Prognostic value of C-reactive protein and other classical factors in patients with advanced non-small cell lung carcinoma treated in routine clinical practice

Napovedna vrednost C-reaktivnega proteina in drugih dejavnikov pri bolnikih z napredovalim nedrobnoceličnim karcinomom pljuč zdravljenih rutinsko v klinični praksi

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Izvleček

Izhodišča: Napovedni dejavniki poteka bolezni so kliniku v pomoč pri izbiri zdravljenja. V različnih analizah je bilo dokazano, da je C-reaktiven protein (CRP) negativen napovedni dejavnik pri bolnikih z različnimi vrstami malignomov. Le malo študij pa je analiziralo napovedno vrednost CRP pri bolnikih z napredovalim nedrobnoceličnim karcinomom pljuč.

Namen naše analize je določitev napovedne vrednosti CRP kakor tudi drugih značilnosti pri neizbranih bolnikih z napredovalim nedrobnoceličnim karcinomom pljuč zdravljenih s standardno platino vsebujočo kemoterapijo.

Metode: Naša retrospektivna analiza je vključevala 53 bolnikov z napredovalim nedrobnoceličnim karcinomom pljuč, ki so bili zdravljeni s kemoterapijo po shemi cisplatin/karboplatin in gemcitabin na Univerzitetni kliniki Golnik od maja 2004 do novembra 2008. Srednja starost vključenih bolnikov je bila 65 let, večina bolnikov je bila moškega spola (75 %), kadilcev ali bivših kadilcev (81 %), v stanju zmogljivosti (performance status-PS) 1 (64.2 %), stadij ob postavitvi diagnoze pa je bil IV v 83 %.

Zbrani so bili podatki o laboratorijskih vrednostih pred začetkom zdravljenja (Hb, število trombocitov, CRP, LDH), informacije o načinu in učinku zdravljenja. Srednje število prejetih krogov kemoterapije je bilo 4 (1–6).

Rezultati: Povprečno preživetje brez bolezni celotne skupine bolnikov je bilo 4,8 meseca (0–20 mesecev). Bolniki s povišano vrednostjo CRP (≥ 20 mg/l) so imeli slabše preživetje brez bolezni v primerjavi z bolniki z nižjo vrednostjo CRP pred začetkom zdravljenja (povprečno PFS 8.4 vs 3,6 meseca, p = 0.006). V Coxovi univariatni analizi so se kot statistično pomembni napovedni dejavniki izkazali CRP (p = 0.016, HR = 1.008, 95 %CI, 1.001–1.014), Hb (p = 0.001, HR = 0.96, 95 %CI, 0.95–0.99), in komorbidnost (p = 0.051, HR = 1.2, 95 %CI, 1.00 -1.45). Starost, LDH in število trombocitov se v naši analizi niso izkazali za pomembne napovedne dejavnike. V multivariatni analizi sta se kot neodvisna napovedna dejavnika izkazala CRP (p = 0.048, HR = 0.50, 95 % CI 0.26–0.99) in Hb (p = 0.005, HR = 0.97, 95 % CI, 0.95–0.99).

Zaključek: Izsledki naše raziskave kažejo, da sta vrednosti CRP in Hb pred pričetkom zdravljenja neodvisna napovedna dejavnika poteka bolezni pri bolnikih z napredovalim nedrobnoceličnim karcinomom pljuč, zdravljenih s kemoterapijo, medtem ko soobolevnost, starost, LDH in število trombocitov nimajo neodvisne napovedne vrednosti. Prednost naše analize je, da smo vključili neizbrane bolnike iz rutinske klinične prakse. Vsi so imeli ob postavitvi diagnoze napredovalo bolezen in so bili zdravljeni po isti kemoterapevtski shemi.

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Abstract

Background: Prognostic factors may help the clinician in treatment decision making. The significance of C-reactive protein (CRP) as a negative prognostic factor has been shown in patients with different malignancies. However, only few studies have analyzed CRP as a prognostic factor in patients with advanced non-small cell lung cancer (NCLCS).

The aim of this study was to evaluate the prognostic value of CRP and other prognostic factors in a group of unselected population of patients with advanced NCLSC treated with platinum based chemotherapy.

Methods: The retrospective study was conducted by reviewing 53 medical files of advanced NSCLC patients treated with platinum/gemcitabine at the University Clinic Golnik between May 2004 and November 2008. The median age of patients was 65 years, most of them were males (75 %), smokers or ex-smokers (81 %), with performance status 1 (64.2 %) and stage IV disease (83 %).

The collected data included laboratory characteristics (Hb, platelet count, CRP, LDH) before chemotherapy, information on each individual patient's therapy and outcome. The median number of chemotherapy cycles received was 4 (range, 1–6).

Results: The median progression free survival (PFS) for the entire group was 4.8 months (range 0–20 months). Patients with elevated CRP levels (≥ 20 mg/l) had inferior PFS compared to those with low pretreatment CRP values (median PFS 8.4 vs 3.6 months, p=0.006). In Cox univariate regression analysis, CRP (p=0.016, HR=1.008, 95 %CI, 1.001–1.014), Hb (p=0.001, HR= 0.96, 95 %CI, 0.95–0.99), and comorbidity (p=0.051, HR=1.2, 95 %CI, 1.00 -1.45) were found to be significant prognostic factors; age, LDH, and platelet count on the other hand were not found to be significant prognostic factors. In multivariate analysis only CRP (p=0.048, HR=0.50, 95 %CI 0.26–0.99) and Hb (p=0.005, HR=0.97, 95 %CI, 0.95 -0.99) retained their independent prognostic value.

Conclusion: The survival of patients with advanced NSCLC treated by chemotherapy is significantly influenced by the patient's pretreatment CRP and Hb levels, and comorbidity only borderline so. The major advantage of this study is that it was performed on an unselected population of patients, but still uniform with respect to diagnosis, stage and agents used in chemotherapy treatment schedule.

Introduction

Lung cancer is the leading cause of cancer death in North America and Europe. The incidence of lung cancer estimated between years 2002 and 2006 in Slovenia was 90.1/100,000 for males and 28.3/100,000 for females.[1] The majority of patients are diagnosed at a late stage, with locally advanced or metastatic disease which is treated with palliative intent.

Approach to lung cancer treatment is multimodal. In recent 15 years, progress has been observed in sytemic as well as in local therapies. Cytotoxic chemotherapy remains the key component of treatment in metastatic setting of NSCLC. The use of third-generation platinum-based chemotherapy doublets improved one-year survival rate from 10–15 to 33 % compared with older chemotherapy regimens. Molecular analysis has evolved from simple histological characterisation of tumors to microarray-based interrogation of thousands of genes. These advances have enabled researchers to focus on molecular pathways that are active in NSCLC and sparked an interest in the development of individualized therapy as a strategy for increasing survival. New specific targeted therapies (bevacizumab, erlotinib, gefitinib) are nowdays also used in lung cancer treatment. For localised disease new less invasive surgical options are being offered to the patients (i.e. VATS). For years the primary approach for patients with early stage lung cancer has been surgery only. Based on the results of the international adjuvant lung cancer trial (IALT), cisplatin-based adjuvant therapy provides additional benefit in the outcome of patients with completely resected stage I, II or III NSCLC. With the introduction of modern 3-dimensional conformal radiotherapy techniques with CT or CT/PET based treatment planning, stereotactic body radiation therapy and hyperfractionated accelerated radiotherapy with concurrent chemotherapy, a benefit in out-

come and a different toxicity profile have been achieved.[2-5]

In the last 15 years, the 5-year relative survival of patients with lung cancer in Slovenia has increased by 2.2 %, but the prognosis still remains poor with 5-year relative survival of 12 %.[1]

Non-small cell lung cancer (NSCLC) is a heterogeneous disease which shares molecular and cellular origin but has different clinical behavior and prognosis. The predictability of population survival outcomes is of limited usefulness to clinicians due to the marked heterogeneity of the patients comprising the overall NSCLC population. Prognostic factors are thus used to divide patients into subgroups with different disease outcomes in order to improve the treatment decision in each individual patient.[6]

The literature on prognostic factors pertaining to the tumor, patient or environment is growing rapidly. Brundage et al.,[6] identified 169 prognostic factors by reviewing 887 articles on the survival of patients with NSCLC. The anatomical spread of the disease, defined by the TNM staging system is still the most powerful prognostic factor of NSCLC patients' survival. However, patients within the same stage of their disease may have very different survivals and a better prognostic information based on biological characteristics of tumor as well as on patients‘ characteristics are needed. Among the most commonly studied prognostic factors, which are also easily and regulary assesed in routine clinical practice, are performance status, female sex, age, hemoglobin and serum LDH levels, and comorbidity. New, putative molecular markers are under study (i.e.markers of tumor proliferation, markers of cellular adhesion and other molecular biological markers).

The relationship between inflammation and cancer has long been demonstrated. Several hypotheses have been proposed to explain this relationship. Tumor growth can cause tissue inflammation and hence an increase in the plasma levels of CRP. Cancer cells are known to produce various cytokines and chemokines that attract leukocytes, and some cancerous cells have been shown to express CRP and secrete IL-6 and IL-8, which in turn stimulate CRP production in the liver. These mechanisms imply that increased CRP is a response to the neoplastic process. On the other hand, chronic inflammation might have a causal role in carcinogenesis. Inflammation namely creates a tissue microenvironment where the reactive oxygen and nitrogen species released by inflammatory cells could cause potentially malignant DNA alterations.[7-10]

The significance of CRP as a prognostic factor for survival has been shown in patients with several malignancies, i.e. gastrointestinal cancer, melanoma, renal cell carcinoma, lymphohaematopoetic neoplasm, hepatic and endometrial cancers.[7-12] In a systematic review of the literature on the association between plasma levels of CRP and cancer published in 2007, 90 distinct studies were identified. In general, patients with cancer were shown to have higher CRP levels than healthy controls, but 5 studies provided some evidence that CRP could be related to colorectal and lung cancer.[8]

Few studies have analyzed CRP as a prognostic factor in advanced NSCLC. Independent prognostic significance was demonstrated in a retrospective study performed on 289 patients with advanced NSCLC.[13] Another study, partially prospective in design, also confirmed an independent negative prognostic value of pretreatment values of CRP in 161 patients treated with different therapies.[14] Prospective study performed in 106 patients with advanced NSCLC demonstrated prognostic significance of CRP, but published no information on the type of treatment.[15] To our knowledge, only one study considered regular measurements of CRP levels during treatment. This was a retrospective study performed on 210 patients receiving platinum based chemotherapy for advanced NSCLC, which was conducted to assess the prognostic value of regular CRP measurements. Elevated CRP levels were associated with decreased overall survival, and normalization of CRP values after 2 cycles of chemotherapy was associated with a lower risk of progression.[16] Studies performed in patients with a limited disease also demonstrated the prognostic significance of CRP. Preoperative CRP values were proven to

Table 1: Patient´s characteristics (Nr (number) = 53)

	Nr. of patients	Percent(%)
1. GENDER:		
Male	40	75.5
Female	13	24.5
2. AGE		
< 70	33	62.3
≥ 70	20	37.7
3. SMOKING STATUS:		
Current or ex-smoker	43	81.1
Never-smoker	10	18.9
4. PERFORMANCE STATUS:		
PS 0	12	22.6
PS 1	34	64.2
PS 2	6	11.3
PS 3	1	1.9
5. CLINICAL STAGE:		
IIIB	9	16.9
IV	44	83
6. TUMOR TYPE:		
adenocarcinoma	33	62,3
squamous cell carcinoma	18	34
7. CRP VALUE		
< 20 mg/l	21	39.6
≥ 20 mg/l	32	60.3

be an independent predictor of survival in 203 patients with NSCLC who underwent curative resection.[17] In series of 93 patients, Jones et al., reported in their study that the pretreatment value of CRP is positively correlated with an increased clinical and pathological tumor size in patients who underwent surgical resection; high values were also associated with the inability to achieve complete surgical resection.[18]

Based on the above mentioned studies, CRP levels seem to give additional prognostic information beyond that provided by cancer stage, histology, age, gender and comorbidity. The aim of our study was to evaluate the prognostic value of CRP in our series of patients with advanced NCLSC treated with platinum-based chemotherapy.

Patients and methods

The study cohort consisted of 53 consecutive patients with advanced NSCLC treated with platinum-based chemotherapy between May 2004 and November 2008 at the University Clinic Golnik, Slovenia. The collected data included demographic data, clinical data and lifestyle characteristics (age, gender, smoking status, stage, pathological tumor type, performance status (PS), comorbidity index), laboratory data and data on chemotherapy treatment.

All patients had cytologically or histologically confirmed disease and were staged according to the American Thoracic Society TNM classification (Mountain, 1991) on the basis of clinical findings, chest X-ray, bronchoscopy and computeed tomography of the thorax and abdomen and, where appropriate, abdominal ultrasound and isotope bone scan.

Comorbidity was assesed using the Comorbidity index and score of Charlson. Patient‘s smoking status was registered at the start of chemotherapy and patients were classified into two categories: (a) smokers or ex-smokers, and (b) non-smokers. Hemoglobine(Hb), CRP, lactate dehydrogenase (LDH) and platelet count were obtained from routine laboratory tests performed before the start of treatment. CRP was (also) observed as a discrete characteristic (to provide the visual Kaplan-Meier plots) with the cut-off set at 20 mg/l.

All patients included in the study were treated with platinum-based combination chemotherapy (cisplatin/carboplatin + gemcitabin) in three week cycle according to the routine clinical protocols. After progression on first-line platinum based chemotherapy patients received second-line chemotherapy and/or palliative therapy according to each individual patient‘s characteristics and preferences.

Table 2: Univariate and multivariate analysis of progression-free survival regarding clinical and laboratory characteristics

Variable	Univariate analysis	Multivariate analysis
	p value HR (95 % CI)	p value HR (95 % CI)
Age (years)	0.528 1.009 (0.981 – 1.039)	ns
Hb (g/l)	0.001 0.967 (0.948 – 0.987)	0.005 0.971 (0.951 – 0.991)
Platelet count (x 10/9/l)	0.093 1.002 (1.000 – 1.005)	ns
LDH (mkat/l)	0.614 1.032 (0.914 – 1.164)	ns
CRP (mg/l)	0.016 1.008 (1.001 – 1.014)	0.048 0.504 (0.256 – 0.993)
Comorbidity	0.051 1.205 (1.000 – 1.453)	0.472 1.075 (0.883 – 1.309)

In Cox univariate regression analysis, CRP and Hb were found to be significant prognostic factors, and comorbidity only borderline so. Age, LDH and platelet count were not found to be significant prognostic factors. In Cox multivariate analysis with Hb, CRP and comorbidity index included as factors, only CRP and Hb level turned out to be independent prognostic factors.

Statistical analysis

The endpoint of this study was progression-free survival (PFS). PFS was calculated from the date of diagnosis to the date of lung cancer progression, the date of death from any cause, or the date of the last follow-up; censored observations correspond to patients who were alive and in whom there was no evidence of disease progression at the time of the last follow-up. PFS as a function of the characteristics studied was estimated by the Kaplan-Meier method and the log-rank test was used to test for differences. The Cox uni- and multivariate hazards models were used to calculate the hazard ratios (HR) and their 95 % confidence intervals (95 % CI) in the analysis of PFS. Computations were done using the SPSS 15 statistical package. All reported p- values are two tailed.

Results

Patients' characteristics are presented in Table 1. The median age of our patients was 65 years (range 41–78 years); 20 patients were older than 70 years. The majority of patients were male (75.0 %), smokers or ex-smokers (81.0 %), with PS 1 (64.2 %), and had stage IV disease (83.0 %). The prevalent histological type was adenocarcinoma (62.3 %). The mean comorbidity index was 8.82 points (range 6–13).

Patients received a median of 4 (range 1–6) cycles of chemotherapy, the majority of patients were treated with cisplatin/gemcitabin regimen (90.5 %); two patients were started on cisplatin/gemcitabin chemotherapy, but were switched to carboplatin/gemcitabin regimen because of nephrotoxicity.

At the start of chemotherapy, the median value of Hb was 136 g/l (range 103–174 g/l), median value of platelet count was 340 x 10/9/ L (range 164–612), the median value of LDH was 3.49 mkat/l (range 1.4–14), and the median value of CRP was 28 mg/L (range 8–199 mg/l). Twenty-one patients (39.6 %) had CRP values lower than the cut-off at 20 mg/l, and 32 patients (60.4 %) had CRP values higher than the cut-off value (Table 1).

In Cox univariate regression analysis, CRP ($p = 0.016$, HR = 1.00, 95 % CI, 1.00–1.01), Hb ($p = 0.001$, HR= 0.96, 95 % CI, 0.95–0.99) and comorbidity ($p = 0.051$, HR = 1.2, 95 % CI, 1.00 -1.45) were found to be significant prognostic factors (comorbidity only borderline so). Patients with higher CRP levels, lower Hb levels and higher comorbidity index had a significantly higher risk of early progression. Age, LDH, and platelet count were not found to be significant prognostic factors. In Cox multivariate analysis with Hb, CRP, and comorbidity index included as factors, only CRP ($p = 0.048$, HR = 0.5, 95 % CI 0.26–0.99) and Hb ($p = 0.005$, HR = 0.97, 95 % CI, 0.95–0.99) level turned out to be independent prognostic factors (Table 2).

The median progression-free survival for the entire group was 4.8 months (range 0–20 months). The patients with elevated CRP levels (≥ 20 mg/l) had inferior PFS

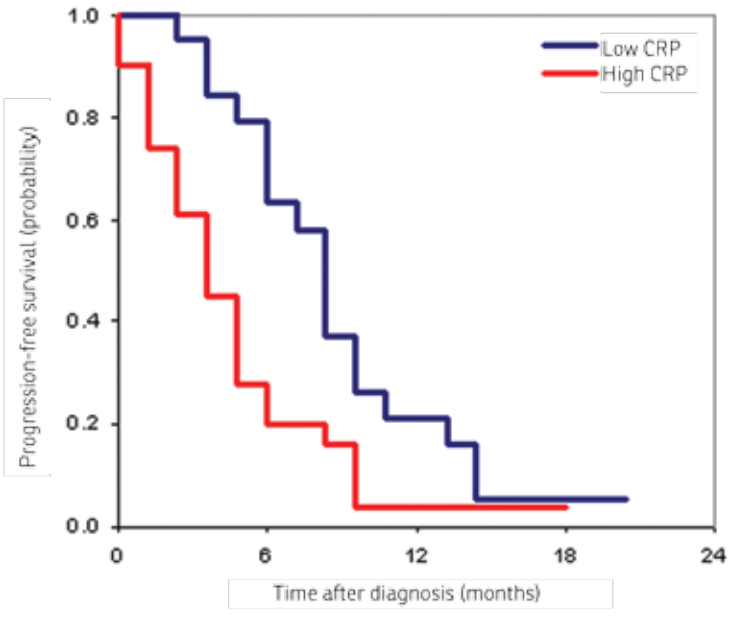

Figure 1: Progression-free survival according to CRP values
Patients with elevated CRP levels (≥ 20 mg/l) have inferior profression-free survival compared to patients with lower values of pretreatment CRP (median progression –free survival 8.4 vs 3.6 months, p=0.006)

compared to patients with lower values of pretreatment CRP (median PFS 8.4 vs 3.6 months, p = 0.006) (Fig. 1). No significant difference in PFS was found with respect to the patient's age (Fig. 2).

Due to the low numbers of patients in the respective subgroups we were unable to evaluate the prognostic value of gender, smoking status, histological type and PS.

Discussion and conclusion

In our retrospective analysis the pretreatment CRP and Hb values turned out to be the most important prognostic factors in advanced NSCLC patients treated with platinum-based chemotherapy. Higher CRP levels (over 20 mg/l) and lower levels of Hb resulted in a worse progression-free survival. While the comorbidity index was found to be a significant prognostic factor in a univariate analysis, it did not retain an independent prognostic value in multivariate analysis.

CRP is a nonspecific marker of inflammation. C-reactive protein (CRP) is an acute-phase reactant and is elevated during bacterial infection, inflammatory disease, trauma, myocardial infarction, surgery and cancer.[8] It is mainly produced by hepatocytes in response to elevated cytokine levels (mainly IL-6) after inflammatory stimulus. Both genetic and environmental factors influence an individual´s basal CRP concentration, and thus circulating CRP levels in apparently healthy people can vary from 0.1 to 10 mg/l.[8]

It is not allways possible to find out whether a CRP elevation is due to acute infection or cancer. In our study we determined the value of CRP in blood samples, which were collected just before the start of chemotherapy and at that time no clinical signs of an infectious disease were present. It is possible that in patients with inoperable NSCLC, an elevated CRP level might reflect the extent of the disease, with the systemic inflammatory reaction being a response to an ongoing malignant process. But also some other explanations should be considered: thus CRP could be a marker of acute infection or a marker of an ongoing low-grade systemic inflammatory reaction in patients with COPD disease. Smoking could also affect CRP; namely, one of the consequences of smoking is persistent low-grade systemic inflammation. However, it should be pointed out that in our series of patients the independent prognostic value of CRP was confirmed in patients with extensive disease, without clinical signs of infection and mainly smokers.

The results of our study are in line with those reported in other studies, which also confirmed the impact of elevated CRP level on the survival of patients with NSCLC. A study by Koch et al., which was performed on 289 patients with advanced NSCLC, demonstrated the prognostic significance of pretreatment CRP values. However patients in this study were treated with various first--line chemotherapy regimens.[13] In a study by Forrest et al., which also confirmed the prognostic value of CRP, only 40 % of the included 161 patients were actively treated by either chemotherapy or radiotherapy. The aim of this study was actually to assess the value of combining CRP and other recognised prognostic factors (stage, PS and hypoalbuminemia) in order to form new prognostic scores.[14] Another previously mentioned prospective study performed on 106 patients with advanced NSCLC demonstrated the prognostic significance of CRP, but published no information on the type of

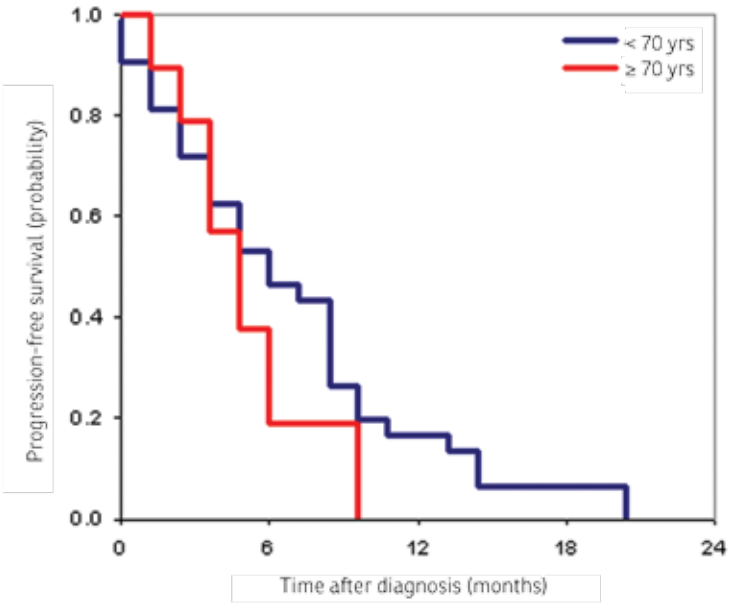

Figure 2: Progression-free survival according to age (cutoff point 70 years)
No significant difference in progression-free survival was found with respect to the patients' age (median progression-free survival for patient younger than 70 years 6 months vs 5.8 months for patients older than 70 years, p=0.17).

treatment.[15] All patients in our analysis were treated with the same first -line chemotherapy schedule.

Of other putative prognostic factors Hb values before the initiation of chemotherapy proved to be the most important prognostic factor in our study. This is in line with some other studies which found Hb to be an independent negative prognostic factor, anemia was also associated with a diminished response to chemotherapy and a decreased survival in patients with advanced NSCLC.[19,20] In our study population Hb values at the beginning of treatment were surprisingly high. It is possible that some of our patients were suffering from COPD and prolonged mild hypoxemia which could explain higher levels of Hb. In that case, the Hb value would not reflect only a malignant disease but also an underlying pulmonary disease.

Comorbidity was found to be of borderline significance in a univariate analysis, but it did not retain an independent prognostic value in a multivariate analysis as CRP and Hb were much stronger prognostic factors. A possible explanation of this result is that most of our patients had one or more concomitant diseases and that the variation in comorbidity index was quite small.

Interestingly enough, the survival of patients younger or older than 70 years in our analysis was similar. In epidemiological literature, the age of 65 years is usually considered a cut-off point to identify an elderly population. On the contrary, the age of 70 is frequently used as a cut-off in clinical trials, and in most of the trials evaluating chemotherapy in various cancers patients older than 70 years were not included. However, the main clinical data on chemotherapy for elderly patients are actually gathered from clinical trials of patients with advanced NSCLC. Based on the results of those studies, chemotherapy can be considered in the treatment of elderly patients with lung cancer. But until now mostly monochemotherapy and non-platinum regimens have been studied and only few prospective clinical experiences with cisplatin-based chemotherapy for elderly patients with advanced NSCLC have been reported.[21] In our analysis, there was no significant difference in PFS between patients older or younger than 70 years, however no data on toxicity and QOL were collected. For any conclusions on this subject, a prospective randomised study in a larger number of patients should be performed.

Most of the studies on prognostic factors in patients with NSCLC conducted so far included patients in various stages of the disease, who were receiving different types of chemotherapy, without taking treatment into consideration. In our analysis, only patients with advanced NSCLC treated with platinum-based chemotherapy were studied. The major advantage of our study is that it was performed on an unselected population of patients, recruiting all the patients treated by platinum-based first line chemotherapy on a routine clinical basis at a single university institution. The major disadvantage is that it was performed retrospectively and on a relatively small group of patients.

In conclusion, the pretreatment value of CRP provides additional prognostic information to well established factors such as stage, PS and Hb in advanced NSCLC. Given the fact that the determination of CRP is done routinely before the beginning of chemotherapy treatment and is readily available to a clinician, it could serve as an additional information when deciding about toxic chemotherapy, especially in patients

with other comorbidities. Large prospective studies evaluating the prognostic as well as predictive values of CRP for the response to various therapies might help us in the future to better tailor our therapy for each individual patient with advanced NSCLC.

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