

DOCETAXEL AND IRINOTECAN AS FIRST-LINE CHEMOTHERAPY IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER : A PILOT STUDY

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ABSTRACT • AIMS : The aim of this study is to evaluate the activity and toxicity of the combination docetaxel and irinotecan as first-line therapy for advanced non-small-cell lung cancer (NSCLC).

MATERIALS & METHODS : Twenty-two chemotherapy-naïve patients with stage IIIB with pleural effusion or stage IV NSCLC received irinotecan 50 mg/m² on days 1, 8, and 15, and docetaxel 50 mg/m² on day 2, every 28 days until disease progression.

RESULTS : Median follow-up was 10 months (range : 2-28 months). The overall response rate was 36.4% (8/22 patients ; 95% confidence interval : 16.8-56.0), with no complete responses. Median time to disease progression was 5 months (range : 1-24 months) and median overall survival was 10 months (range : 2-28). Grade 3-4 diarrhea was observed in 2 patients (9.1%). Grade 3-4 neutropenia occurred in 2 patients (9.1%) : 1 episode of febrile neutropenia in one patient, and 1 death due to neutropenic sepsis in another patient. One patient received transfusion for grade 4 anemia.

CONCLUSIONS : Irinotecan showed a moderate response rate and overall survival of clinical interest. Diarrhea was the main toxicity. This regimen may be suitable for patients unable to tolerate cisplatin-based therapy, for elderly and/or for patients with poor performance status, and should be investigated in a larger trial.

RÉSUMÉ • OBJECTIF : Le but de l'étude est d'évaluer l'efficacité et la toxicité de l'association docetaxel et irinotecan dans le traitement en première ligne des tumeurs bronchiques non à petites cellules.

MATÉRIELS & MÉTHODES : Vingt-deux patients porteurs d'une tumeur pulmonaire non à petites cellules stade IIIB avec effusion pleurale ou stade IV ont reçu, chaque 28 jours, irinotecan 50 mg/m² les 1^{er}, 8^e, et 15^e jours, avec docetaxel 50 mg/m² le 2^e jour, jusqu'à la progression tumorale.

RÉSULTATS : Après un suivi moyen de 10 mois (extrêmes : 2-28 mois), 36,4% ont présenté une réponse objective (8/22 patients, intervalle de confiance de 95% : 16,8-56). Il n'y a pas eu de réponse complète. La durée moyenne du temps de progression était de 5 mois (extrêmes : 1-24 mois) et celle de la survie de 10 mois (extrêmes : 2-28 mois). Une diarrhée grade 3-4 a été observée chez 2 patients (9,1%), ainsi qu'une neutropénie grade 3-4 chez 2 patients (9,1%) dont un a présenté une neutropénie fébrile et le second est décédé d'un choc septique. Un patient a été transfusé pour anémie grade 4.

CONCLUSIONS : Irinotecan a offert une réponse objective modérée et une moyenne de survie intéressante. La diarrhée était sa toxicité majeure. Cette association peut convenir aux patients âgés et/ou à ceux qui ont un état général altéré ou qui ne tolèrent pas la cisplatine. Elle nécessite des investigations plus amples.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related death worldwide with an estimated 900 000 new cases diagnosed each year in men and 330 000 in women [1]. Non-small-cell lung cancer (NSCLC) represents about 75% of all lung cancer cases [2]. Historically, NSCLC has been considered a chemotherapy-resistant disease and the use of chemotherapy in patients with

advanced NSCLC was controversial until recently [3]. Four meta-analyses of chemotherapy for advanced NSCLC have now shown an absolute survival benefit, with a modest improvement in median survival, compared with best supportive care alone [4-7].

Cisplatin-based therapy is the most widely used chemotherapy regimen and is currently recommended to prolong survival, prevent or reduce tumor-related symptoms, and maintain the quality of life for patients with

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advanced NSCLC who have a good performance status [8]. Despite the poor survival of patients with advanced (stage IIIB with pleural effusion or stage IV) NSCLC, the introduction of new chemotherapeutic agents has improved survival and quality of life with reduced toxicity compared with older cisplatin-based therapies [9]. The development of newer drugs with different mechanisms of action has raised expectations for further improvement in survival outcomes. Significant activity (response rates > 15%) has been observed with single non-platinum agents of chemotherapy, such as ifosfamide, gemcitabine, vinorelbine and, recently, the taxanes (docetaxel and paclitaxel) [10-14].

In particular, single-agent docetaxel has demonstrated extensive activity in phase II studies in NSCLC, with overall response rates of 19-54% [15-20]. For example, in a multicenter trial 43 non-pretreated patients with advanced NSCLC were treated with docetaxel. The overall response rate was 23%, with one complete response and seven partial responses. Stable disease was found in 16 patients [15]. In another study by Goh et al. [19], the response rate was 34% in 35 patients with no complete response observed [19]. Indeed, the response rates, median and one-year survival achieved with docetaxel in combination with carboplatin or cisplatin were not substantially better than those seen in phase II studies of docetaxel alone [21].

Irinotecan, a topoisomerase I inhibitor, has also shown good activity as a single agent in both previously treated and chemotherapy-naïve patients with NSCLC, with overall response rates in the range of 15-34% [19, 22].

Phase I data suggest that combination therapy with docetaxel and irinotecan is a feasible treatment option for NSCLC and advanced solid tumors [23-24]. In phase II studies docetaxel and irinotecan were given as first-line chemotherapy for patients with locally advanced or metastatic NSCLC. The preliminary analysis showed only one partial response (7%) and no complete responses. However, 5 patients experienced stable disease (36%) for a clinical benefit of 43%. The median survival time was 11 months. This combination chemotherapy was well tolerated with only few grade 3/4 toxicities [25]. Given the suboptimal activity and considerable toxicity associated with cisplatin-based NSCLC regimens, and given the fact that both irinotecan and docetaxel are effective as single agents in NSCLC, a pilot study was initiated to test the efficacy and toxicity of a two-drug combination regimen of docetaxel and irinotecan as first-line therapy in patients with advanced NSCLC.

MATERIALS AND METHODS

Eligibility

Patients with histologically or cytologically confirmed unresectable (stage IIIB with pleural effusion) or metastatic (stage IV) NSCLC with the presence of at least one measurable or evaluable lesion were eligible

for the study. Other inclusion criteria were : Eastern Cooperative Oncology Group, performance status (PS) 2 ; age 75 and >18 years ; absolute neutrophil count 1500/mm³ ; platelet count 100 000/mm³ ; serum creatinine 1.5 mg/dl ; liver function tests 5 times the upper limit of normal. Patients who had received prior chemotherapy were excluded. Previous palliative radiotherapy to symptomatic metastases was allowed, provided that these lesions were not considered for tumor response assessment. Patients with a history of previous or concomitant neoplasm, other than epithelial skin tumors or *in situ* carcinoma of the uterine cervix, were ineligible.

All patients gave written informed consent and the study was submitted and approved by the Scientific Committee for Research Institutional Review Board at the American University of Beirut Medical Center, Lebanon.

Treatment

The regimen consisted of irinotecan 50 mg/m² (30-minute intravenous [IV] infusion) on days 1, 8, and 15 and docetaxel 50 mg/m² (1-hour IV infusion) on day 2. The cycles were repeated every 4 weeks on an outpatient basis. Chemotherapy was preceded by dexamethasone 8 mg IV once daily and 5-HT₃ receptor antagonists (ondansetron) 8 mg IV once daily on days 1 and 2.

Doses of irinotecan and docetaxel were reduced and cycles delayed as follows : chemotherapy was delayed by one week in the event of a neutrophil count < 1500/mm³ and/or platelet count < 100 000/mm³ on day 1. On day 8, if the neutrophil count was > 1500/mm³ and the platelet count was > 100 000/mm³, full doses of study medication were administered ; if the neutrophil count was 500-1499/mm³ and/or the platelet count was 50 000-99 000/mm³, 75% of the dose was administered ; if the neutrophil count was < 500/mm³ and/or the platelet count was < 50 000/mm³, chemotherapy was delayed for a second week. If a cycle delay lasted more than two weeks and/or hematologic toxicity was persistent, the patient was withdrawn from the study. If grade 4 diarrhea occurred, doses of both drugs were reduced by 25% in subsequent cycles, even if normal values for neutrophils and platelets were found on day 1.

All patients received treatment for a maximum of eight cycles unless there was disease progression or unacceptable toxicity. Responders with stage IIIB disease were not allowed to receive local treatment (surgery and/or radiotherapy) after response to chemotherapy.

CLINICAL ASSESSMENT

Pretreatment evaluations included a complete history and physical examination, complete blood cell count and blood chemistry, chest X-ray, bone scan, and chest and abdominal computed tomography (CT) scans. Evaluation of complete blood cell count was performed weekly ; serum liver function and creatinine were measured before each chemotherapy cycle.

Tumor response was evaluated using World Health Organization (WHO) criteria and was assessed after two, four, six, and eight cycles with a CT scan. Patients who received at least one cycle of chemotherapy were considered evaluable for response. Any patient who died early after the first cycle either due to chemotherapy toxicity or disease progression was considered a non-responder. A complete response was defined as the total disappearance of all objective disease. A partial response was defined as 50% reduction from baseline in the size of all measurable tumor areas (as measured by the sum of the products of the longest perpendicular diameters of all measurable lesions) without the appearance of any new disease and no increase > 25% in the product of the bi-dimensional measurements of an individual tumor. Progressive disease was defined as an increase of 25% in the size of one or more measurable lesions or the appearance of any new lesion. Stable disease was defined as an evaluation that failed to qualify for any of the responses described above. In-house reviewers in each center performed the evaluation of responses.

Toxicity, graded using WHO criteria, was evaluated weekly. All patients were evaluable for toxicity by frequent clinical assessment and complete blood cell count every week, and serum creatinine and liver function test before each chemotherapy cycle.

Statistical analyses

The primary endpoints were objective response rate and degree of toxicity. Secondary endpoints were median time to progression and overall survival. Overall survival was measured from the date of entry to the date of death or last follow-up evaluation. Time to progression was calculated from the start of treatment to the first documented occurrence of disease progression. Time-to-event data were estimated by the Kaplan-Meier product-limit method.

RESULTS

Patients

Between January 2001 and March 2003, 22 patients with stage IIIB/IV NSCLC were enrolled in the study. Pretreatment patients' characteristics are summarized in Table I. Of 22 patients, 3 patients did not complete the study treatment. One patient had neutropenic sepsis after the second cycle and eventually died of septic shock before evaluation for response; 2 patients were withdrawn from the study after the first cycle – one had progressive disease and died after the first cycle and one refused to continue chemotherapy after the first cycle.

A total of 88 cycles was administered and the median number of cycles per patient was 4 (range : 1-8); one (4.54%) patient received eight cycles, 7 (31.8%) patients received six cycles, 2 (9.1%) patients received five cycles, 2 (9.1%) patients received four cycles, 2 (9.1%) patients received three cycles, 6 (27.3%) patients received two cycles, and 2 (9.1%) patients received one cycle.

TABLE I
PRETREATMENT PATIENTS' CHARACTERISTICS

CHARACTERISTIC	Value
TOTAL NO. OF PATIENTS	22
MEDIAN AGE [range], years	68 [47-75]
SEX, N (%)	
Male	20 (90.9)
Female	2 (9.1)
ECOG PERFORMANCE STATUS, N (%)	
0-1	16 (72.7)
2	6 (27.3)
HISTOLOGY, N (%)	
Squamous cell	7 (31.8)
Adenocarcinoma	9 (40.9)
Poorly differentiated large cell carcinoma	6 (27.3)
STAGE, N (%)	
IIIB	8 (36.4)
IV	14 (63.6)

ECOG : Eastern Cooperative Oncology Group

Tumor response and survival

All patients were evaluated for response by intent-to-treat analysis. Eight partial responses and no complete responses were observed, giving an overall response rate of 36.4% (95% confidence interval : 16.8-56.0) (Table II). Seven (31.8%) patients had stable disease. In March 2004, 4/22 (18.2%) patients were still alive. Median follow-up time was 10 months (range : 2-28 months). Median time to progression was 5 months (range : 1-24 months). Median overall survival was 10 months (range : 2-28) (Figure 1). The 1- and 2-year survival rates were 18.2% and 13.6%, respectively.

Toxicity

Toxicity was evaluated in all 22 patients for a total of 88 cycles. One patient with grade 4 anemia received transfusion (6 units of packed red blood cells). One patient with grade 4 febrile neutropenia died owing to neutropenic sepsis. The only grade 3-4 non-hematologic toxicity reported was diarrhea. No cases of grade 3-4 renal toxicity were reported. Toxicities are reported in Table III.

TABLE II
TUMOR RESPONSES (N = 22)

Response	No. of patients (%)
Complete response	0
Partial response	8 (36.4)
Stable disease	7 (31.8)
Disease progression	7 (31.8)
Non-evaluable patients	0

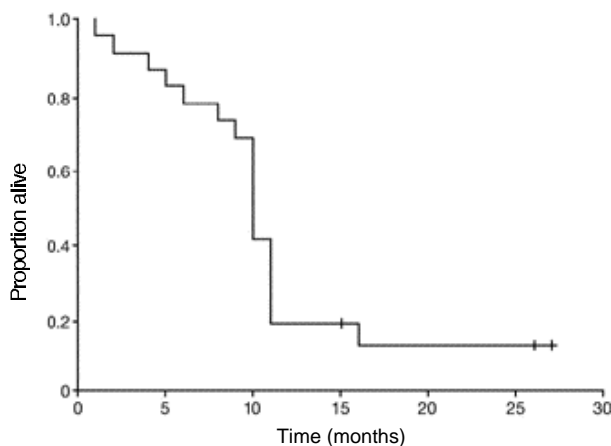


FIGURE 1
Kaplan-Meier curve of the overall survival of patients.

DISCUSSION

This study was designed to evaluate the efficacy and toxicity of a non-cisplatin doublet chemotherapy, docetaxel-irinotecan, in chemotherapy-naïve patients with advanced NSCLC. The activity of the docetaxel was reported in several phase II studies with good tolerability when given to patients with NSCLC [15-20]. When both docetaxel and irinotecan were given to patients with NSCLC, the results were promising [25-27]. The rationale of this study was based on phase I studies which established the feasibility and efficacy of docetaxel-irinotecan combination [24]. Accrual was slow due to the low rate of referrals in patients with advanced stage NSCLC, with only 22 patients entered after 26 months. The initial planned accrual was 40 patients.

This study demonstrated acceptable clinical activity of the docetaxel-irinotecan combination, with an overall response rate of 36.4% in patients with stage IIIB/IV disease. These results are particularly interesting if one considers that 63.6% of the population had stage IV disease and 27.3% had a PS = 2. Moreover, the response evaluation was performed on an intent-to-treat basis, 3/22 (13.6%) patients did not complete study treatment, the first patient died from neutropenic sepsis, the second patient had progressive disease, and the third patient refused further chemotherapy. The overall response rate with docetaxel-irinotecan in our study was similar to that seen in phase II studies of these agents when used alone [28]. In comparison with a large randomized phase III trial [29] which reported median survival times of 7.9 months, our study obtained a relatively longer median survival time (10.0 months); however, the one-year survival rates were 18.2%, which is lower than that seen with cisplatin-based therapy 33% [29].

Efficacy was comparable to other commonly used regimens [29]. The nonhematologic and hematologic toxicity profile in our study was tolerable indicating that the docetaxel-irinotecan combination is suitable for

TABLE III
INCIDENCE OF TOXICITIES (N = 22)

TOXICITY	No. of patients (%)		
	WHO grade		
	2	3	4
Neutropenia	0	1 (4.5)	1 (4.5)
Anemia	0	0	1 (4.5)
Diarrhea	3 (13.6)	1 (4.5)	1 (4.5)
Nausea/Vomiting	2 (9.1)	0	0
Mucositis	1 (4.5)	0	0
Neurotoxicity	1 (4.5)	0	0

WHO : World Health Organization

administration on an outpatient basis. Diarrhea was the main toxicity. The incidence of grade 3-4 anemia and neutropenia was fairly low despite the fact that neither prophylactic granulocyte colony-stimulating factor nor erythropoietin was used in this study, although one patient with grade 4 neutropenia died from sepsis. The low percentage of patients experiencing grade 3-4 toxicity can in part be explained by the fact that a low dose of docetaxel (50 mg/m²) was given with a longer interval between doses (28-day cycle).

The interest in using docetaxel or irinotecan as a component in combination therapy for advanced NSCLC is demonstrated by the recent study by Rocha Lima et al. [30] that reported results of chemotherapy with gemcitabine plus irinotecan or docetaxel in 80 chemo-naïve patients with stage IIIB/IV NSCLC (20% of whom had stage IV disease) [30]. Although higher doses of docetaxel and irinotecan were used by Rocha Lima et al. [30] than in our study – docetaxel was given in a dose of 50 mg/m² and irinotecan was given in a dose of 100 mg/m², both on days 1 and 8, every 21 days – the response rates obtained were markedly lower than those reported here (12.8% in the gemcitabine-irinotecan arm and 23.1% in the gemcitabine-docetaxel arm versus 36.4% with docetaxel-irinotecan). This may suggest a synergism between docetaxel and irinotecan that is not obtained when either of them is combined with gemcitabine.

Studies showing a high response rate with non-cisplatin-based therapy include a recent phase II trial of weekly docetaxel plus capecitabine in 39 patients with advanced NSCLC in which the response rate reached 53%, median duration of response was 6.2 months, and one-year survival was 56.4% [31]. However, this combination was associated with moderate to severe toxicity. Another phase II trial compared docetaxel plus cisplatin and docetaxel plus irinotecan for advanced NSCLC. Although both regimens had different toxicity profiles, there was no significant difference in survival [32].

The role of docetaxel-irinotecan in the management of advanced NSCLC cannot be established from this

small pilot study alone, although the efficacy results and survival data obtained are encouraging. Furthermore, docetaxel-irinotecan in combination may be particularly useful in patients who have experienced unacceptable toxicities (such as severe vomiting or neurotoxicity) with platinum-based regimens and for those who will be susceptible to platinum-related toxicity (e.g. patients with pre-existing renal disease). The toxicity profile seen with the docetaxel-irinotecan regimen may also make it suitable for patients of advanced age and/or those likely to have poor tolerance to chemotherapy. Further studies with larger numbers of patients are needed to define better the clinical benefits with this combination.

The survival rates in the current study are low – perhaps because we included 14 (63.6%) patients with stage IV NSCLC. It is also worth noting that 6 (27.3%) patients had a PS = 2, which may have also affected survival. The doses and schedule were based on the phase I trial undertaken by Masuda et al. [24]. Other phase II trials [30] using docetaxel as part of their chemotherapy regimens administered docetaxel more frequently than we did (our study used a 28-day cycle). Hence, the low survival rate in our study may in part be due to the infrequent administration of docetaxel.

In conclusion, considering the substantially poor prognosis of our patient population, the tumor response and survival results of this small pilot study suggest that the docetaxel-irinotecan combination is feasible as first-line therapy for patients with advanced NSCLC and should be considered for further investigation in larger phase II and III studies.

REFERENCES

1. Stewart BW, Kleihues P. World Cancer Report. International Agency for Research on Cancer. Lyon : IARC Press, 2003 : 182-7.
2. Cortes-Funes H. New treatment approaches for lung cancer and impact on survival. *Semin Oncol* 2002 ; 29 : 26-9.
3. Hansen HH. Is there a role for chemotherapy of non-small-cell lung cancer ? *Ann Oncol* 1995 ; 6 : 79-82.
4. Grilli R, Oxman AD, Julian JA. Chemotherapy for advanced non-small-cell lung cancer : how much benefit is enough ? *J Clin Oncol* 1993 ; 11 : 1866-72.
5. Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F. Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. *Chest* 1994 ; 106 : 861-5.
6. Non-Small-Cell Lung Cancer Collaborative Group. Chemotherapy in non-small-cell lung cancer : a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ* 1995 ; 311 : 899-909.
7. Souquet PS, Chauvin F, Boisse JP et al. Polychemotherapy in advanced non-small-cell lung cancer : a meta-analysis. *Lancet* 1993 ; 342 : 19-21.
8. Manegold C. Chemotherapy for advanced non-small-cell lung cancer : standards. *Lung Cancer* 2001 ; 34 : S165-S170.
9. Bunn PA Jr. Chemotherapy for advanced non-small-cell lung cancer: who, what, when, why ? *J Clin Oncol* 2002 ; 20 : S23-S33.
10. Anderson H, Lund B, Bach F, Thatcher N, Walling J, Hansen HH. Single-agent activity of weekly gemcitabine in advanced non-small-cell lung cancer : a phase II study. *J Clin Oncol* 1994 ; 12 : 1821-6.
11. Depierre A, Lemarie E, Dabouis G, Garnier G, Jacoulet P, Dalphin JC. A phase II study of Navelbine (vinorelbine) in the treatment of non-small-cell lung cancer. *Am J Clin Oncol* 1991 ; 14 : 115-19.
12. Fossella FV, Lee JS, Murphy WK et al. Phase II study of docetaxel for recurrent or metastatic non-small-cell lung cancer. *J Clin Oncol* 1994 ; 12 : 1238-44.
13. Hainsworth JD, Thompson DS, Greco FA. Paclitaxel by 1-hour infusion : an active drug in metastatic non-small-cell lung cancer. *J Clin Oncol* 1995 ; 13 : 1609-14.
14. Johnson DH. Overview of ifosfamide in small-cell and non-small-cell lung cancer. *Semin Oncol* 1990 ; 17 : 24-30.
15. Cerny T, Kaplan S, Pavlidis N et al. Docetaxel (Taxotere) is active in non-small-cell lung cancer : a phase II trial of the EORTC Early Clinical Trials Group (ECTG). *Br J Cancer* 1994 ; 70 : 384-7.
16. Fossella FV, Lee JS, Berille J, Hong WK. Summary of phase II data of docetaxel (Taxotere), an active agent in the first- and second-line treatment of advanced non-small-cell lung cancer. *Semin Oncol* 1995 ; 22 : 22-9.
17. Fossella FV, Lee JS, Shin DM et al. Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small-cell lung cancer. *J Clin Oncol* 1995 ; 13 : 645-51.
18. Francis PA, Rigas JR, Kris MG et al. Phase II trial of docetaxel in patients with stage III and IV non-small-cell lung cancer. *J Clin Oncol* 1994 ; 12 : 1232-7.
19. Goh BC, Lehnert M, Lim HL et al. Phase II trial of docetaxel in Asian patients with inoperable stage III non-small-cell lung cancer. *Acta Oncol* 2000 ; 39 : 225-9.
20. Rigas JR. Docetaxel in stage III and IV non-small-cell lung cancer. *Eur J Cancer* 1995 ; 31 : S18-S20.
21. Gandara DR, Edelman MJ, Lau D. The emerging role of docetaxel (Taxotere) in advanced non-small-cell lung cancer. *Semin Oncol* 1999 ; 26 : 3-7.
22. Fukuoka N, Niitani H, Suzuki A et al. A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. *J Clin Oncol* 1992 ; 10 : 16-20.
23. Couteau C, Risse M, Ducreux M et al. Phase I and pharmacokinetic study of docetaxel and irinotecan in patients with advanced solid tumors. *J Clin Oncol* 2000 ; 18 : 3545-52.
24. Masuda N, Negoro S, Kudoh S et al. Phase I and pharmacologic study of docetaxel and irinotecan in advanced non-small-cell lung cancer. *J Clin Oncol* 2000 ; 18 : 2996-3003.
25. Raez LE, Rosado MF, Santos ES, Reis IM. Irinotecan and docetaxel as first line chemotherapy in patients with stage IIIB/IV non-small-cell lung cancer – experience from a prematurely closed phase II study. *Lung Cancer* 2004 ; 45 : 131-2.
26. Pectasides D, Pectasides M, Farmakis D et al. Comparison of docetaxel and docetaxel-irinotecan combination as second-line chemotherapy in advanced non-small-cell lung cancer : a randomized phase II trial. *Ann Oncol* 2005 ; 16 : 294-9.

27. Ziotopoulos P, Androulakis N, Mylonaki E et al ; for the Lung Cancer Committee of the Hellenic Oncology Research Group (HORG). Front-line treatment of advanced non-small-cell lung cancer with irinotecan and docetaxel : a multicentre phase II study. Lung Cancer 2005 ; 50 : 115-22.
28. Adjei AA, Argiris A, Murren JR. Docetaxel and irinotecan, alone and in combination, in the treatment of non-small-cell lung cancer. Semin Oncol 1999 ; 26 : 32-40.
29. Schiller JH, Harrington D, Belani CP et al ; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002 ; 346 : 92-8.
30. Rocha Lima CM, Rizvi NA, Zhang C et al ; Cancer Leukemia Group B. Randomized phase II trial of gemcitabine plus irinotecan or docetaxel in stage IIIB or stage IV NSCLC. Ann Oncol 2004 ; 15 : 410-18.
31. Han JY, Lee DH, Kim HY et al. A phase II study of weekly docetaxel plus capecitabine for patients with advanced non-small-cell lung carcinoma. Cancer 2003 ; 98 : 1918-24.
32. Yamamoto N, Fukuoka M, Negoro SI et al. Randomised phase II study of docetaxel/cisplatin vs docetaxel/irinotecan in advanced non-small-cell lung cancer : a West Japan Thoracic Oncology Group Study (WJTOG9803). Br J Cancer 2004 ; 90 : 87-92.

دوسيتكسيل وايرينوتيكان لمعالجة اولية كيميائية للمصابين بسرطان متقدم ليس ذو خلايا صغيرة. دراسة ارشادية موجز: الموضوع - غاية الدراسة تقييم فعالية وسمية دو سيتكسيل وايرونوتيكان لمعالجة اولية للاورام القصية ليست ذات الخلايا الصغيرة.

المرضى والطرق - ٢٢ مريضا مصابون باورام رئوية ليست ذات الخلايا الصغيرة بمرحلة B III مع انضباب جنبي او بالمرحلة IV ، اعطوا ايرينوتيكان ٥٠ ملغ/م² لايام ١،٨ - ١٥ بالاشترار مع دوسيتكسيل ٥٠ ملغ/م² اليوم الثاني كل ٢٨ يوما حتى تقدم الورم.

النتائج - بعد متابعة ١٠ شهور (٢ - ٢٨ شهرا) ايدى ٣٦،٤٪ جوابا موضوعيا (٢٢/٨) مريضا بفترة ثقة ٩٥٪ : ١٦،٨ - ٥٦). لم نشاهد نتيجة كاملة. المدة الوسطى للترقي كانت ٦ شهور (١ - ٢٤ شهرا) ومدة الحياة ١٠ شهورا (٢ - ٢٨ شهرا)، لوحظ اسهال بدرجة ٤ عند مريضين (٩،١٪) ونقص للخلايا العدلة بدرجة ٣ - ٤ عند مريضين (٩،١) ايدى واحد منهما حمى مع نقص الخلايا العدلة وتوفي الثاني بصدمة انتانية واجري اعطاء الدم لمصاب بفقر الدم بدرجة ٤.

الخلاصة - ايرينوتيكان اعطى جوابا موضوعيا والحياة وسطيا كانت مفيدة. كان الاسهال بسبب شدة الانسمام. هذا الاشرار ذو فائدة عند المسنين وبحالة سيئة متقدمة او عند الذين لا يتحملون سيسبلاتين، وهذا يتطلب ابحاثا اكثر سعة.