The predictive value of pre-treatment inflammatory markers in advanced non-small-cell lung cancer

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ABSTRACT

Background

Accurate prediction of outcome in advanced non-small-cell lung cancer (NSCLC) remains challenging. Even within the same stage and treatment group, survival and response to treatment vary. We set out to determine the predictive value of inflammatory markers C-reactive protein (CRP) and white blood cells (WBCs) in patients with advanced NSCLC.

Patients and Methods

Patients were assigned a prognostic index (PI):

- 0 for CRP 10 mg/L or less and WBCs 11×10^9/L or less,
- 1 if one of the two markers was elevated, and
- 2 if both markers were elevated.

We then used chest computed tomography (CT) imaging to evaluate response after 2 cycles of chemotherapy treatment.

Results

Of 134 patients, 46 had a PI of 0; 60, a PI of 1; and 28, a PI of 2. Disease progressed in 41 patients. Progression was significantly more frequent among patients with a PI of 2 (p = 0.008). Median survival was 20.0 months for the PI 0 group, 10.4 months for the PI 1 group, and 7.9 months for the PI 2 group (p < 0.001). The PI was the only significant prognostic factor for survival even after adjustment for performance status, smoking, and weight loss (hazard ratio: 1.57; 95% confidence interval: 1.2 to 2.14; p = 0.004).

Conclusions

Inflammatory state correlates significantly with both chemotherapy response and survival in stage IV NSCLC. The PI may provide additional guidance for therapeutic decision-making.

KEY WORDS

Non-small-cell lung cancer, NSCLC, predictive factors, prognostic factors, CRP, response, survival

1. INTRODUCTION

Patients with NSCLC have heterogeneous tumour and host biology that leads to wide predictive and prognostic variance. To improve medical decision-making and to deliver the most suitable treatment, predictive and prognostic factors are used to divide the NSCLC population into subgroups. Most studies have focused on the clinical characteristics of tumour and host, such as disease stage and performance status. However, even within the same stage and with a similar performance status, response to treatment and survival varies from patient to patient.

Basic scientists have clearly demonstrated the importance of molecular and cellular pathways linking cancer and inflammation. Many blood markers, including acute-phase C-reactive protein (CRP), were identified. The CRP induced by a cytokine consortium in which interleukin-6 (IL-6) is the dominant partner was shown to be an important adverse survival determinant—indepedent of stage and performance status—in advanced cancer, including non-small-cell lung cancer (NSCLC)..

In an effort to further refine prognostic accuracy, a variety of indices based on inflammatory markers have been proposed. The Glasgow Prognostic Score (GPS) was shown to be superior to a subjective assessment of Eastern Cooperative Oncology Group
(ECOG) performance status (PS) in predicting the survival of patients with advanced NSCLC. However, little is known about the effect of underlying inflammation on the response of NSCLC to chemotherapy.

In the present study, we evaluated the association between baseline systemic inflammation and two outcome measures in advanced NSCLC: freedom from progression in response to chemotherapy, and survival.

2. PATIENTS AND METHODS

2.1 Participant Identification

This prospective study was conducted between January 1, 2005, and January 10, 2009, in a cohort of consecutive patients with newly diagnosed stage IV (per the 7th edition of the International Association for the Study of Lung Cancer staging system) NSCLC who had been treated with 2 cycles of platinum-based double-agent chemotherapy.

Computed tomography (CT) imaging of chest and abdomen, followed by metabolic imaging using positron-emission tomography, was used for staging. The particular chemotherapy regimen prescribed was chosen according to protocols used at the Jewish General Hospital, Montreal, Quebec. Possibilities included cisplatin or carboplatin in combination with paclitaxel, gemcitabine, vinorelbine, docetaxel, or etoposide. The choice of the treatment regimen was at the discretion of the treating physician.

The study protocol was approved by the Institutional Review Board at the Jewish General Hospital, and all patients provided informed consent.

2.2 Prognostic Index

Standard techniques were used to determine CRP, albumin, white blood cell count (WBCs), hemoglobin, and lactate dehydrogenase. A particle-enhanced turbidimetric assay was used to measure CRP. The upper limits of the normal ranges for CRP (10 mg/L) and for WBCs (11 × 10⁹/L) were used as cut-off points. Based on previous work by our group, the CRP and WBC results were used to categorize patients into 3 different “prognostic index” (PI) groups (Table 1):

- PI 0 if CRP 10 mg/L or less and WBCs 11 × 10⁹/L or less,
- PI 1 if one of the two markers was elevated, and
- PI 2 if both markers were elevated.

2.3 Response to Chemotherapy

Response to chemotherapy was evaluated by chest CT after 2 cycles of chemotherapy. The response was categorized as progressive disease or freedom from progression. Freedom from progression was defined as an absence of objective progression; it included patients with either a complete response, a partial response, or stable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST).

2.4 Statistical Analysis

The primary outcomes of the study were the response to 2 cycles of platinum-based chemotherapy (as defined earlier) and overall survival. The association between PI and freedom from progression was investigated by chi-square test. Using t-tests and chi-square tests as appropriate, baseline blood parameters and the covariates of interest (age, sex, PS, smoking history, stage, and weight loss at first presentation) for the 3 PI groups were compared to confirm the homogeneity of the groups. Contingency tables and the chi-square test were used for categorical variables; t-tests were used for continuous variables.

Overall survival was defined as the time in months from diagnosis to the end of the study. Patients alive at the time of the last observation (March 30, 2009) were censored. Survival analysis was performed using the Kaplan–Meier method. Differences were assessed using a log-rank test. A Cox proportional hazards model was used to estimate the predictive power of the PI. The potential baseline prognostic factors included in the model were age, sex, CRP, hemoglobin, weight loss, smoking status (smokers and ex-smokers vs. never-smokers), ECOG PS, and PI. The likelihood ratio was used to test the contribution of each variable to the model when added last (that is, after adjustment for all of the other covariates).

All statistical analyses were carried out using the SPSS software package (version 14.0: SPSS, Chicago, IL, U.S.A.). All statistical tests were two-tailed. Statistical significance was accepted at p values of 0.05 or less.

3. RESULTS

The study identified 303 patients with stage IV NSCLC. Of those 303 patients, 206 received chemotherapy and 97 were offered palliative radiation or supportive care (Figure 1). Of the 206 patients given chemotherapy, 69 were treated with a single agent and 137 received double-agent chemotherapy. In 3 patients, CRP data were missing. The remaining 134 patients who had received 2 cycles of therapy and whose records had no missing data were analyzed.
Table II shows the characteristics of the patient cohort. Mean age was 62 years (range: 31–83 years). Most had adenocarcinoma, a good PS, and no weight loss. Sites of metastases included lung, lymph nodes, bone, liver, and adrenal glands. The group included 65 ex-smokers (48%) who had quit more than 1 year before diagnosis, 40 patients (30%) who were still smoking at the time of diagnosis, and 29 never-smokers (22%). The most common treatment regimens were carboplatin–gemcitabine and carboplatin–paclitaxel.

Most patients had normal hemoglobin, albumin, and lactate dehydrogenase levels. The median CRP concentration before chemotherapy was 13.2 mg/L. In 77 patients (57%), CRP exceeded 10 mg/L. Median WBCs were 9.4×10⁹/L. Before chemotherapy, WBCs were elevated in 39 patients (29%).

We calculated the PI for each patient based on binary CRP and WBC values. In 46 patients (34%), the PI was 0; in 60 (45%), the PI was 1; and in 28 (21%), the PI was 2. We observed no association of PI with age or ECOG PS (Table III); however, significantly more men, smokers and ex-smokers, and patients with a weight loss of 5% or more were in the PI 2 group.

After 2 cycles of chemotherapy, 41 patients (31%) were found to have progressive disease. The PI and progression (Table IV) were weakly positively correlated (\( \chi^2 = 0.233; \ p = 0.007 \)). In the logistic regression analysis, the PI was the only significant predictor of progression. Age, sex, ECOG PS, cancer stage, and smoking status were nonsignificant (Table V).

Median follow-up was 10.3 months (range: 2.69–41.87 months). At the time of censoring, 86 patients (64%) had died. Overall median survival was 11.9 months [95% confidence interval (CI): 9.9 to 13.8 months]. Median survival for the PI 0 group was 20.0 months (95% CI: 19.5 to 30.5 months); for the PI 1 group, it was 10.4 months (95% CI: 8.3 to 12.5 months); and for the PI 2 group, it was 7.9 months (95% CI: 4.2 to 11.7 months; \( p < 0.001 \); Figure 2).

Univariate analysis identified CRP and WBCs as significant prognostic factors in addition to PS. We observed no interaction between CRP and WBCs. When CRP and WBCs were combined into the PI, the effect was even stronger.

In a multivariate analysis, using the backward logistic regression method in a Cox model with all the variables of interest included, only the PI retained significance (hazard ratio: 1.57; 95% CI: 1.2 to 2.14; \( p = 0.004 \)). The hazard for death was 2.5 for PI 1 and 3.9 for PI 2.

4. DISCUSSION

To our knowledge, this is the first prospective study aimed at evaluating the predictive value of pretherapeutic inflammatory markers in NSCLC.
TABLE III  Clinical difference among the prognostic index (pi) groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients by pi group (n)</th>
<th>p Value (Spearman correlation)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(N=46)</td>
<td>(N=60)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>≥65</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Smoking</td>
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<td></td>
</tr>
<tr>
<td>Smoker or ex-smoker</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>ECOG performance status</td>
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</tr>
<tr>
<td>0–1</td>
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</table>

ECOG = Eastern Cooperative Oncology Group.

We found that, combined into a pi, elevated plasma CRP and WBCs at the time of NSCLC diagnosis are independently associated with disease progression in response to 2 cycles of first-line treatment and with shorter overall survival in advanced NSCLC. A lower pi score was associated with a reduction in the probability of disease progression after chemotherapy. The hazard for death was elevated by a factor of 2.5 for the pi 1 group and by a factor of 3.9 for the pi 2 group as compared with the pi 0 group. The development of the pi provides improved prediction accuracy for progression after 2 cycles of first-line treatment.

Despite advances in the accuracy of clinical staging, predictive and prognostic modeling for patients with advanced NSCLC is still not satisfactory. A search is underway for molecular factors that might account for variation in tumour biology and its effect on survival. It is now becoming clear that the tumour microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process. This environment promotes proliferation, survival, and migration of tumour cells and results in increased tumour aggressiveness. Some lung cancer cell lines have been shown to produce IL-6. Indeed, there is evidence that IL-6 is strongly related to CRP and that CRP, a routinely available and well-standardized clinical laboratory measurement, is a useful surrogate measure of tumour biology in patients with NSCLC.

An increased serum CRP level has been recognized as an ominous prognostic factor for several malignant tumours, including lung cancer. In a prospective cohort study, Siemes et al. hypothesized that CRP level and CRP gene variation are associated with an altered risk of colorectal, lung, breast, and prostate cancer. In addition, CRP is known to modulate both innate and adaptive immunity.

Other biologic factors such as baseline leucocytes and polynuclear cells have been less frequently studied in cancer patients in terms of their significance as predictive factors. A few studies demonstrated that in addition to PS, WBCs are an independent prognostic factor for poor survival in advanced NSCLC.

These insights are encouraging new anti-inflammatory therapeutic approaches to cancer treatment. However, the association between elevated inflammatory markers and chemotherapy response has not been clearly established.

The success of chemotherapy in esophageal and prostate cancer may relate to CRP status. Wilop et al. correlated changes in CRP over time with response to treatment in lung cancer patients receiving chemotherapy. Those authors reported that normalization of CRP was associated with a low risk for progression, but that patients with an increase in CRP of more than 25% showed progressive disease in most cases. However, their retrospective study was underpowered, given the small sample size and lack of control for stage and PS.
Several prognostic indices based on inflammatory factors have recently been described in NSCLC. The most widely recognized is the GPS, which uses a combination of CRP and albumin. When compared with PS and WBCs, GPS was superior in predicting survival. However, we found that serum albumin at diagnosis was occasionally low in our population and that adding WBCs to CRP resulted in superior stratification of the resulting subgroups.

There are several possible explanations to account for the association between CRP and chemotherapy response. Chronic inflammation results in excessive cell proliferation and activation of a cascade of cellular actions that can lead to induction of irreversible DNA damage and subsequent tumour progression. Chronic inflammation might also be responsible for activation, in peripheral leucocytes, of messenger RNAs for nuclear factor κB inhibitor and for the effect of that inhibitor on cytochrome systems. A tumour-associated inflammatory response involving CRP and IL-6 downregulates the CYP3A4 gene and correlates with suppression of drug metabolism, resulting in increased toxicity during chemotherapy.

Incorporated into a PI, CRP and WBCs identified 3 subgroups of stage IV NSCLC patients with distinct risks of progression and death. This information might be pertinent to treatment decision-making and might also influence a revised staging system. If the objective is prognostic stratification, then using anatomic features alone for staging is no longer sufficient.

The major strength of the present study is the uniformity of the patient population with respect to diagnosis, stage, and treatment. The study is limited by the relatively small cohort and the weak correlation between PI and freedom from tumour progression.

5. CONCLUSIONS

Based on widely available, inexpensive, and easy-to-perform measurements, we developed a novel PI. The proposed PI may improve the accuracy of predictions of freedom from progression and of survival in response to first-line treatment. It may also provide information to complement other prognostic models, such as those based on gene profiling. The biologic markers that form the PI could be incorporated into the more traditional anatomic methods of staging.
6. ACKNOWLEDGMENTS

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7. CONFLICT OF INTEREST DISCLOSURES

All authors declare that there are no financial conflicts of interest.

8. REFERENCES

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