Does chemotherapy-induced leukopenia predict a response in small-cell lung cancer?

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Abstract The correlation between chemotherapy-induced toxicity and treatment outcome in cancer patients has not been studied thoroughly. Our aim was to evaluate whether there is any relationship between chemotherapy-induced leukopenia and response to treatment in small-cell lung cancer (SCLC). Data derived from records of 228 patients treated within two prospective multicentre phase II studies were analysed. In the first study (101 patients) chemotherapy included vincristine, epirubicin and cyclophosphamide and, in the second (127 patients), cyclophosphamide, etoposide and epirubicin; both regimens were given every 3 weeks. In the present analysis, the correlation between treatment outcome (response rate and survival) and highest scores of leukopenia within the first two and up to the fourth chemotherapy cycle, respectively, was evaluated. The objective response rate for the entire group was 66%; 53% in patients whose white blood cells remained normal and 85% in those who developed leukopenia within the first two cycles ($P = 0.000$). In multifactorial analysis, also including other treatment- and patient-related factors, independent correlation with response to chemotherapy was found for leukopenia ($P = 0.001$), chemotherapy regimen ($P = 0.002$) and the combined relative dose intensity ($P = 0.018$), but not for patient sex, age, performance status, pre-study weight loss, extent of disease and initial white blood cell count. Leukopenia within the first two cycles of chemotherapy was not correlated with survival, whereas such correlation for leukopenia occurring up to the fourth cycle was at the borderline level ($P = 0.060$). These findings suggest a relationship between chemotherapy-induced leukopenia and tumour response in SCLC.

Key words Dose intensity · Leukopenia · Small-cell lung cancer · Tumour response

Introduction

Small-cell lung cancer (SCLC) is a well-recognised tumour, distinct from non-small-cell lung carcinomas in its particular clinical and biological features. This tumour is highly responsive to chemotherapy and many studies have been carried out to evaluate the relation between dose level, total dose, dose intensity and treatment effect. It has been suggested that chemotherapy efficacy is dependent both on dose intensity and on individual patient sensitivity. These factors are also determinants of treatment toxicity. Consequently, a potential correlation between chemotherapy-induced toxicity and treatment efficacy may be expected, but this problem has only occasionally been studied. Clinically, the predominant toxicity accompanying chemotherapy is myelosuppression, manifested most frequently by leukopenia. This side-effect is also the most suitable parameter for the
analysis of correlation between treatment toxicity and efficacy since leucocyte counts are routinely checked during treatment and represent a measurable and objective value.

The aim of the present study was to evaluate the correlation between chemotherapy-induced leukaemia and tumour response in SCLC, with special reference to the predictive value of leucocyte counts during the initial period of treatment.

Materials and methods

The subject of this analysis was data derived from the records of SCLC patients treated within two prospective non-randomised multicentre phase II trials (named here CEE and VEC, from the abbreviations of the regimens used) performed between 1986 and 1991 by the Polish Lung Cancer Co-operative Group (seven centres listed above). Results of both trials have previously been published (Jassem et al. 1992, 1994).

Treatment protocols

Eligibility criteria for both trials included histological or cytological diagnosis of SCLC and measurable or evaluable disease. The VEC study included only patients with limited disease and the CEE study included patients with both limited and extensive disease but not those presented with brain metastases. In both studies no prior chemotherapy or radiotherapy was allowed, the initial white blood cell count had to be above $4.0 \times 10^9/l$, the platelet count above $100 \times 10^9/l$, total serum bilirubin less than $25 \mu mol/l$, serum creatinine less than $130 \mu mol/l$, and there had to have been no recent myocardial infarction or uncontrolled arrhythmia. All patients had to give informed consent in accordance with institutional practice.

Pretreatment evaluation included physical examination, electrocardiogram, left ventricular ejection fraction (optional), chest radiography and tomography, fibre-optic bronchoscopy, a complete blood count and biochemistry, an abdominal computed tomography (CT) scan or ultrasound and bilateral posterior iliac crest bone marrow biopsy. A bone scan or radiological survey and brain CT scan were performed in patients suspected of having bone or brain metastases respectively.

The VEC study was designed as a three-step phase II trial. Chemotherapy consisted of cyclophosphamide 1000 mg/m$^2$ i.v. on day 1, vincristine 1 mg/m$^2$ i.v. on day 1, and escalating doses of etoposide: 50, 70, and 90 mg/m$^2$ i.v. on day 1 in three consecutive groups of patients. Cycles were repeated every 3 weeks. In responders, thoracic irradiation was administered 2 weeks after the fourth chemotherapy cycle. Chemotherapy was then continued up to nine cycles unless progression or excessive toxicity occurred earlier.

The CEE study was a non-randomised phase II trial. Chemotherapy consisted of cyclophosphamide 1000 mg/m$^2$ i.v. on day 1, etoposide 70 mg/m$^2$ on day 1 and etoposide 100 mg/m$^2$ i.v. on days 1, 3 and 5. Cycles were repeated every 3 weeks. Chemotherapy was continued up to a total number of five cycles, unless progressive disease or excessive toxicity occurred earlier.

In both studies, before each cycle patients were assessed by physical examination, ECOG performance status, electrocardiogram, complete blood count and biochemistry. Chemotherapy administration was delayed a week if, on the day of therapy, either the white blood cell count was less than $3.5 \times 10^9/l$ (VEC trial) or $3.0 \times 10^9/l$ (CEE trial) or and the platelet count was less than $100 \times 10^9/l$. If postponement of chemotherapy was necessary for more than 3 weeks, the patient was taken off the study. No dose reduction was foreseen in either protocol. No haemopoietic growth factors were administered for leukaemia.

Assessment of correlation between leukaemia and treatment efficacy

Patients were eligible for the analysis of correlation between leukaemia and treatment outcome if they received at least two cycles of chemotherapy and data on their treatment efficacy and myelotoxicity were available.

Response to chemotherapy following WHO criteria (Miller et al. 1981) and overall survival were selected as measures of treatment efficacy. In the present analysis in VEC patients the best response up to the fourth cycle was recorded, and in CEE patients the best response up to the fifth cycle (the response after the fourth cycle was not assessed in the latter study).

Two analyses were performed in which the highest score of leukaemia (following WHO criteria) within the first two cycles and up to the fourth cycle were recorded. Body temperature and neutrophil counts were not recorded in patient study forms, therefore these parameters could not be analysed, nor was the correlation between other treatment-related complications and tumour response addressed.

Apart from leukaemia, the significance of the following factors was tested: patient age, sex, pre-therapy weight loss, performance status, extent of the disease, chemotherapy regimen, combined relative dose intensity (CRDI) and initial white blood cell count. Histologically bone marrow metastases were found in only five CEE patients, therefore no separate analysis of leukaemia scores was done in this group.

Relative dose intensity (RDI) was defined according to the previously described formula $(RD_{m}/ID_{d})/(ID_{d}/RD_{m})$ where $RD_{m}$ is the received dose, $ID_{d}$ the intended dose, $ID_{t}$ the intended duration and $RD_{t}$ the actual duration (Souhami et al. 1994). The RDI represents the ratio between actual and projected DI. In our study the RDI was referred to the actual number of cycles administered in each patient up to a maximum of four cycles. To compare three different levels of etoposide in VEC patients, the highest level (90 mg/m$^2$) was considered a 1.0 reference dose. RDI was calculated for each of the three drugs in both regimens (i.e. cyclophosphamide, etoposide and etoposide for CEE and vincristine, etoposide and cyclophosphamide for VEC). A combined RDI (CRDI) for all three drugs in each regimen was calculated as an arithmetic mean of the three respective RDI values (Sirzea et al. 1994).

The correlation between clinical factors and response was assessed with the use of $\chi^2$, Student's $t$ or univariate linear regression tests. The independent impact of particular factors on tumour response was computed with the use of a multifactorial linear regression test. The impact on survival was assessed with the multifactorial Cox analysis. A value of $P < 0.05$ was regarded as significant. Survival was calculated from the first day of treatment. Survival curves were generated by the Kaplan-Meier method and compared with the use of the log-rank test.

Results

A total of 254 SCLC patients were treated within both studies, of whom 228 were eligible for the analysis of correlation between leukaemia and response. A total of 101 patients (44%) received the VEC regimen and 127 patients (56%) the CEE regimen. The ages of the patients ranged from 24 to 74 years (mean 55 years) (Table 1). There were 174 men (76%) and 54 women (24%); 160 patients (70%) had limited disease and 68 (30%) extensive disease (in the VEC study only patients with limited disease were allowed).

Tumour response and CRDI were assessed in the entire group after a median of four cycles (range two to five). Four planned cycles of VEC and five planned