Keywords: carboplatin, chemotherapy, irinotecan, paclitaxel, phase I

[a]Department of Medical Oncology, Ioannina University Hospital, Ioannina, [b]Department of Medical Oncology, Papageorgiou Hospital, Aristotle University of Thessaloniki School of Medicine, Thessaloniki and [c]Department of Medical Oncology, Hippokrateio General Hospital, Athens, Greece

Correspondence to Professor Evangelos Briasoulis, MD, Medical School of the University of Ioannina, Ioannina 45110, Greece
Tel/fax: +302651007713; e-mail: ebriasou@otenet.gr

Received 16 April 2010 **Revised form accepted** 19 June 2010

Introduction

Carboplatin, paclitaxel, and irinotecan are potent anticancer chemotherapy drugs commonly used in the treatment of several tumor types [1]. They have different mechanisms of action, dissimilar toxicity profiles, a synergistic potential, and relative lack of cross-resistance, which are characteristics that make their combination particularly attractive [2,3]. Of these drugs, the carboplatin/paclitaxel combination evolved as a reference regimen, applicable in the treatment of various cancers, and other doublets were also found to be active and worthy of further investigation [4–6]. Moreover, investigation of a combination of the three drugs given once every 3 weeks in patients with non-small cell lung cancer and ovarian cancer was shown to be very active but also considerably toxic. The primary grade 3 and 4 toxicities in these three trials were neutropenia and diarrhea and approximately 20% developed febrile neutropenia [7–9]. In this study, we report the results on safety, tolerability, and recommended safe dose (RSD) for phase II/III trials and provide preliminary evidence of activity of this three-drug combination with irinotecan and paclitaxel given weekly (CIP regimen). The carboplatin dose was fixed, whereas the optimal recommended dosage of weekly paclitaxel and irinotecan was investigated. The target population of this trial was patients with advanced refractory cancer. This was a Hellenic Cooperative Oncology Group trial, registered at the Australian New Zealand Clinical Trials Registry (Registration number, ACTRN12609000790246).

Methods and patients

Study design and objectives

This was a multicenter, open-label, uncontrolled, dose-finding trial. The study design followed the current revision of the Declaration of Helsinki and was conducted

0959-4973 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e32833d5ec0

in accordance with the principles of good clinical practice. The study protocol and informed consent were reviewed and approved by the institutional review boards and ethics committees of the participating centers.

The primary objective of the trial was to determine the maximum tolerated dose (MTD) and propose a RSD for phase II/III evaluation; the secondary objectives were to characterize the dose-limiting toxicity (DLT) and to collect preliminary evidence of antitumor activity of this three-drug chemotherapy regimen.

Treatment scheme

The drug regimen consisted of carboplatin administered over 30 min at a fixed dose of area under the curve (AUC) 5 mg*min/ml given on day 1 and irinotecan and paclitaxel infused over 1 h each at a starting dose of 50 mg/m^2 of body surface area on days 1 and 8. Irinotecan infusion preceded paclitaxel. The dose levels for both irinotecan and paclitaxel were planned to be increased or decreased in successive cohorts of patients by 10 mg/m^2, according to toxicity occurrence. The treatment was repeated every 21 days. If grade 2 or higher neutropenia, or thrombocytopenia, or diarrhea was recorded on the scheduled day of treatment, then chemotherapy would be withheld until recovery to grade 1 or to a maximum delay of 2 successive weeks. The treatment would be continued for a maximum of eight cycles.

A minimum of three assessable patients (receiving at least one course of treatment) would be entered at any dose level in the absence of grade 2 or higher toxicity. In the case of grade 2 or higher nonhematologic toxicity, except alopecia, inadequately treated nausea and vomiting, or grade 3 or higher hematologic toxicity, three more patients were to be treated at a minimum. At a given dose level, at least 2 weeks should have passed between the entry of the first and next patient's recruitment. If no more than one patient in a cohort of six patients experienced DLT, the next patients should be treated at an immediately higher dose level. If two or more patients experienced DLT in a cohort of six or fewer patients treated at a given dose level, then that dose was considered the MTD. After the definition of MTD, accrual would continue at a dose level below the MTD. A minimum of eight patients had to be treated at that dose to be investigated as a RSD. Standard prophylactic antiemetic treatment consisted of intravenous administration of a 5HT3 inhibitor before each chemotherapy session, which could be followed by oral anti-5HT3 on indication. All patients also received standard intravenous antiallergic prophylaxis with dexamethasone (8 mg), a histamine H1 antagonist (dimetindene maleate 0.1 mg/kg), and a histamine H2 antagonist (ranitidine 50 mg). Before patients were administered irinotecan, they were given subcutaneous atropine sulfate (0.25 mg) as a prophylaxis to cholinergic reactions. In the case of severe hypersensitivity reactions, the patients were treated with adrenaline, nebulized bronchodilators, and intravenous fluids. For delayed diarrhea (onset >24 h from the end of irinotecan infusion) the patients were advised to take loperamide (4 mg three times a day). Somatostatin [100 μg subcutaneously (s.c.) twice a day] was considered in the case of persisting diarrhea failing to respond to loperamide. In the case of neutropenia complicating persisting diarrhea, the patients were treated with prophylactic oral ciprofloxacin (500 mg two times a day) for 7 days. If diarrhea persisted for more than 72 h despite loperamide and possibly ciprofloxacin treatment, the patients would be hospitalized for intravenous fluid support plus ocreotide.

Patients

Patients with advanced cancer, refractory to standard chemotherapy regimens, were eligible for participation in this trial if they fulfilled the inclusion/exclusion criteria and signed a written informed consent. Key inclusion criteria included age between 19 and 75 years, performance status 0–2 on the WHO scale, a life expectancy of at least 12 weeks, and no residual toxicity from earlier therapy. Adequate reserves of bone marrow, hepatic, and renal functions were also required, as documented by a white blood cell count of greater than or equal to 3.5×10^9/l, an absolute neutrophil count of greater than or equal to 1.5×10^9/l, platelet count of greater than or equal to 150×10^9/l, total serum bilirubin of less than or equal to 1.5 mg/dl, serum transaminases of less than or equal to 2 × upper normal limit unless attributed to liver metastases, and serum creatinine no greater than 1.4 mg/dl. Exclusion criteria were serious chronic illnesses, such as congestive heart failure, unstable angina pectoris, chronic bowel disease, and significant neurologic or psychiatric disease, symptomatic peripheral neuropathy, active or uncontrolled infection, pregnant or nursing women, and earlier abdominal or pelvic radiotherapy.

Safety and efficacy assessment

Within 7 days before treatment started, the patients had their tumor lesions assessed by computed tomography scans and underwent careful and thorough clinical and laboratory investigation, including concomitant medications used within 1 month before study entry.

All patients were seen at outpatient clinics and had hematology and biochemistry tests performed at baseline and every week for the first cycle, on treatment-day appointments thereafter, and again 4 weeks after the last treatment administration. Adverse events were recorded throughout the treatment and were graded according to the National Cancer Institute Common Toxicity Criteria version 2 (*http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20*_4-30-992.pdf). DLT was defined as the occurrence of any of the following: grade of greater than or equal to 3 nonhematological toxicity except nausea/vomiting, grade 4 hematological toxicity of more than 4 days duration without the use of recombinant human

granulocyte colony-stimulating factor (G-CSF), concurrent diarrhea grade of greater than or equal to 2 and neutropenia grade of greater than or equal to 3, and a delay of the next scheduled treatment of greater than or equal to 14 days because of toxicity. Any abnormal outcomes were documented as adverse events and characterized by their relationship with the study drug. The MTD for this study was defined as the highest dose at which at least two of maximum six treated patients suffered DLT because of chemotherapy during the first cycle of treatment. The RSD for this study was defined as one level below the MTD. If treatment was discontinued because of adverse events, or if treatment-related adverse events occurred at the end of treatment, toxicity would be assessed until resolution of the abnormality at weekly intervals.

Although efficacy evaluation was not an endpoint in this phase I study, unidimensionally measurable tumor lesions were assessed for response at every two treatment cycle intervals using the Response Evaluation Criteria for Solid Tumors [10]. Patients were assessable for antitumor activity if disease measurements were recorded for at least 6 weeks after the first dose of therapy.

Results

Patient characteristics

Sixteen patients were enrolled in this trial, whose characteristics are shown in Table 1. There was a wide distribution of the earlier treatments received and tumor types in the patient population of this study. The majority of the patients (75%) had already received chemotherapy earlier, but they maintained (81%) a relatively good performance status of less than or equal to 1. Overall, the trial patients received a total of 38 treatment cycles (median: 2, range: 1–6).

Table 1 Study demographics

Characteristics	Patients	Percentage (%)
Dose level		
1		
5/50/50[a]	4	
−1		
5/40/40[a]	12	
Sex		
Female	4	25
Male	12	75
Age (years)		
Median (range)	61 (39–75)	
Performance status		
0	3	19
1	10	62
2	3	19
Earlier treatment		
Chemotherapy		
None	6	
One line	4	
Two or more lines	6	
Radiotherapy	3	
Tumor types		
Unknown primary	4	
Gastric	4	
Ovarian	2	
Head and neck	2	
Pancreatic	2	
Endometrial	1	
NSCLC	1	
Cycles administered		
Total	38	
Median (range)	2 (1–6)	

NSCLC, non-small cell lung carcinoma.
[a]Dose figures refer to: carboplatin area under the curve (AUC)/irinotecan (mg/m^2)/paclitaxel (mg/m^2).

Table 2 Dose-limiting toxicity during the first cycle of treatment (G = toxicity grade)

	Dose level (mg/m^2)	
Dose-limiting toxicity	5/50/50	5/40/40
Neutropenia grade 4 for greater than or equal to 4 days (plus diarrhea G3)	1	0
Febrile neutropenia	1	1
Diarrhea G3 and neutropenia G3	0	1
Delay for greater than or equal to 14 days	1	0
Occurrence rate	75%	17%

Toxicity–maximum tolerated dose–recommended safe dose

All 16 enrolled patients were assessable for safety analysis. At the introductory dose level, three of the four treated patients developed DLTs, which defined the starting dose as the MTD. According to the dose escalation plan, if two patients experienced DLT in a cohort of six or fewer treated patients, this would be enough to define the MTD. However, in this trial, after the uneventful treatment of the first patient, we allowed parallel involvement of three patients, one per participating center. After MTD definition we continued patient accrual with irinotecan and paclitaxel doses de-escalated one step below MTD. Twelve patients were enrolled at this dose level, and only two of them developed DLT, defining that dose as the RSD (Table 2). We concluded that the MTD of weekly irinotecan and paclitaxel, when given in combination with carboplatin AUC 5 mg*min/ml, was 50 mg/m^2 and the RSD was 40 mg/m^2. DLTs were febrile neutropenia, concurrent neutropenia (G3), and diarrhea (G2 and G3) and prolonged treatment delay due to toxicity (Table 2). Non-DLT toxicity events at this trial were rather infrequent and modest (Table 3). The most common non-DLT G3/G4 toxicity observed during all cycles was leukopenia and neutropenia (18%) and thrombocytopenia and diarrhea (6%), whereas all four patients who completed six treatment cycles also developed grade 1 or 2 alopecia. Nausea and vomiting were fully controlled with administered prophylaxis and did not occur with the regimen. Note that G-SCF support was allowed after the first treatment cycle in patients developing granulocytopenia G3 and higher. For this reason, white blood cell toxicity was not worsened with treatment progressing to completion.

Activity

A complete response of retroperitoneal lymph node metastases, which lasts for more than 3 years, was

achieved in a female patient with metastatic endometrial carcinoma treated at the RSD (Fig. 1). Two other patients had minimal tumor responses documented with symptomatic improvement.

Discussion

In the context of our continuing research interest in patient-friendly low-toxicity chemotherapy, and after our earlier experience with weekly taxanes, we investigated the CIP regimen [11–14]. This triplet combination has already drawn the attention of several clinical research groups during recent years, but these groups focused mainly on investigating 3-weekly dosing schedules. Phase II studies of this triplet combination in ovarian and non-small cell lung cancer found this chemotherapy combination to be very active but also considerably toxic [8,9,15].

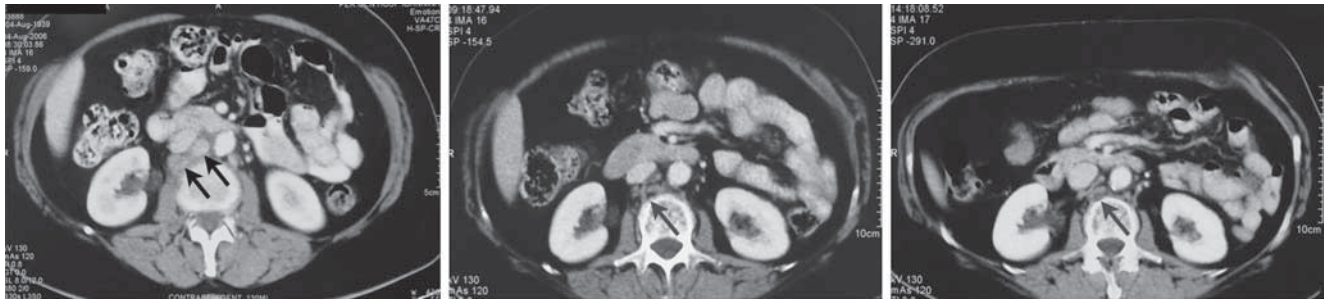
Table 3 Non-dose-limiting toxicity in patients treated at the recommended safe dose during all cycles of treatment

	Patients	
Toxicity	Number	Percentage (%)
Anemia		
Grade 1–2	4	25
Grade 3–4	1	6
Leukopenia		
Grade 1–2	4	25
Grade 3–4	3	18
Neutropenia		
Grade 1–2	4	25
Grade 3–4	3	18
Thrombocytopenia		
Grade 1–2	4	25
Grade 3–4	1	6
Diarrhea		
Grade 1–2	2	12
Grade 3–4	1	6
Neurotoxicity		
Grade 1–2	2	12
Grade 3–4	0	0
Fatigue		
Grade 1–2	2	12
Grade 3–4	0	0

An interesting finding of this study was the admittedly low tolerated doses of weekly irinotecan and paclitaxel that could be safely given in this combination. Similar to our findings, dose-exploring studies of the irinotecan/paclitaxel doublet, without the addition of carboplatin, defined the MTDs of weekly administration of both these drugs, and especially of irinotecan, to be particularly low when compared with single agent administration [16–18]. However, phase II evaluation of the irinotecan/paclitaxel doublet given every 1 or 2 weeks at similar low doses was found to be active in most trials [19–21]. It should be noted that drug potency should be judged by the pharmacodynamic effects produced and not the dose administered [22,23]. In support of this consideration, pharmacokinetic studies have indicated that paclitaxel can suppress the clearance of irinotecan and its metabolites, resulting in higher drug exposure [24,25].

Similar results have also been shown with the docetaxel–irinotecan–carboplatin triplet. Fujita *et al.* [26] concluded from a phase I trial that the triplet could be safely administered at the following doses: carboplatin AUC 5 mg*min/ml on day 1, irinotecan (60 mg/m^2) on days 1 and 8, and docetaxel (30 mg/m^2) on days 1 and 8, every 3 weeks, with G-CSF support. In a phase II study, Pectasides *et al.* [27] evaluated the efficacy and tolerability of carboplatin AUC 2 mg*min/ml in combination with docetaxel (20 mg/m^2) and irinotecan (60 mg/m^2) given weekly (on days 1, 8, and 15, repeated every 5 weeks) with G-CSF support in 50 patients with advanced non-small cell lung cancer. They found this regimen to be highly

Fig. 1



Before treatment start
CA 19-9 = 139

Post third treatment cycle
CA 19-9 = 29

At the end of treatment
CA 19-9 = 28

Complete response of retroperitoneal lymph node metastases in a female patient with metastatic endometrial carcinoma, which continues for more than 3 years. The black arrows in picture (a) show enlarged metastatic lymph nodes and the gray arrows in pictures (b and c) indicate the site of response. CA 19-9 = 139 indicates that the measured blood levels of tumor marker CA 19-9 in patient before the treatment started were 139 U/ml, CA 19-9 = 29 indicates that the measured blood levels of tumor marker CA 19-9 in patient after the third treatment cycle were 29, and CA 19-9 = 28 indicates that the measured blood levels of tumor marker CA 19-9 in patient at the end of the treatment were 28.

effective (overall intent-to-treat response rate 56%, median survival 14.8 months, and actuarial 1-year survival 55%) with moderate, manageable toxicity. Finally, a regimen of weekly cisplatin, irinotecan, and paclitaxel, tested in patients with advanced gastrointestinal cancer, at doses similar to those recommended in our study was also effective [28].

In conclusion, we suggest that paclitaxel (40 mg/m^2) and irinotecan (40 mg/m^2) can safely be administered on days 1 and 8 in combination with carboplatin AUC 5 mg*min/ml given on day 1. The adverse events observed in patients treated at the recommended dose were modest and manageable, and the activity in patients with advanced refractory cancer was noticeable. We also suggest that it is worth considering low dose regimens that are comparably active with standard-dosed regimens of similar combinations because of a potential economic benefit, particularly in countries with limited funds [29,30]. We conclude that the CIP regimen deserves further evaluation at the recommended doses in phase II studies.

Acknowledgement

The authors thank Olga Siarabi for excellent management of the data of this trial.

References

1 DeVita VT Jr, Chu E. A history of cancer chemotherapy. *Cancer Res* 2008; **68**:8643–8653.
2 Gore ME, Preston N, A'Hern RP, Hill C, Mitchell P, Chang J, Nicolson M. Platinum-taxol non-cross resistance in epithelial ovarian cancer. *Br J Cancer* 1995;**71**:1308–1310.
3 Jensen PB, Holm B, Sorensen M, Christensen IJ, Sehested M. In-vitro cross-resistance and collateral sensitivity in seven resistant small-cell lung cancer cell lines: preclinical identification of suitable drug partners to taxotere, taxol, topotecan and gemcitabin. *Br J Cancer* 1997; **75**:869–877.
4 Briasoulis E, Kalofonos H, Bafaloukos D, Samantas E, Fountzilas G, Xiros N, *et al.* Carboplatin plus paclitaxel in unknown primary carcinoma: a phase II Hellenic Cooperative Oncology Group Study. *J Clin Oncol* 2000; **18**:3101–3107.
5 Fountzilas G, Kalofonos HP, Dafni U, Papadimitriou C, Bafaloukos D, Papakostas P, *et al.* Paclitaxel and epirubicin versus paclitaxel and carboplatin as first-line chemotherapy in patients with advanced breast cancer: a phase III study conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol* 2004; **15**:1517–1526.
6 Saltz LB, Spriggs D, Schaaf LJ, Schwartz GK, Ilson D, Kemeny N, *et al.* Phase I clinical and pharmacologic study of weekly cisplatin combined with weekly irinotecan in patients with advanced solid tumors. *J Clin Oncol* 1998; **16**:3858–3865.
7 Socinski MA, Sandler AB, Miller LL, Locker PK, Hanover CK, Elfring GL, *et al.* Phase I trial of the combination of irinotecan, paclitaxel, and carboplatin in patients with advanced non-small cell lung cancer. *J Clin Oncol* 2001; **19**:1078–1087.
8 Socinski MA, Sandler AB, Israel VK, Gillenwater HH, Miller LL, Locker PK, *et al.* Phase II trial of irinotecan, paclitaxel and carboplatin in patients with previously untreated Stage IIIB/IV non-small cell lung carcinoma. *Cancer* 2002; **95**:1520–1527.
9 Escobar PF, Markman M, Rose P, Zanotti K, Webster K, Belinson J. Phase 2 trial of carboplatin, paclitaxel, and irinotecan in ovarian, fallopian tube, and primary peritoneal cancers. *Gynecol Oncol* 2004; **92**:192–196.
10 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**:205–216.
11 Briasoulis E, Pentheroudakis G, Karavasilis V, Tzamakou E, Rammou D, Pavlidis N. Weekly paclitaxel combined with pegylated liposomal doxorubicin (Caelyx) given every 4 weeks: dose-finding and pharmacokinetic study in patients with advanced solid tumors. *Ann Oncol* 2004; **15**:1566–1573.
12 Briasoulis E, Karavasilis V, Anastasopoulos D, Tzamakou E, Fountzilas G, Rammou D, *et al.* Weekly docetaxel in minimally pretreated cancer patients: a dose-escalation study focused on feasibility and cumulative toxicity of long-term administration. *Ann Oncol* 1999; **10**:701–706.
13 Briasoulis E, Karavasilis V, Tzamakou E, Haidou C, Piperidou C, Pavlidis N. Pharmacodynamics of non-break weekly paclitaxel (Taxol) and pharmacokinetics of Cremophor-EL vehicle: results of a dose-escalation study. *Anticancer Drugs* 2002; **13**:481–489.
14 Briasoulis E, Pappas P, Puozzo C, Tolis C, Fountzilas G, Dafni U, *et al.* Dose-ranging study of metronomic oral vinorelbine in patients with advanced refractory cancer. *Clin Cancer Res* 2009; **15**:6454–6461.
15 Stinchcombe TE, Morris DE, Lee CB, Moore DT, Hayes DN, Halle JS, *et al.* Induction chemotherapy with carboplatin, irinotecan, and paclitaxel followed by high dose three-dimension conformal thoracic radiotherapy (74 Gy) with concurrent carboplatin, paclitaxel, and gefitinib in unresectable stage IIIA and stage IIIB non-small cell lung cancer. *J Thorac Oncol* 2008; **3**:250–257.
16 Rushing DA. Phase I/II study of weekly irinotecan and paclitaxel in patients with SCLC. *Oncology (Williston Park)* 2000; **14** (**7 Suppl 5**):63–66.
17 Hotta K, Ueoka H, Kiura K, Tabata M, Kuyama S, Satoh K, *et al.* A phase I study and pharmacokinetics of irinotecan (CPT-11) and paclitaxel in patients with advanced non-small cell lung cancer. *Lung Cancer* 2004; **45**:77–84.
18 Yamada K, Ikehara M, Tanaka G, Nomura I, Oshita F, Noda K. Dose escalation study of paclitaxel in combination with fixed-dose irinotecan in patients with advanced non-small cell lung cancer (JCOG 9807). *Oncology* 2004; **66**:94–100.
19 Stathopoulos GP, Dimitroulis J, Antoniou D, Katis C, Tsavdaridis D, Armenaki O, *et al.* Front-line paclitaxel and irinotecan combination chemotherapy in advanced non-small-cell lung cancer: a phase I-II trial. *Br J Cancer* 2005; **93**:1106–1111.
20 Oshita F, Saito H, Yamada K, Noda K. Phase II study of paclitaxel and irinotecan chemotherapy in patients with advanced non-small cell lung cancer. *Am J Clin Oncol* 2007; **30**:358–360.
21 Murren JR, Peccerillo K, DiStasio SA, Li X, Leffert JJ, Pizzorno G, *et al.* Dose escalation and pharmacokinetic study of irinotecan in combination with paclitaxel in patients with advanced cancer. *Cancer Chemother Pharmacol* 2000; **46**:43–50.
22 Rowinsky EK. The taxanes: dosing and scheduling considerations. *Oncology (Williston Park)* 1997; **11** (**3 Suppl 2**):7–19.
23 Gonzalez-Angulo AM, Hortobagyi GN. Optimal schedule of paclitaxel: weekly is better. *J Clin Oncol* 2008; **26**:1585–1587.
24 Asai G, Yamamoto N, Kurata T, Tamura K, Uejima H, Nakagawa K, Fukuoka M. Phase I and pharmacokinetic study of combination chemotherapy using irinotecan and paclitaxel in patients with lung cancer. *J Thorac Oncol* 2006; **1**:226–230.
25 Kasai T, Oka M, Soda H, Tsurutani J, Fukuda M, Nakamura Y, *et al.* Phase I and pharmacokinetic study of paclitaxel and irinotecan for patients with advanced non-small cell lung cancer. *Eur J Cancer* 2002;**38**:1871–1878.
26 Fujita A, Ohkubo T, Hoshino H, Takabatake H, Tagaki S, Sekine K. Phase I study of carboplatin, irinotecan and docetaxel on a divided schedule with recombinant human granulocyte colony stimulating factor support in patients with stage IIIB or IV non-small cell lung cancer. *Anticancer Drugs* 2002; **13**:505–509.
27 Pectasides D, Visvikis A, Kouloubinis A, Glotsos J, Bountouroglou N, Karvounis N, *et al.* Weekly chemotherapy with carboplatin, docetaxel and irinotecan in advanced non-small cell lung cancer: a phase II study. *Eur J Cancer* 2002; **38**:1194–1200.
28 Tew WP, Radovich D, O'Reilly E, Schwartz G, Schrag D, Saltz LB, *et al.* Phase I trial of weekly cisplatin, irinotecan and paclitaxel in patients with advanced gastrointestinal cancer. *Invest New Drugs* 2009; **27**:366–373.
29 Bocci G, Tuccori M, Emmenegger U, Liguori V, Falcone A, Kerbel RS, Del Tacca M. Cyclophosphamide-methotrexate metronomic chemotherapy for the palliative treatment of metastatic breast cancer. A comparative pharmacoeconomic evaluation. *Ann Oncol* 2005; **16**:1243–1252.
30 Obralic N, Beslija S. How to make the best use of limited resources in breast cancer treatment–experiences in Bosnia & Herzegovina. *J Buon* 2006; **11**:21–29.