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Short communication

A feasibility study of testing new drugs for small-cell lung cancer in patients with a poor performance status

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Summary. Testing of new drugs in small-cell lung cancer is definitely necessary for the development of agents that might be effective against this tumor. However, testing such drugs in previously untreated patients with a good performance status (PS) may give rise to ethical problems. When previously treated patients are used in testing, potentially effective agents could well elude discovery. Patients who are not eligible for "standard" combination chemotherapy, e.g. untreated patients with a poor PS, may be suitable for testing of new drugs. To evaluate the potential usefulness of such patients in the testing of new agents, we evaluated an effective drug (etoposide) at a relatively nontoxic dose in a group of 14 patients with a PS of 4 (WHO). Oral etoposide resulted in a response in only 3 cases, whereas 5 subjects died of therapy-related toxicity. We conclude that previously untreated patients with a poor PS are not suitable candidates for the testing of new drugs.

Introduction

Small-cell lung cancer (SCLC) is a chemosensitive tumor. For the past two decades, chemotherapy has universally been considered to be the treatment of choice in this disease. Despite its initial success, which in the majority of patients usually results in a rapid tumor response, only subjects with a good performance status (PS) and a limited tumor load are candidates for long-term disease-free survival and/or cure [6]. The further development of currently used chemotherapy regimens is necessary to improve the outcome in a much larger group of patients. However, attempts with high-dose chemotherapy [12] and late-intensification chemotherapy [5] and the use of so-called non-cross-resistant regimens [7] have all failed. Further improvement of the results thus far obtained using currently available drugs is hardly to be expected; therefore, new drugs are needed.

Testing of drugs potentially effective against SCLC is difficult; most patients who are candidates for phase II studies have either failed treatment or shown disease progression after "standard" combination chemotherapy, usually developing a poor PS and drug resistance. In this situation, the chance that a new drug will be effective is small [9], and it may produce excessive toxicity. It would be more effective to test these drugs in untreated patients; however, withholding the benefits of available treatment modalities from such patients might create ethical problems.

Patients with a poor PS have a very short life expectancy and are therefore usually excluded from phase II studies; this implies that this group of patients is the only one for whom no standard therapy is known. To evaluate the potential usefulness of this group of previously untreated patients in the testing of new drugs, we treated them with a drug that has proven efficacy and produces minimal toxicity [11].

Patients and methods

A total of 14 patients with histologically or cytologically proven SCLC were treated; their median age was 62 years (range, 44–76 years). All subjects had a WHO PS of 4 and had not previously undergone chemo- or radiotherapy. All patients were hospitalized. Staging procedures were limited to a minimum, but it was clear that all subjects had extensive disease.

A total dose of 800 mg/m^2 etoposide was given orally over 5 consecutive days at 4-week intervals. The drug was given in 50-mg capsules. The daily dose was taken before or shortly after breakfast. Toxicity and response were scored according to WHO criteria; response was evaluated after each cycle.

Results

Toxicity was severe, with 8 of 14 patients developing grade 3/4 leukopenia and/or thrombocytopenia. Gastro-in-

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testinal toxicity of grade 2–3 was observed, and grade 3 diarrhoea occurred in three patients. In all, 11 subjects died before the second course was started; 6 deaths were due to tumor progression; 3 to aplasia-related septicemia; and 2, to massive haemorrhage during thrombocytopenia. A partial response was achieved by 3 patients (21%), resulting in a significant improvement of their PS; 2 of them subsequently received combination chemotherapy. These partial responders survived for 11, 19 and 21 months, respectively.

Discussion

A poor initial PS is an adverse prognostic factor in SCLC [8]. PS is a complex parameter that apparently results from the impairment of the function of several organ systems by the tumor burden in the patient.

In the small group of patients described in the present study, the toxicity of this etoposide regimen was considerable. Myelosuppression was especially notable in these subjects as compared with a group of elderly patients (>70 years) with SCLC who were given the same regimen in another study [11]. In the latter investigation, only mild hematologic toxicity was observed. The reasons for the unexpectedly severe toxicity observed in the present study are unclear. One possible explanation for the severe hematologic toxicity could involve the extensive bone marrow metastases found in patients with a large tumor burden.

This study clearly shows that in patients with a PS of 4, a good tumor response cannot be expected following the administration of known chemotherapy regimens, even if they are treated with a single agent known to be among the most active against SCLC [11]. Therefore, these patients should not be considered as candidates for experimental chemotherapy. The toxicity of oral etoposide in our subjects was unpredictable and severe, and the response rate was much lower (21%) than that obtained in other previously untreated patients [11]. If this investigation had been a formal phase II study using an unknown cytostatic drug, the conclusion would have been that oral etoposide is a highly toxic agent that shows only marginal activity against SCLC. The question remains as to whether these patients should be subjected to antitumor therapy or be given only symptomatic palliative treatment.

The question as to which group of patients should be selected for the evaluation of new drugs remains difficult and depends heavily on ethical arguments for and against a given approach. It is probably impossible to obtain advice that is universally applicable to solving this problem. The most ideal candidates are fit, untreated patients with extensive disease [4]. However, arguments rejecting this strategy have been presented in the literature: pretreatment of such patients with an inactive new drug might result in the enhancement of resistance to normally active chemotherapy combinations [3]. A second possibility involves patients who have suffered a relapse following a long therapy-free interval; about two-thirds of the tumors in these patients remain sensitive [10]. Again, the ethically complicated question arises as to whether one should withhold an effective reinduction therapy that prolongs survival and probably provides the most palliative benefit to the subject.

For both of these approaches, the chance of finding an active new drug is quite good. However, considering the large number of agents that are active against SCLC, it remains questionable as to whether we really need new drugs that can be found only by testing in patients with so-called drug-sensitive tumors. One of the most recent examples of such an active drug, teniposide [1, 9], has not yet become the basis of new chemotherapy regimens, and this drug is not expected to have a major impact on the extremely poor results obtained in the large majority of SCLC patients.

The only new drugs relevant for the treatment of SCLC are those that are active in patients who are clinically resistant to currently used cytotoxic drugs. In such patients, agents that obtain a response rate of $\geq 10\%$ should be considered to be possibly active and to warrant further investigation in previously untreated patients with SCLC [2].

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