A Retrospective Analysis of Non-platinum-based First- and Second-line Chemotherapy in Patients with Advanced Non-small Cell Lung Cancer

ATHANASIOS KOTSAKIS, DORA HATZIDAKI, LAMBROS VAMVAKAS, NIKOLAOS VARDAKIS, ANTONIA KALYKAKI, VASILIKI BOZIONELOU, NIKOLAOS ANDROULAKIS, KOSTAS KALBAKIS, ZACHARENIA SARIDAKI, VASSILIS GEORGOULIAS and SOPHIA AGELAKI

Hellenic Oncology Research Group (HORG), 11470 Athens, Greece

Abstract. *Background: Platinum-based chemotherapy represents the standard of care for advanced non-small cell lung cancer (NSCLC) while non-platinum-based regimens are frequently administered in patients with relapse. A retrospective analysis of the sequence administration of these regimens in the first- and second-line setting was performed. Patients and Methods: The records of patients enrolled in the Hellenic Oncology Research Groups's randomized advanced NSCLC trials from February 1997 to September 2006 were retrospectively reviewed. The efficacy of non-platinum-based chemotherapy administered as first- or second-line treatment (n=94, cohort A) was compared to that of non-platinum-based first-line followed by platinum-based second-line chemotherapy (n=267, cohort B), and the reverse sequence (n=123, cohort C). Results: The objective response rate (ORR) to first-line chemotherapy was higher in cohort C compared to cohort A (45.5% vs. 25.5%, respectively, p=0.002) and cohort B (45.5% vs. 21.3%, p=0.0001). The ORR to second-line therapy was 17%, 13.1% (p=0.349) and 7.3% (p=0.027) in cohorts A, B and C, respectively. Time to progression and the overall survival were comparable among the three cohorts in both first- and second line therapy. Conclusion: Platinum-based first-line chemotherapy improved response rate compared to non-platinum-based regimens; however, the overall survival was comparable, irrespective of the sequence administration of these regimens is the first- and second-line setting.*

About 80% of patients with non-small cell lung cancer (NSCLC) are diagnosed with advanced disease. Moreover, a significant percentage of patients with local or locoregional disease will develop metastatic disease. For these patients treatment is of palliative intent aiming in the prolongation of patients' survival and in the improvement of their quality of life (QOL).

Several meta-analyses have demonstrated a significant benefit in terms of response rate, overall survival (OS) and QOL associated with the use of chemotherapy in patients with advanced disease (1-3). Platinum-based chemotherapy represents the cornerstone of treatment for these patients. During the last decade, new agents such as paclitaxel, docetaxel, gemcitabine, vinorelbine, pemetrexed and irinotecan have shown activity against NSCLC. Randomized trials evaluating the combination of these agents with cisplatin and carboplatin demonstrated comparable results in terms of clinical efficacy. Despite the large number of trials, no particular regimen has emerged as the best option for the treatment of advanced disease (4).

The use of platinum-based regimens is associated with significant toxicity, primarily anemia, nephrotoxicity, neurotoxicity, nausea and vomiting. The necessity to reduce toxicity led to the development of non-platinum-containing combinations. Individual studies comparing non-platinum- to platinum-based regimens, demonstrated comparable efficacy results in terms of objective response, time to tumor progression and overall survival (OS) rates. However, several meta-analyses demonstrated a slight, but statistically significant, reduction in the risk of death for patients receiving front-line platinum- compared to non-platinum-containing regimens (5-7). Thus, the American Society of Clinical Oncology (ASCO) guidelines recommend that first-line therapy should consist of platinum-based doublets, whereas non-platinum-containing combinations should be considered for patients who are not fit to receive platinum agents (8).

Most of the patients treated with first-line chemotherapy will eventually experience relapse, usually within 3-6 months from the initiation of treatment. Approximately 40-50% of these patients subsequently receive second-line chemotherapy (10).

Correspondence to: A. Kotsakis, MD, Ph.D., Department of Medical Oncology, University General Hospital of Heraklion, PO Box 1350, 71110 Heraklion, Crete, Greece. Tel: +30 2810392783, Fax: +30 2810392857, e-mail: georgsec@med.uoc.gr

Key Words: Non-small cell lung cancer, first and second line chemotherapy, survival.

Table I. *Second-line regimens*.

Cohort A	Cohort B	Cohort C
Irinotecan (n=5)	Vinorelbine/platinum (n=84)	Irinotecan (n=26)
Irinotecan/gemcitabine (n=12)	Taxane/platinum (n=60)	Gemcitabine (n=1)
Irinotecan/temozolamide (n=3)	Gemcitabine/platinum (n=5)	Vinorelbine (n=2)
Vinorelbine (n=9)	Pemetrexed/platinum (n=5)	Vinorelbine/ifosfamide (n=20)
Vinorelbine/ifosfamide (n=3)	Irinotecan/platinum (n=80)	Docetaxel (n=6)
Vinorelbine/gemcitabine (n=3)	Cisplatin/etoposide (n=30)	Docetaxel/gemcitabine (n=3)
Gemcitabine (n=3)	Oxaliplatin (n=1)	Vinorelbine/gemcitabine (n=2)
Pemetrexed (n=18)	Ifosfamide/mitomycin/cisplatin (n=2)	Irinotecan/gemcitabine (n=60)
Pemetrexed/GEM (n=2)		Etoposide (n=3)
Docetaxel/gemcitabine (n=5)		
Docetaxel (n=21)		
Docetaxel/pemetrexed (n=2)		
Docetaxel/zactima (n=1)		
Paclitaxel (n=1)		
Etoposide (n=6)		

Fossella *et al*. (10) demonstrated that single agent docetaxel was associated with a survival benefit in pre-treated patients with advanced/metastatic NSCLC. Similarly, Shepherd *et al*. (11) demonstrated that the administration of docetaxel plus best supportive care (BSC) was superior to BSC alone, regarding median OS and 1-year survival rate, as well as QOL. Moreover, pemetrexed (12) and erlotinib (13) have been approved as second-line treatment based on equivalent efficacy in comparison with docetaxel and the improvement of progression free survival (PFS) and OS compared to BSC, respectively.

There is very littele information in the literature concerning the impact of second-line platinum- and non-platinum-containing regimens on OS; in addition, it is still unclear whether the sequence of administration of platinum- and non-platinum-based regimens in the first- and second-line setting may influence OS. The Hellenic Oncology Research Group (HORG) has conducted randomized phase III trials evaluating the efficacy and the toxicity of non-platinum-based first-line chemotherapy (14-17). Relapsing patients that maintained an adequate performance status (PS) were treated with second-line chemotherapy, mostly in the context of clinical trials (18-21). In a retrospective review of the records of patients enrolled in first-line phase III chemotherapy trials, we identified a group of patients that received non-platinum-based regimens, in both the first-and second-line setting. The aim of the current study was to analyze their clinical outcome with respect to the outcome of patients that received platinum-based chemotherapy either as first- or second-line treatment.

Materials and Methods

Patients. The records of 1.624 patients with histologically or cytologically confirmed locally advanced (stage IIIB with pleural effusion) or metastatic NSCLC who had been enrolled in randomized first-line chemotherapy trials conducted by HORG from February 1997 to September 2006 were retrospectively reviewed. One thousand and seventy-nine (66.4%) patients who received non-platinum-based chemotherapy in the first-line setting were identified. Among them: (i) 94 (9%) patients were treated with a non-platinum-based regimen in the second-line setting (cohort A). (ii) 267 (25.0%) patients received a platinum-based second-line chemotherapy regimen (cohort B). (iii) During the same period, 545 patients were treated with a platinum-based regimen in the first-line setting. Among them, 123 (23.0%) received non-platinum-based regimens upon relapse (cohort C). The second-line regimens are shown in Table I.

Statistical analysis. Survival was calculated both from the day that the patient was registered to receive first-line chemotherapy until death and from the day of registration for second-line chemotherapy until death. Time-to-tumor progression (TTP) was calculated from the day of administration of the first cycle until progression or death from any cause for both first- and second-line chemotherapy. The interval between first- and second-line chemotherapy was calculated from the day that the patient completed the last cycle of first-line chemotherapy until the day of administration of the first cycle of second-line chemotherapy. Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria, version 2 (22) and the worst toxicity for each patient across all first- or second-line chemotherapy cycles were used in the toxicity analysis. Two separate analyses comparing cohort A with cohort B, and cohort C were performed. The Kaplan-Meier method was used to estimate survival and TTP curves. Differences in rates between groups were assessed by Pearson's χ^2 test or Fisher's test where appropriate. Differences of cohorts in terms of continuous variables were assessed by the non-parametric Mann-Whitney test, while those in terms of survival by the log-rank and Wilcoxon tests.

Results

Patient demographics. The clinical characteristics of patients are listed in Table II. The three groups are well balanced as it concerns the main patients' clinical characteristics. However, there were significant imbalances between cohorts A and C

Table II. *Patient characteristics at diagnosis*.

	Cohorts				
	A (n=94) n (%)	B (n=267) n (%)	*p*-Value	C (n=123) n (%)	*p*-Value
Age (years)					
Median	63.0	61.0	0.170	60.0	0.106
Range	43-82	34-85		38-75	
Gender					
Male	86 (91%)	231 (87%)	0.205	112 (91%)	0.911
Female	8 (9%)	36 (13%)		11 (9%)	
Performance status					
0-1	85 (90%)	254 (95%)		118 (96%)	
2	9 (10%)	13 (5%)	0.101	5 (4%)	0.102
Histology					
Squamous cell carcinoma	24 (25%)	86 (32%)		43 (35%)	
Non-squamous carcinomas	56 (60%)	132 (49%)	0.374	45 (37%)	0.006
Undifferentiated carcinomas	11 (12%)	35 (13%)		24 (20%)	
Unknown	3 (3%)	14 (5%)		11 (9%)	
Stage					
IIIB	25 (27%)	92 (35%)	0.161	50 (41%)	0.031
IV	69 (73%)	175 (65%)		73 (59%)	
No. of cycles received					
Median (range)	4 (1-10)	3 (1-12)	0.704	6 (1-9)	0.001
Interval between 1st and 2nd line treatment (months)					
Median (range)	2.2 (0.6-50.4)	1.4 (1-34.6)	0.013	2.6 (1-35)	0.634

in terms of histologic subtype (p=0.006) and the number of patients with stage IIIB disease (p=0.031). Moreover, the median number of administered cycles in the first-line was 4 and 6 in cohorts A and C, respectively (p=0.001).

Response to treatment. Twenty-four (25.5%) out of 94 patients in cohort A and 56 (45.5%) out of 123 patients in cohort C achieved an objective response to first-line chemotherapy (p=0.002); conversely, there was no difference in terms of response rates to first-line chemotherapy between patients treated in cohorts A and B (25.5% and 21.3%, respectively; p=0.403) (Table III). The objective response rate (ORR) to second-line treatment (Table IV) was 17% in cohort A, 13.1% in cohort B (p=0.349) and 7.3% in cohort C (p=0.027). The objective response to second-line chemotherapy was not correlated to tumor histology, gender, PS at the time of enrolement to second-line treatment or to response to first-line treatment for patients treated within cohorts A, B and C. The median duration of response to first-line treatment was 6.5, 4.9 and 4.7 months (p=0.066 and p=0.185) and to second-line treatment 4.8, 5.4 and 5.6 months (p=0.988 and p=0.792) in cohorts A, B and C, respectively.

TTP and survival. Median TTP to first-line chemotherapy (Figure 1) was 4.3 months for patients in cohort A and 5.8 months for patients in cohort C (p=0.324), whereas patients in cohort B had a median TTP of 3.1 months (p=0.112). Median TTP in the second-line settings did not differ significantly among the three cohorts of patients (3.6, 3.0 and 3.1 months for cohorts A, B and C, respectively).

Median OS calculated from the initiation of first-line chemotherapy (Figure 2) was 16, 13.3 and 15.7 months, with 1-year survival rates of 64.6%, 54.8% and 67.5% in cohorts A, B and C respectively (cohort A *vs*. B, p=0.101 and cohort A *vs*. C, p=0.268). Median OS calculated from the initiation of second-line chemotherapy was 9.5, 7.9 and 7.9 months for cohorts A, B (p=0.157) and C (p=0.063), respectively.

Toxicity profile. Grade III-IV anemia, neutropenia and thrombocytopenia rates observed in the first-line treatment did not differ significantly among cohorts (Table V). The incidence of febrile neutropenia was 1.1%, 6.4% and 6.5% for cohorts A, B (p=0.042) and C (p=0.046), respectively. If patients who received monotherapy were excluded from the analysis, neutropenia rates were 1.4% and 5.4% for groups A and B, respectively (p=0.150). Concerning non-hematologic toxicity, lower rates of nausea and vomiting were observed in group A compared to group C (p=0.008). No significant differences were observed between cohorts A and B, or C, in terms of diarrhea, mucositis, asthenia or neurotoxocity (Table

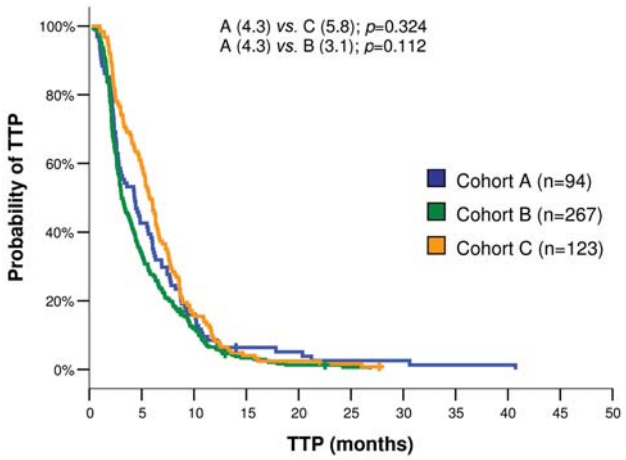

Figure 1. *Time-to-tumor progression in the first-line chemotherapy.*

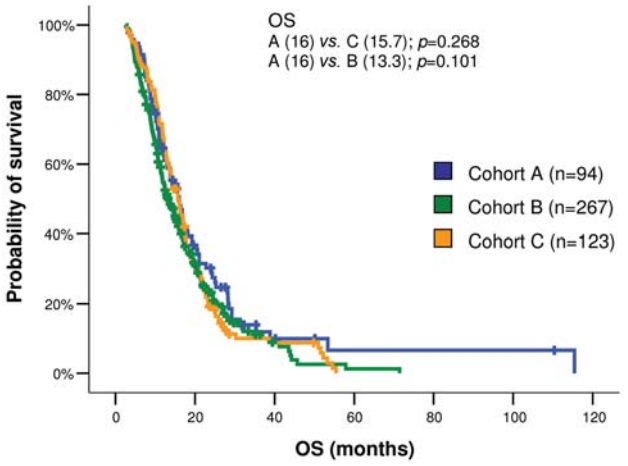

Figure 2. *Overall survival from the first-line treatment.*

Table III. *Objective response rates to first-line chemotherapy.*

	Cohort		
	A	B	C
CR	3 (3.2%)	2 (0.7%)	2 (1.6%)
PR	21 (22.3%)	55 (20.6%)	54 (43.9%)
ORR	24 (25.5%)	57 (21.3%)	56 (45.5%)
95% CI	16.72%-34.35%	16.43%-26.26%	36.73%-54.33%
SD	29 (30.9%)	67 (25.1%)	36 (29.3%)
PD	41 (43.6%)	143 (53.6%)	31 (25.2%)

CR, Complete response; PR, partial response; ORR, overall response rate; SD, stable disease; PD, progressive disease; 95% CI, 95% confidence interval. Cohort A *vs*. C: p=0.002; cohort A *vs*. B: p=0.403.

Table IV. *Objective response rates to second-line chemotherapy.*

	Cohort		
	A	B	C
CR	-	2 (0.7%)	-
PR	16 (17%)	33 (12.4%)	9 (7.3%)
ORR	16 (17%)	35 (13.1%)	9 (7.3%)
95% CI	-	9.06%-17.16%	2.7%-11.92%
SD	26 (27.7%)	76 (28.5%)	44 (35.8%)
PD	52 (55.3%)	156 (58.4%)	70 (56.9%)

CR, Complete response; PR, partial response; ORR, overall response rate; SD, stable disease; PD, progressive disease; 95% CI, 95% confidence interval. Cohort A *vs*. C: p=0.027; cohort A *vs*. B: p=0.349.

V). No deaths from toxicity were reported with first-line chemotherapy. Regarding the toxicity profile of the second-line treatment, no significant differences in severe toxicity were observed between the three cohorts of patients with the exception of grade III/IV diarrhea which was significantly more common for patients treated within cohort C compared to cohort A (2.6% *vs*. 9%, p=0.036; Table VI).

Discussion

Platinum-based chemotherapy has been established as the standard first-line treatment of patients with advanced NSCLC that maintain an adequate PS. According to ASCO guidelines, non-platinum-based doublets should be reserved for patients who cannot tolerate cisplatin toxicity. Our group had conducted several randomized phase III trials evaluating the efficacy and the toxicity profile of non-platinum-based regimens (14-17). Relapsing patients that were eligible for further chemotherapy received second-line treatment mostly in the context of clinical trials. In the present study, we were interested to retrospectively assess the outcome of patients who did not receive platinum agents either in the first- or second-line setting. For this purpose, we identified three cohorts of patients: cohort A was treated with non-platinum containing regimens administered both in the first- and second-line; cohort B received non-platinum- first-line followed by platinum-based second-line chemotherapy and cohort C was comprised of patients who received the reverse sequence of first- and second-line chemotherapy regimens.

Non-platinum-based first-line chemotherapy resulted in significantly lower response rates compared to platinum-based regimens (Table III) which could explain the higher number of cycles administered to the patients of this cohort C (Table II). The above observation is in accordance with individual trials and meta-analyses suggesting that response is significantly higher with platinum-containing chemotherapy

Table V. *Severe toxicity profile of first-line chemotherapy according to the treatment cohort.*

Cohort	Grade III						Grade IV						*p*-Value
	A		B		C		A		B		C		A *vs.* B A *vs.* C
	N	%	N	%	N	%	N	%	N	%	N	%	
Neutropenia	12	12.8	43	16.1	13	10.6	11	11.7	23	8.6	23	18.7	0.961 0.431
Anemia	1	1.1	2	0.7	2	1.6	-	-	-	-	-	-	0.772 0.725
Thrombocytopenia	1	1.1	3	1.1	1	0.8	-	-	1	0.4	-	-	0.757 0.848
Nausea/vomiting	1	1.1	1	0.4	10	8.1	-	-	-	-	2	1.6	0.439 0.008
Diarrhea	2	2.1	6	2.2	7	5.7	-	-	-	-	1	0.8	0.946 0.128
Mucositis	1	1.1	1	0.4	3	2.4	1	1.1	1	0.4	1	0.8	0.272 0.617
Neurotoxicity	1	1.1	3	1.1	3	2.4	-	-	-	-	2	1.6	0.962 0.182
Asthenia	5	5.3	8	3.0	7	5.7	-	-	1	0.4	1	0.8	0.400 0.716

Table VI. *Severe toxicity profile of second-line chemotherapy according to the treatment cohort.*

Cohort	Grade III						Grade IV						*p*-Value
	A		B		C		A		B		C		A *vs.* B A *vs.* C
	N	%	N	N	%	N	N	%	N	%	N	%	
Neutropenia	7	9.2	32	4	5.3	21	4	5.3	21	14.0	12	12.0	0.104 0.156
Anemia	-	-	8	-	-	1	-	-	1	3.5	3	3.0	0.079 0.128
Thrombocytopenia	1	1.3	4	-	-	2	-	-	2	1.8	4	4.0	0.508 0.182
Nausea/vomiting	1	1.3	13	5.7	7	7.0	-	-	3	1.3	-	-	0.061 0.075
Diarrhea	2	2.6	11	4.8	9	9.0	-	-	9	3.9	2	2.0	0.074 0.036
Mucositis	-	-	-	-	-	-	-	-	-	-	1	1.0	0.483 0.382
Neurotoxicity	-	-	3	1.3	2	2.0	-	-	-	-	1	1.0	0.315 0.128
Asthenia	8	10.5	13	5.7	10	10.0	-	-	1	0.4	1	1.0	0.201 0.292

(5-7). Nevertheless, the median duration of response, as well as the median TTP was comparable between the three cohorts of patients. Moreover, in accordance with previous studies, platinum-based first-line chemotherapy resulted in higher rates of severe nausea or vomiting compared to non-platinum-based treatment (14-17). However, no difference was observed in the incidence of grade III and IV anemia probably due to the administration of erythropoietin in patients developing anemia during the course of chemotherapy.

Second-line chemotherapy has been shown to prolong OS in advanced NSCLC. Single agent therapy with docetaxel, pemetrexed or erlotinib has been approved for patients failing first-line treatment (10-13). Combination regimens have demonstrated efficacy and acceptable toxicity in the second-

line setting (23-30); however, studies comparing combination regimens to single agent chemotherapy (20, 21, 31) failed to demonstrate a significant advantage in terms of OS for patients treated with combinations. Moreover, a recent meta-analysis of five randomized trials comparing second-line single-agent with combination chemotherapy showed that combinations are associated with slightly higher response rates but at the expense of increased toxicity and without any survival benefit (32). Patients included in the present analysis received second-line treatment that consisted of either single agent or combination chemotherapy due to their enrolment in clinical trials.

Platinum-containing regimens are considered as the standard front-line treatment in advanced NSCLC, therefore their use in the second-line setting is limited. Several phase II trials that explored the efficacy of second-line platinum-containing chemotherapy revealed their activity even in platinum-pretreated patients (33, 34). Moreover, limited data are available on the role of second-line platinum-containing chemotherapy in patients that received non-platinum-based first-line treatment. The HORG conducted a randomized phase II trial comparing the combination of cisplatin with irinotecan to cisplatin monotherapy in pretreated with taxanes and gemcitabine patients. Although, the response rate was significantly higher in the combination arm (ORR=22.5% *vs*. 7%; p=0.012) there was no difference in terms of OS (7.8 *vs*. 8.8 months, respectively, p=0.934) between the two treatment arms (21). In the current analysis patients treated with second-line platinum-based chemotherapy (cohort B), achieved a 13.1% ORR associated with OS rates of 7.9 months. Comparable response and survival results (7.3% and 7.9 months, respectively) were obtained with second-line non-platinum-based chemotherapy in patients treated within cohort C.

It is of interest to note that the ORR to second-line non-platinum-based chemotherapy was significantly lower in patients pretreated with platinum-based (cohort C) as compared to those treated with non-platinum-based (cohort A) first-line regimens (7.3% *vs*. 17%, p=0.027). The explanation for this observation is not obvious; although it could be attributed to a patient selection bias because patients with a better PS had a higher probability of receiving platinum-based chemotherapy in the first-line setting, we cannot exclude that additional factors such as the histology or the tumor genotype could account for this phenomenon. Moreover, the results of the present analysis are in contrast to a recent retrospective study which revealed that gender, PS and best response to first-line therapy significantly influenced the survival of patients treated in the second-line setting (35). Indeed, our group has previously reported that patients with adenocarcinoma histology achieved a significantly higher ORR with a docetaxel/gemcitabine regimen compared to patients with a non-adenocarcinoma histology who responded significantly better to the docetaxel/ cisplatin regimen (15). Moreover, recent data demonstrated that pemetrexed has limited efficacy in squamous cell NSCLC, whereas gemcitabine seems to be more effective in patients with squamous cell histology (37). However, in the present study, there was no patient who received pemetrexed as first-line treatment, while very few patients received it in the second-line setting. Thus, the observed differences among the distinct cohorts cannot be attributed to the administration of pemetrexed in patients with squamous cell pathology.

An interesting observation in the present analysis was that patients treated within cohort A, despite the fact that they did not receive platinum agents, achieved a favourable median survival of 16 months that was comparable to the outcome of patients treated with platinum-based chemotherapy, either in the first- or second-line setting. In addition, patients treated within all three cohorts achieved a favourable median survival of more than 13 months that had not been previously reached in first-line phase III chemotherapy trials (5, 15). This finding is most probably related to the fact that the population included in this analysis was in fact subjected to a selection based on eligibility for further second-line treatment.

The role of the excision repair cross-complementation group 1 (*ERCC1*) gene has emerged as a potential predictor for tumor response to chemotherapy since it has been demonstrated that low expression of *ERCC1* is associated with a better response to platinum-based regimens (37, 38). However, there is inconsistency concerning the expression of *ERCC1* and the histological subtype of NSCLC. Squamous cell carcinomas have been found to have lower *ERCC1* expression (39) than in adenocarcinomas, whereas in another study the opposite was reported (40). Etxensive investigation is required regarding the tumoral expression of various genes (*e.g*. *ERCC1*, ribonucleoside-diphosphate reductase subunit 1[*RRM1*], breast cancer 1 [*BRCA1*, *etc*.) in the different histological subtypes of NSCLC in association with the efficacy of platinum-and non-platinum-based regimens.

In conclusion, the results of the present study show that the use of non-platinum-based regimens both as first- and second-line treatment of advanced NSCLC, does not seem to negatively affect patient survival and therefore, these regimens could be an alternative therapeutic option to the standard platinum-based first-line treatment. Although, the superiority of first-line, platinum-containing therapy was confirmed in the present retrospective study, non-platinum-based treatment should be reserved for those cases where the administration of cisplatin is contraindicated. In addition, the lower response rates obtained with non-platinum-containing chemotherapy should be taken into account, especially when tumor shrinkage is clinically important. The results of the present study also verify the significant role of second-line treatment and underline the likely contribution of pharmacogenomic studies to the selection of a more customized treatment. It is

anticipated that the incorporation of the new biologic agents will further improve the outcome of NSCLC treatment.

Acknowledgements

This work was partly supported by a research grant from the Cretan Association for Biomedical Research (CABR). ZS is a recipient of a CABR clinical fellowship.

References

1 Spiro SG, Rudd RM, Souhami RL, Brown J, Fairlamb DJ, Gower NH, Maslove L, Milroy R, Napp V, Parmar MK, Peake MD, Stephens RJ, Thorpe H, Waller DA and West P: Chemotherapy *versus* supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life. Thorax *59*: 828-836, 2004.

2 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 randomised clinical trials. BMJ *311*: 899-909, 1995.

3 Shanafelt TD, Loprinzi C, Marks R, Novotny P and Sloan J: Are chemotherapy response rates related to treatment-induced survival prolongations in patients with advanced cancer? J Clin Oncol *22*: 1966-1974, 2004.

4 Schiller JH, Harrington D, Belani C, Langer C, Sandler A, Krook J, Zhu J and Johnson DH: Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med *346*: 92-98, 2002.

5 D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T and Shepherd FA: Platinum-based *versus* non-platinum-based chemotherapy in advanced non-small cell lung cancer: a meta-analysis of the published literature. J Clin Oncol *23*: 2926-2936, 2005.

6 Pujol JL, Barlesi F and Daurès JP: Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials. Lung Cancer *51*: 335-345, 2006.

7 Rajeswaran A, Trojan A, Burnand B and Giannelli M: Efficacy and side-effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens *versus* non-platinum-based doublet chemotherapeutic regimens as first-line treatment of metastatic non-small cell lung carcinoma: A systematic review of randomized controlled trials. Lung Cancer *59*: 1-11, 2008.

8 Pfister DG, Johnson D.H, Azzoli CG, Sause W, Smith TJ, Baker S Jr, Olak J, Stover D, Strawn JR, Turrisi AT and Somerfield MR: American Society of Clinical Oncology Treatment of Unresectable Non–Small Cell Lung Cancer Guideline: J Clin Oncol *22*: 330-353, 2004.

9 Socinski MA, Schell MJ, Peterman A, Bakri K, Yates S, Gitten R, Unger P, Lee J, Lee JH, Tynan M, Moore M and Kies MS: Phase III trial comparing a defined duration of therapy *versus* continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small cell lung cancer. J Clin Oncol *20*: 1335-1343, 2002.

10 Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F and Hammershaimb L: Randomized phase III trial of docetaxel *versus* vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol *18*: 2354-2362, 2002.

11 Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, Coughlin S, Kim Y and Berille J: Prospective randomized trial of docetaxel *versus* best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol *18*: 2095-2103, 2000.

12 Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, Gatzemeier U, Tsao TC, Pless M, Muller T, Lim HL, Desch C, Szondy K, Gervais R, Shaharyar, Manegold C, Paul S, Paoletti P, Einhorn L and Bunn PA Jr.: Randomized phase III trial of pemetrexed *versus* docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol *22*: 1589-1597, 2004.

13 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P and Seymour L: Erlotinib in previously treated non-small cell lung cancer. N Engl J Med *353*: 123-132, 2005.

14 Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, Palamidas P and Vlachonikolis I: Platinum-based and non-platinum-based chemotherapy in advanced non-small cell lung cancer: a randomised multicentre trial. Lancet *357*: 1478-1484, 2001.

15 Georgoulias V, Ardavanis A, Agelidou A, Agelidou M, Chandrinos V, Tsaroucha E, Toumbis M, Kouroussis C, Syrigos K, Polyzos A, Samaras N, Papakotoulas P, Christofilakis C, Ziras N and Alegakis A: Docetaxel *versus* docetaxel plus cisplatin as front-line treatment of patients with advanced non-small cell lung cancer: a randomized, multicenter phase III trial. J Clin Oncol *22*: 2602-2629, 2004.

16 Georgoulias V, Ardavanis A, Tsiafaki X, Agelidou A, Mixalopoulou P, Anagnostopoulou O, Ziotopoulos P, Toubis M, Syrigos K, Samaras N, Polyzos A, Christou A, Kakolyris S, Kouroussis C, Androulakis N, Samonis G and Chatzidaki D: Vinorelbine plus cisplatin *versus* docetaxel plus gemcitabine in advanced non-small cell lung cancer: a phase III randomized trial. J Clin Oncol *23*: 2937-2945, 2005.

17 Georgoulias V, Androulakis N, Kotsakis A, Hatzidaki D, Syrigos K, Polyzos A, Agelidou A, Varthalitis I, Ziras N, Agelidou M, Chandrinos V, Boukovinas I, Geroyianni A, Vamvakas L and Mavroudis D: Docetaxel *versus* docetaxel plus gemcitabine as front-line treatment of patients with advanced non-small cell lung cancer: a randomized, multicenter phase III trial. Lung Cancer *59*: 57-63, 2008.

18 Kakolyris S, Kouroussis C, Kalbakis K, Mavroudis D, Souglakos J, N Vardakis, Kremos S and Georgoulias V: Salvage treatment of advanced non-small cell lung cancer previously treated with docetaxel-based front-line chemotherapy with irinotecan (CPT-11) in combination with cisplatin. Ann Oncol *11*: 757-760, 2000.

19 Kakolyris S, Souglakos J, Agelaki S, Kourousis CH, Mavroudis D, Sarra E, Malliotakis P and Georgoulias V: A dose-escalation study of irinotecan (CPT-11) in combination with cisplatin in patients with advanced non-small cell lung cancer previously treated with a docetaxel-based front line chemotherapy. Lung Cancer *30*: 193-198, 2000.

20 Georgoulias V, Kouroussis C, Agelidou A, Boukovinas I, Palamidas P, Stavrinidis E, Polyzos A, Syrigos K, Veslemes M, Toubis M, Ardavanis A, Tselepatiotis E and Vlachonikolis I: Irinotecan plus gemcitabine *vs*. irinotecan for the second-line treatment of patients with advanced non-small cell lung cancer pretreated with docetaxel and cisplatin: a multicentre, randomised, phase II study. Br J Cancer *91*: 482-488, 2004.

21 Georgoulias V, Agelidou A, Syrigos K, Rapti A, Agelidou M, Nikolakopoulos J, Polyzos A, Athanasiadis A, Tselepatiotis E, Androulakis N, Kalbakis K, Samonis G and Mavroudis D: Second-line treatment with irinotecan plus cisplatin *vs*. cisplatin of patients with advanced non-small cell lung cancer pretreated with taxanes and gemcitabine: a multicenter randomised phase II study. Br J Cancer *93*: 763-769, 2005.

22 NCI Common Toxicities Criteria (CTC), version 2, 1999; April 30.

23 Hainsworth JD, Burris HA, Litchy S, Erland JB, Hon JK, Brierre JE and Greco FA: Gemcitabine and vinorelbine in the second-line treatment of non-small cell lung carcinoma patients: a Minnie Pearl Cancer Research Network phase II trial. Cancer *88*: 1353-1358, 2000.

24 Kosmas C, Tsavaris N, Panopoulos C, Vadiaka M, Stavroyianni N, Kourelis T, Malamos N, Antonopoulos M and Kalofonos HP: Gemcitabine and vinorelbine as secondline therapy in non-small cell lung cancer after prior treatment with taxane plus platinum-based regimens. Eur J Cancer *37*: 972-978, 2001.

25 Androulakis N, Kouroussis C, Kakolyris S, Tzannes S, Papadakis E, Papadimitriou C, Geroyianni A, Georgopoulou T, Dimopoulou I, Souglakos J, Kotsakis A, Vardakis N, Hatzidaki D and Georgoulias V: Salvage treatment with paclitaxel and gemcitabine for patients with non-small cell lung cancer after cisplatin- or docetaxel-based chemotherapy: a multicenter phase II study. Ann Oncol *9*: 1127-1130, 1998.

26 Niho S, Kubota K, Goto K, Ohmatsu H, Matsumoto T, Kakinuma R and Nishiwaki Y: Combination second-line chemotherapy with gemcitabine and docetaxel for recurrent non-small cell lung cancer after platinum-containing chemotherapy: a phase I/II trial. Cancer Chemother Pharmacol *52*: 19-24, 2003.

27 Kakolyris S, Papadakis E, Tsiafaki X, Kalofonos C, Rapti A, Toubis M, Bania E, Kouroussis C, Chainis K, Androulakis N, Agelaki S, Sarra E, Vardakis N and Georgoulias V: Docetaxel in combination with gemcitabine plus rhG-CSF support as second-line treatment in non-small cell lung cancer. A multicenter phase II study. Lung Cancer *32*: 179-187, 2001.

28 Rinaldi DA, Lormand NA, Brierre JE, Cole JL, Barnes BC, Mills G, Yadlapati S, Felicia Fontenot M, Buller EJ and Rainey JM: A Phase II trial of topotecan and gemcitabine in patients with previously treated, advanced non-small cell lung carcinoma. Cancer *95*: 1274-1278, 2002.

29 Gonzalez Cao M, Aramendia JM, Salgado E, Aristu J, Martínez Monje R, Algarra SM, Ordoñez JM and Brugarolas A: Second-line chemotherapy with irinotecan and vinorelbine in stage IIIB and IV non-small cell lung cancer: a phase II study. Am J Clin Oncol *25*: 480-484, 2002.

30 Pectasides D, Mylonakis N, Farmakis D, Nikolaou M, Koumpou M, Katselis I, Gaglia A, Kostopoulou V, Karabelis A and Kosmas C: Irinotecan and gemcitabine in patients with advanced non-small cell lung cancer, previously treated with cisplatin-based chemotherapy. A phase II study. Anticancer Res *23*: 4205-4211, 2003.

31 Wachters FM, Groen HJ, Biesma B, Schramel FM, Postmus PE, Stigt JA and Smit EF: A randomised phase II trial of docetaxel *versus* docetaxel and irinotecan in patients with stage IIIb-IV non-small cell lung cancer who failed first-line treatment. Br J Cancer *92*: 15-20, 2005.

32 Di Maio M, Chiodini P, Georgoulias V, Hatzidaki D, Takeda K, Wachters FM, Gebbia V, Smit EF, Morabito A, Gallo C, Perrone F and Gridelli C: Single- agent *vs*. combination chemotherapy (CT) as second-line treatment of advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data of five randomized trials. J Clin Oncol *27*: 1836-1843, 2009.

33 Kakolyris S, Ziras N, Vamvakas L, Varthalitis J, Papakotoulas P, Syrigos K, Vardakis N, Kalykaki A, Amarantidis K and Georgoulias V: Gemcitabine plus oxaliplatin combination (GEMOX regimen) in pretreated patients with advanced non-small cell lung cancer (NSCLC): a multicenter phase II study. Lung Cancer *54*: 347-352, 2006.

34 Wachters FM, van Putten JW, Boezen HM and Groen HJ: Phase II study of docetaxel and carboplatin as second-line treatment in NSCLC. Lung Cancer 45: 255-262, 2004.

35 Weiss GJ, Rosell R, Fossella F, Perry M, Stahel R, Barata F, Nguyen B, Paul S, McAndrews P, Hanna N, Kelly K and Bunn PA Jr: The impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in the patients with advanced non-small cell lung cancer. Ann Oncol *18*: 453-460, 2007.

36 Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis F, Simms L, Sugarman KP and Gandara D: Phase III Study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small cell lung cancer. J Clin Oncol *26*: 3543-3551, 2008.

37 Lord RV, Brabender J, Gandara D, Alberola V, Camps C, Domine M, Cardenal F, Sánchez JM, Gumerlock PH, Tarón M, Sánchez JJ, Danenberg KD, Danenberg PV and Rosell R: Low *ERCC1* expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res *8*: 2286-2291, 2008.

38 Yu D, Zhang X, Liu J, Yu D, Zhang X, Miao X, Liu J, Zhao D, Li H, Tan W and Lin D: Characterization of functional excision repair cross-complementation group 1 variants and their association with lung cancer risk and prognosis. Clin Cancer Res *14*: 2878-2886, 2008.

39 Simon GR, Sharma S, Cantor A, Smith P and Bepler G: *ERCC1* expression is a predictor of survival in resected patients with non-small cell lung cancer. Chest *127*: 978-983, 2005.

40 Olaussen KA, Dunant A, Fouret P, Brambilla E, André F, Haddad V, Taranchon E, Filipits M, Pirker R, Popper HH, Stahel R, Sabatier L, Pignon JP, Tursz T, Le Chevalier T and Soria JC: DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med *355*: 983-991, 2006.

Received January 21, 2010
Revised July 27, 2010
Accepted August 9, 2010