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Perspectives in Cancer Research

Identification of New Drugs in Pretreated Patients with Small Cell Lung Cancer

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THE SEARCH for new drugs in the treatment of small cell lung cancer (SCLC) is at the present time a difficult issue, as Dr Aisner pointed out in his recent editorial [1]. Patients pretreated by aggressive chemotherapy become widely refractory to multiple antineoplastic agents and the activity of novel drugs may be underestimated when studied in these patients; on the other hand, administration of investigational agents as initial treatment is a subject of ethical and scientific debate.

In order to increase the chance of finding new active drugs in patients previously pretreated by chemotherapy, one might lower the acceptability threshold of response rate to 10%, as suggested by Dr Aisner [1]. However, such an approach will necessitate that about double the number of patients be treated in phase II studies and thereby raise the number of patients treated potentially with inactive drugs. The new drugs teniposide (VM26) and carboplatin have been clearly shown to be very effective drugs in SCLC when they were tested in untreated patients [2, 3], although some activity was also observed in pretreated patients. However, when an inactive drug is given as the first line treatment, it is definitely possible that survival could be reduced: if the drug turns out to be inactive, it is conceivable that the number of resistant cells will increase in conjunction with the tumor mass, during the 3–6 weeks which are required to adequately test a new agent. Patients treated with one of two inactive drugs, mitoxantrone [4] or 4-demethoxydaunorubicin [5], as first line chemotherapy responded much less favorably to standard polychemotherapy afterwards and overall survival seemed to be shorter, in comparison to that obtained by upfront combination chemotherapy. Moreover, there is little doubt that single drug chemotherapy is less effective than polychemotherapy in SCLC and administration of single active agents should therefore be reserved for patients unfit for more aggressive chemotherapy.

Although testing new agents in pretreated patients would not seem to be a fully reliable screening method at the present time; however, if exposure to prior chemotherapy is carefully considered in each patient, a different new approach might be applied.

The tendency in recent years to reduce the length of time of chemotherapy allows us to observe a number of patients who respond to initial chemotherapy, relapse after a long interval from the end of treatment and respond again to second line chemotherapy [6]. Rechallenge with the same drugs used in the initial chemotherapy still achieves around 50% response rate and about 3 months is the shortest time required from the end of previous chemotherapy in order to see frequent responses to reinduction [7, 8]; however, remission duration and complete response rate of second therapy are inferior to those achieved by initial chemotherapy [6–8]. Response rates to reinduction as high as 50% or more are not unique to SCLC, but have also been observed in other chemosensitive malignancies (e.g. breast cancer, lymphomas, testis cancer).

In a phase II study with VM26 a subset of pretreated patients with sufficient off-therapy time (>2.6 months) was seen to respond to the drug in 53% of cases vs. 12% of patients with shorter off-therapy time and the former response rate was not

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significantly different from that obtained in patients untreated by chemotherapy [9]. The time from prior chemotherapy and the effectiveness of prior chemotherapy were found to be the most important predictors for response to VM26 in pretreated patients. This experience, together with the knowledge of the reinduction phenomenon obtained by the same initial chemotherapy, strongly suggests the need to consider in more detail prior chemotherapy exposure characteristics of pretreated patients to be enrolled in future phase II in SCLC.

In the VM26 phase II study [9], prior chemotherapy mainly consisted of a combination of cyclophosphamide, doxorubicin and VP16. Since cross-resistance *in vitro* does exist between VP16 and VM26 and between epipodophyllotoxins and anthracyclines [10], it seems reasonable to think that sensitive tumor cells, which were not completely eradicated by induction chemotherapy, regrow spontaneously after chemotherapy suspension and eventually constitute again a clinically significant part of the tumor burden. This thought explains how responses to second line chemotherapy can still be achieved by the same initial drugs or by analogs (VM26). Moreover, the wide range of response rates obtained with the cisplatin–VP16 combination as second line chemotherapy can also be explained in this way: while an average of 50% response is obtained, worse results were attained in patients with refractory neoplasms, i.e. progressing while on first line chemotherapy or shortly after its discontinuation [11].

On the basis of all these findings a new approach in planning future phase II trials in SCLC seems appropriate: the target response rate of 20% can be maintained, providing that a significant number of patients included in the study (at least 14) responded to prior chemotherapy which was suspended at least 3 months earlier. Reports of more detailed information on the type of prior chemotherapy exposure are hence to be recommended in phase II trials in SCLC.

Of extreme importance is, of course, the search for new drugs in patients who are definitely refractory to prior treatment, although this may involve enrollment in phase II trials of patients with little chance to respond to the new drug. However, the evidence of ineffectiveness of a new agent cannot be relied upon testing only in this type of patient; before discarding a drug from further investigation an adequate population of patients with better chances of responding, despite prior treatment, should be studied and the characteristics of this group of patients should be clearly defined in the report.

As far as standard induction chemotherapy in SCLC is concerned, it is now approaching durations of around 4–5 months in most institutions and it is quite possible that complete responders to initial chemotherapy, as well as partial responders, will stay long enough off-treatment and will then drop into the group of patients with a good chance of responding to a second series of treatment (reinduction, or a new active agent). In the VM26 phase II study the majority of patients who responded had experienced a partial remission to prior chemotherapy, simply because complete responses are by far less common than partial responses. This was possible because the median duration of prior chemotherapy was only 4 months (median 6 cycles) [9]. It is therefore quite likely that the type of population selected for new drugs phase II trials with this intention will be large enough to enable achievement of both fast and adequate clinical results, since it includes patients with a definitely better chance of responding and because it is representative of the initial population. Similar guidelines might be applied to the search for new active agents in other tumors in which first line chemotherapy is also very effective, but recurrence almost invariably ensues, like breast and ovary cancers.

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