Journal of BUON **14:** 203-209, 2009

ORIGINAL ARTICLE

Do the time to chemotherapy response and the dose intensity have an impact on patient outcome in advanced non-small cell lung cancer?

D. Radosavljevic[1], I. Golubicic[2], D. Gavrilovic[3], I. Kezic[3], S. Jelic[1]

[1]Clinic for Medical Oncology, [2]Clinic for Radiation Oncology, [3]Data Center, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

Summary

Purpose: *To better define the importance of early response rate (RR) as well as dose intensity (DI) in advanced non small cell lung cancer (NSCLC) patients treated with platinum-based combination chemotherapy.*

Patients and methods: *Analysed were stage IIIB and IV NSCLC patients included in 4 prospective clinical trials. All of them were treated with cisplatin 120 mg/m^2 (the majority of patients) or carboplatin 500 mg/m^2, and since 2000 with AUC 5 (the minority of patients) with second-generation platinum-based regimens. Responding patients (complete response/CR and partial response/PR) were divided into 4 different categories, depending on the time when response was first registered. DI and total dose (TD) of cisplatin was calculated for 93 patients with response or stable disease (SD).*

Results: *Among 362 patients analysed, 117 (32%) were responders. Although "early" responders (54 patients after the 2nd cycle, median survival 10 months; 42 patients after the 3rd cycle, median survival 11 months) lived shorter than "late" responders (11 patients after the 4th cycle median survival 12 months; 10 patients after the 5th cycle, median survival 19 months), these differences were not statistically significant, neither in terms of overall survival (OS) nor in time to progression (TTP). DI in patients with CR+PR+SD was 30 mg/m^2/week (median). TD of cisplatin in CR+PR patients was 577 mg, whereas it was 475 mg in patients with SD (p=0.004). These differences followed significant differences in the number of the cycles received and median survival between CR+PR vs. SD patients.*

Conclusion: *Early response was not associated with better survival, DI in SD patients did not differ from responding patients, but responding patients received more cisplatin and lived longer.*

Key words: advanced NSCLC, cisplatin, dose intensity, response rate, stable disease, total dose

Introduction

Advanced NSCLC still remains a therapeutic challenge, with a relatively low response rate to chemotherapy, short-term symptom relief and only a modest impact on OS. In patients treated with combination chemotherapy the median survival is less than a year, usually 8-10 months, with 1-year survival rate of 20-30%. Today standard usage of taxanes, gemcitabine or docetaxel with platinum doublets produce slightly better results, in comparison with results seen with vinca alkaloids or etoposide. In recent years, there were attempts to introduce non platinum doublets into everyday practice but without significant success. Still, cisplatin is the basic and most active agent for advanced NSCLC and platinum compounds continue to constitute the backbone in first-line chemotherapy. In recent metaanalyses [1,2] cisplatin proved to have a slightly higher activity than carboplatin in advanced NSCLC.

It has been known for a long time that response to chemotherapy can only be seen in patients with a better prognosis, without determining the relationship between response and survival [3,4]. In 1997 the Belgian group [5] concluded, based on 1052 patients from 7 clinical studies, that the response rate is the dominant predictive factor for survival of these patients, but with no final conclusion about the causal relationship of

Correspondence to: Davorin Radosavljevic, MD, PhD. Clinic for Medical Oncology, Institute for Oncology and Radiology of Serbia, Pasterova 14, 11000 Belgrade, Serbia. Tel: +381 11 2067166, Fax: +381 11 2685300, E-mail: davorr@ncrc.ac.rs

Received 14-07-2008; Accepted 05-09-2008

response rate and survival on the treatment outcome. In the past years efforts have been undertaken to better define the importance of tumor response for the NSCLC patient outcome [6-9].

For a long time, the question of DI has not been an important issue in the chemotherapy of advanced NSCLC. Standard doses of cisplatin are today 75-80 mg/m^2 every 3 weeks, while doses of 100-120 mg/m^2 every 3 or 4 weeks have largely been abandoned [10]. The intriguing question today may be to explore the DI in different response categories during platinum-based chemotherapy.

The time needed to achieve a response is a more interesting issue, as current data [11] show that early response as well as early-achieved disease control rate (CR+PR+SD) have an optimal effect on treatment outcome, and therefore they may exert a positive impact on the duration of the first-line chemotherapy. This duration is of importance, bearing in mind the efficacy/toxicity ratio of platinum-based chemotherapy, as well as raising possibilities of second- or even -third-line chemotherapy in advanced NSCLC.

In this paper we analysed time to tumor response (TTR) and its impact on TTP and OS in patients with advanced NSCLC who were treated with platinum-based chemotherapy, along with the association of DI and TD of cisplatin with treatment outcome in patients with CR+PR+SD.

Patients and methods

This study was based on the analysis of NSCLC patients included in 3 phase II and 1 phase III clinical studies, conducted between 1990-2005 at the Institute for Oncology and Radiology of Serbia.

Inclusion criteria

Inclusion criteria were: histologically proven NSCLC, clinical stage IIIB (locally advanced disease with supraclavicular lymphadenopathy or malignant pleural effusion) or IV (distant metastases), at least one measurable lesion on chest radiography or CT, no previous exposure to chemotherapy or radiotherapy, age 18-75 years, ECOG performance status (PS) 0-2 or Karnofsky PS 60-100, except patients with painful bone metastases where ECOG PS 3 was allowed, adequate renal, bone marrow and cardiac function, absence of symptomatic metastases in the CNS, expected survival longer than 2 months, no previous malignancies with the exception of non melanoma skin cancer or cervical cancer *in situ*, and verbal informed consent.

Chemotherapy

Chemotherapy regimens and schedules included in this analysis were:

1. Mitomycin 8 mg/m^2 d1 + vindesine 3 mg/m^2 d 1 + cisplatin 120 mg/m^2 d2 (109 patients) every 4 weeks vs. mitomycin 8 mg/m^2 d1 + vindesine 3 mg/m^2 d 1 + carboplatin 500 mg/m^2 d2 (101 patients) every 4 weeks.

2. Hydroxyurea 3000 mg d 1 + cytarabine 1000 mg/m^2 d1 + cisplatin 30 mg/m^2 d 1-4 (49 patients) every 4 weeks.

3. Mitomycin 8 mg/m^2 d1 + vinblastine 6 mg/m^2 d 1 + cisplatin 120 mg/m^2 d2 (80 patients) every 4 weeks.

4. Etoposide 120 mg/m^2 d 1-3 + carboplatin AUC 5 d 1 (23 patients) every 4 weeks.

All of the patients were treated with the same dose of cisplatin (120 mg/m^2 every 4 weeks); carboplatin was given at a dose of 500 mg/m^2 and since 2000 at AUC 5.

DI was defined as the amount of the drug administered in the time unit, marked as mg/m^2/week. Relative DI was defined as the ratio of planned/received DI.

World Health Organization (WHO) response criteria were used for response evaluation [8]. Response evaluation was performed before every other cycle with clinical examination and imaging assessments (chest radiography and/or CT, abdominal and pelvic CT and/or US, bone scintigraphy).

Patients with CR, PR and SD were planned to receive up to 6 cycles, with a maximum of 8, depending on their doctor's discretion. The possibility of change of the platinum compound during therapy was not predicted (crossover from cisplatin to carboplatin and *vice versa*).

Once evidence of progressive disease (PD) was apparent, patients were switched to best supportive care and no second-line chemotherapy was administered. In addition, therapy was stopped in case of patient's refusal, or when the attending physician believed it was in the patient's best interest.

Statistical analysis

Microsoft Office Excel was used to prepare all graphics. For data processing the statistical package R (version 2.6.0 [2007-10-03]; Copyright [C] 2007). The R Foundation for Statistical Computing; ISBN 3-900051-07-0) was used. The methods of descriptive statistics used were: frequencies, percentages, and measures of central tendention (mean value and median) and measures of variability (standard deviation

- SD, and range). For testing the differences between parameters the Kruskal-Wallis and Mann-Whitney tests were used. Curves of probabilities for OS and TTP were constructed using the Kaplan-Meier product-limit method; for testing the differences between curves the log-rank test was used.

Results

The patients' follow up ranged between 1-56 months (median 7). Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

Characteristic	*Patients, n*	*%*
Gender		
Male	318	87.85
Female	44	12.15
Age (years)		
Median: 57.5 (range 25-77)		
<65	303	83.70
>65	59	16.30
Clinical stage		
IIIB	165	45.58
IV	197	54.42
Performance status (WHO)		
0	31	8.56
1	187	51.66
2	113	31.22
3	31	8.56

Table 2. Number of chemotherapy cycles received by the patients

Number of cycles	*Patients, n*	*%*
1	362	100
2	325	90
3	246	68
4	193	53
5	121	33
6	81	22
7	30	8
8	17	5

The number of cycles received by the patients is presented in Table 2: 90% of patients received at least 2 cycles, 53% received 4 cycles, 22% 6 cycles and only 5% received the maximum number of 8 cycles.

One third of the patients achieved CR+PR, almost half of the patients achieved SD as maximal response, while 20% of the patients progressed during chemotherapy (Table 3). The categories of response to chemotherapy were significantly different in relation to the number of cycles of chemotherapy received (Kruskal-Wallis test; x^2_2=165.368; p=0.00) and overall survival (log rank test; x^2_2=118.06; p=0.00) (Table 4).

Responding patients (CR+PR; n=117) were divided into 4 groups, depending on the time when response was first registered.

Over 80% of patients achieved response after the 2nd or 3rd cycle of chemotherapy, but late responders (after the 4th cycle) lived longer, as shown in Table 5. However, the differences among median survival times,

Table 3. Response to chemotherapy, number of received cycles and overall survival

Response	*Patients, n (%)*	*Median number of cycles received (range)*	*Median OS - months (95% CI)*
RR (CR+PR)	117 (32.32)	5 (2-8)	11 (10-12)
SD	172 (47.51)	4 (2-8)	7 (6-8)
PD	73 (20.17)	1 (1-3)	3 (3-4)
Total	362 (100)	4 (1-8)	7 (7-8)

RR: response rate, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, OS: overall survival, 95% CI: 95% confidence interval

Table 4. Statistical differences in number of cycles received and overall survival among response categories

Groups	*Test*	
	Number of cycles (Mann Whitney test)	*OS (log rank)*
RR vs. SD	U=5832.5; p<0.017*	x^2_1=16.2; p<0.017*
RR vs. PD	U=309.0; p<0.017*	x^2_1=97.7; p<0.017*
SD vs. PD	U=11884.5; p<0.017*	x^2_1=58.7; p<0.017*

*Bonferroni correction: α/3=0.05/3=0.017, RR: response rate (CR+PR), SD: stable disease, PD: progressive disease

Table 5. Median overall survival in relation with time to response

Groups of responding patients	*Patients, n (%)*	*Median overall survival (months)*	*95% CI**
Response after 2nd cycle	54 (46.16)	10	7-13
Response after 3rd cycle	42 (35.90)	11	9-14
Response after 4th cycle	11 (9.40)	12	9-9$^{+\S}$
Response after ≥5th cycle	10 (8.54)	19	12-12$^{+\S}$
Total	117 (100.0)	11	10-12

*95% confidence interval, §upper limit could not be calculated

shown on Figure 1 and Table 6, were not statistically significant (log rank test; x^2_3=3.022; p=0.388; Figure 1).

The results of TTP are presented in Tables 7 and 8 and Figure 2. Again, there was no difference in TTP among categories of responding patients, depending on the time when response was first registered (log rank test; x^2_3=4.173; p=0.243).

Analysis of DI and TD of cisplatin was carried out for 93 CR, PR and SD patients with adequate data, receiving cisplatin 120 mg/m^2 every 4 weeks.

Descriptive data about DI, relative DI and TD in relation to the initial PS are presented in Table 9.

No statistically significant differences were identified among PS categories in terms of DI (Kruskal-Wallis test; x^2_3=2.417; p=0.49), TD (Kruskal-Wallis test; x^2_3=6.766; p=0.08) and relative DI (Kruskal-Wallis test; x^2_3=1.057; p=0.79).

In Table 10 the results of DI, relative DI, and TD analyses in CR and PR patients and in those with SD are shown.

Responding and SD patients received 30 mg/m^2/week (median), which represent 98% and 99% of the planned dose. Responding patients received in total 577 mg (median), while SD patients received 475 mg (median) of cisplatin.

No statistically significant differences in DI or relative DI between responding and SD patients was noted. Significant difference was demonstrated in terms of TD favoring the CR and PR patients.

This advantage was in accordance with the significant difference in the number of the cycles received (Mann-Whitney test; U=673.5; p=0.004) and also of the median survival (log rank test; x^2_1=5.225; p=0.022), both favoring responding patients (Table 11).

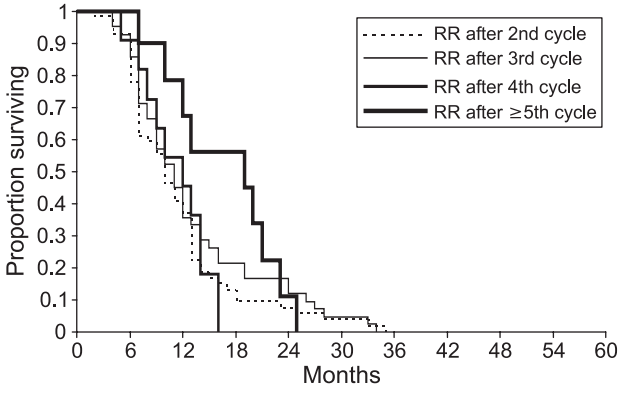

Figure 1. Kaplan-Meier estimate of overall survival in relation with time to response.

Table 6. Statistical differences in overall survival among different time to response categories

Groups	*Log rank test* x^2_1	*p-value*
RR after 2 vs. RR after 3 cycles	0.6	0.432
RR after 2 vs. RR after 4 cycles	0.0	1.000
RR after 2 vs. RR after 5 cycles	1.1	0.303
RR after 3 vs. RR after 4 cycles	0.4	0.546
RR after 3 vs. RR after 5 cycles	0.3	0.563
RR after 4 vs. RR after 5 cycles	2.5	0.111

RR: response rate

Table 7. Median time to progression depending on time when response was first registered

Group	*Patients, n (%)*	*Median time progression (months)*	*95% CI**
Response after 2nd cycle	54 (46.15)	6	4-8
Response after 3rd cycle	42 (35.90)	5.5	5-10
Response after 4th cycle	11 (9.40)	8	6-6$^{+\S}$
Response after ≥5th cycle	10 (8.55)	12.5	6-6$^{+\S}$
Total	117 (100.0)	5	4-6

*95% confidence interval, §upper limit could not be calculated

Discussion

The data presented and analysed in this paper showed no statistically significant difference either in

Table 8. Statistical differences in time to progression among different time to response categories

Groups	*Log rank test* x^2_1	*p-value*
RR after 2 vs. RR after 3 cycles	1.9	0.165
RR after 2 vs. RR after 4 cycles	0.2	0.686
RR after 2 vs. RR after 5 cycles	0.5	0.468
RR after 3 vs. RR after 4 cycles	0.3	0.585
RR after 3 vs. RR after 5 cycles	0.0	0.844
RR after 4 vs. RR after 5 cycles	0.5	0.496

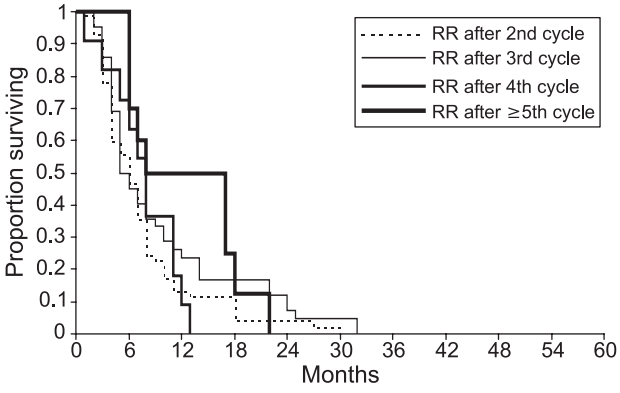

Figure 2. Kaplan-Meier estimate of time to tumor progression in relation to time to tumor response.

Table 9. Median and range of dose intensity, total dose and relative dose intensity of cisplatin, according to initial performance status category

PS	*Patients, n (%)*	*DI - median (range) (mg/m²/week)*	*TD - median (range) (mg)*	*Relative DI - median (range)*
0	4 (4.3)	31.17 (28.57-40.91)	748.5 (525.70-943.80)	96.77 (93.89-116.90)
1	52 (55.9)	29.99 (24.17-35.81)	490.8 (231.30-1070.00)	98.85 (80.57-103.60)
2	28 (30.1)	29.62 (27.14-36.62)	481.9 (236.10-909.60)	98.45 (77.54-104.60)
3	9 (9.7)	30.00 (27.86-37.58)	416.2 (233.80-901.20)	99.11 (79.60-107.40)
Total	93 (100)	29.89 (24.17-40.91)	484.2 (231.30-1070.00)	98.70 (77.54-116.90)

PS: performance status, DI: dose intensity, TD: total dose

Table 10. Dose intensity, total dose and relative dose intensity of cisplatin in CR, PR and SD patients

Response category	*DI (mg/m²/wk)*	*TD (mg)*	*Relative DI (%)*
CR+PR (n=36)			
mean (SDev)	30.23 (2.40)	615.92 (213.08)	97.22 (5.09)
median (range)	30 (24-37)	577 (236-1070)	98 (79-105)
SD (n=57)			
mean (SDev)	30.98 (2.70)	480.86 (182.18)	97.93 (5.56)
median (range)	30 (27-41)	475 (231-929)	99 (78-117)
CR+PR+SD (n=93)			
mean (SDev)	30.69 (2.60)	533.14 (204.57)	97.96 (5.36)
median (range)	30 (24-41)	484 (231-1070)	99 (78-117)
Mann-Whitney test	1163	665.5	1081
CR+PR vs. SD	p= 0.281	p= 0.004	p= 0.667

CR: complete response, PR: partial response, SD: stable disease, DI: dose intensity, TD: total dose, SDev: standard deviation

Table 11. Number of cycles received and overall survival for responding and SD patients

Response	*Patients, n*	*Median number of cycles received (range)*	*Median survival (months) (95%CI)*
CR+PR	36	5 (2-8)	9 (7-13)
SD	57	4 (2-8)	6 (5-8)
CR+PR+SD	93	4 (2-8)	7 (6-9)

For abbreviations see footnote of Table 3

OS or TTP between early and late responders. Thus, it seems unnecessary to obtain an early response in advanced NSCLC. Response rate can help differentiate patients with a better prognosis from those with a poor prognosis, and its prognostic value for survival is proven in metastatic colorectal [13] and breast cancer [14]. In advanced NSCLC the median survival remains generally poor, and the response rate to chemotherapy usually can not offer long-term survival. SD is most frequently encountered in the majority of solid tumors, particularly in advanced NSCLC, where it probably expresses, at least partially, the natural course of the disease more than the impact of chemotherapy.

Is SD also a positive "response" category, despite an obvious difference in survival, compared with responders? The term "disease control rate" (DCR) has a rising popularity, particularly in modestly chemosensitive tumors like NSCLC or pancreatic cancer. In a recently published study Lara et al. [15] demonstrated that there was a greater similarity in patient outcome between responding and SD patients than between SD and PD patients. The authors hypothesized that the rate of non-progressive disease is a stronger predictor of clinical benefit than the traditional response rate. Both CR+PR and SD categories were associated with better survival compared with PD patients, but the hazard ratio (HR) for responders vs. nonresponders was 0.61, while HR for DCR vs. nonresponders was 0.45, meaning that DCR better predicted survival. These results support the recognition of stabilization as a positive outcome in advanced NSCLC. In a British study [11], patients receiving mostly second-generation platinum doublets were analysed. The results were somewhat conflicting with those in the aforementioned study: the prognosis of patients who achieved response after the 2nd cycle was significantly better than those with SD after the 2nd cycle. Even if the SD patients achieved a

response after the 4th cycle, they remained the population with the poorer outcome. Some recent *post hoc* analyses also revealed the importance of achieving response in relation to better survival: in the Paccagnella et al. [16] and Bruzzi et al. [17] studies response rate was a powerful prognostic factor for survival.

The duration of chemotherapy in advanced NSCLC is an often revisited issue, especially after the establishment of second-line chemotherapy and the introduction of molecular targeted agents in standard chemotherapy. With our finding that late responders do not live significantly longer, the ASCO 2003 recommendation of 4 cycles, in the absence of any response, sounds very reasonable. Early responses offer a better planning of further sequential or second-line chemotherapy. On the other hand, more prolonged chemotherapy is associated with more toxicity. Of special interest may be the finding of Hotta et al. [18] that in second-line chemotherapy, where the response rate was only 6.8% but DCR 42.4%, there was not association between response rate and survival (p=0.69) but there was a significant association between DCR and survival (p=0.013). The limitation of this study was the quality of data, which were extracted from abstracts, not from individual patient data.

For second- and third-line chemotherapy, important questions such as prediction of response, patient selection and individualization of therapy, still remain unresolved. Of note, physicians are traditionally fascinated with response rates, while patients are not essentially interested in tumor shrinkage, whereas both of them feel that the primary aim of therapy is to halt or delay the progression of disease.

Analysis of cisplatin DI and TD, as an essential drug in NSCLC, was performed after finding greater similarity in the outcome of responding and SD patients than of SD and PD patients in the majority of recent publications [15,18]. Concerning dose delivery, there were no differences between either responding and SD categories or among the categories of PS. TD were different with respect to responding and SD patients, and this difference followed the differences in the number of received cycles and the median survival of responding and SD patients (responders received more drug and lived longer).

Theoretically, DI is the dominant treatment variable regarding the degree of therapeutic response, while TD correlates best with the duration of response in advanced disease [19]. Our results support this approach, i.e. patients should receive initially an intensive regimen, capable of inducing CR, PR or SD. In a similar analysis performed by Murray et al. [20] it was found that, using second-generation of cisplatin-based regimens, the median TD of cisplatin was similar for both responding and SD patients, and 3-fold greater compared with patients with PD. Biologically, it is easy to understand that TD is an important factor in chemotherapy drug delivery. Our analysis suggested that there is no need to force a greater DI in order to achieve response in advanced NSCLC.

Achieving response retains its importance in the short-term outcome in advanced NSCLC, but more insight should be given to the relationship between response and SD. While we are still in the cisplatin era, how much chemotherapy and for how long is a matter of debate.

Acknowledgements

This paper is a part of the Research Project No 145055, supported by Ministry of Science of Serbia.

References

1. Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small cell lung cancer. J Clin Oncol 2004; 22: 3852-3859.
2. Ardizzoni A, Boni L, Tiseo M et al. Cisplatin versus carboplatin-based chemotherapy in first-line treatment of advanced non-small cell lung cancer: An individual patient data meta-analysis. J Natl Cancer Inst 2007; 99: 1-11.
3. Oye RK, Shapiro MF. Reporting results from chemotherapy trials. JAMA 1984; 252: 2722-2725.
4. Anderson JR, Cain KC, Gelber RD. Analysis of survival by response. J Clin Oncol 1983; 1: 710-719.
5. Paesmans M, Sculier JP, Libert P et al. Response to chemotherapy has predictive value for further survival of patients with advanced non-small cell lung cancer: 10 years experience of the European Lung Cancer Working Party. Eur J Cancer 1997; 33: 2326-2332.
6. Shanafelt TD, Loprinzi C, Marks R et al. Are chemotherapy response rates related to treatment-induced survival prolongations in patients with advanced cancer? J Clin Oncol 2004; 22: 1966-1974.
7. Prokakis Ch, Koletsis EN, Apostolakis E, Chatzimichalis A, Dougenis D. Preoperative chemotherapy in early-stage (stage IB-IIIA) resectable non small cell lung cancer. Is it justified? J BUON 2008; 13: 161-168 (Review).
8. Massarelli E, Andre F, Liu DD et al. A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small cell lung cancer. Lung Cancer 2003; 39: 55-61.
9. Dediu M, Median D, Alexandru A, Vremes G, Gal C. Tyrosine kinase inhibitors in non-small cell lung and pancreatic cancer: the emerging role of erlotinib. J BUON 2007; 12 (Suppl 1): S137-S149 (Review).
10. Gralla RJ, Casper ES, Kelsen DP et al. Cisplatin and vindesine

combination therapy for advanced carcinoma of the lung. A randomized trial investigating two dosage schedules. Ann Int Med 1981; 95: 414-420.
11. Sirohi B, Ashley S, Norton A et al. Early response to platinum-based first-line chemotherapy in non-small cell lung cancer may predict survival. J Thorac Oncol 2007; 2: 735-740.
12. Miller AB, Hoogstraten B, Staquet M Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207-214.
13. Buyse M, Thirion P, Carlson RW, Burzykowski T, Molenberghs G, Piedbois P. Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. Lancet 2000; 356: 373-378.
14. Bruzzi P, Del Mastro L, Sormani MP et al. Objective response to chemotherapy as a potential surrogate end-point of survival in metastatic breast cancer patients. J Clin Oncol 2005; 23: 5117-5125.
15. Lara PN, Redman MW, Kelly K et al. Disease control rate at 8 weeks predicts clinical benefit in advanced non-small cell lung cancer: results from Southwest Oncology Group randomized trials. J Clin Oncol 2008; 26: 463-467.
16. Paccagnella A, Oniga F, Bearz A et al. Correlation of tumor response and survival in advanced NSCLC patients treated with paclitaxel plus carboplatin (PC) versus paclitaxel plus carboplatin plus gemcitabine (PCG). J Clin Oncol 2007; 25 (Suppl): 7650 (abstr).
17. Bruzzi P, Sormani MP, Tiseo M, Boni l, Rossell R, Ardizzoni A. Tumor response to chemotherapy as a surrogate endpoint of survival in advanced non-small cell lung cancer (NSCLC): results of an individual patients data meta-analysis. J Clin Oncol 2007; 25 (Suppl): 7548 (abstr).
18. Hotta K, Fujiwara Y, Kiura K et al. Relationship between response and survival in more than 50,000 patients with advanced non-small cell lung cancer treated with systemic chemotherapy in 143 phase III trials. J Thorac Oncol 2007; 2: 402-407.
19. Skipper HE. Dose intensity versus total dose of chemotherapy: An experimental basis. In: DeVita V, Hellman S, Rosenberg S (Eds): Important Advances in Oncology. Philadelphia, PA, Lippincott, 1990, pp 43-64.
20. Murray N, Coppin C, Coldman A Pater J, Rapp E. Drug delivery analysis of the Canadian multicenter trial in non-small cell lung cancer. J Clin Oncol 1994; 12: 2333-2339.