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*Letter to the editors*

# Failure of response to ifosfamide in squamous cell bronchogenic carcinoma

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Sirs,

The prognosis for non-resectable squamous cell carcinoma of the lung is extremely poor. Current chemotherapeutic regimens are unimpressively effective, but promising results have been reported for treatment with ifosfamide [2, 3, 5, 6]. We studied the effect of this drug in 14 patients with histologically confirmed squamous cell bronchogenic carcinoma. They were considered unsuitable for treatment by resection or radio-therapy due to locally advanced or metastatic disease, but all were expected to survive for at least 6 weeks. None of the patients had received previous chemotherapy or showed cerebral metastases; all had a Karnofsky status of $>60$ and levels of serum gamma glutamyl transferase $<150$ IU/l.

Each treatment cycle consisted of 4.5 g/m$^2$ ifosfamide given i.v. in dextrose saline over 3 days accompanied by the same i.v. dose of 2-mercaptoethane sulphonate (mesna) plus a further 900 mg/m$^2$ given orally on day 4. Treatment was repeated at 28-day intervals for a further two cycles and then at 2-month intervals for three cycles. Conventional criteria were used for complete and partial remissions.

There were no responders and all patients with progressive disease died, with a median survival of 10 weeks. Eight patients received two or more cycles of chemotherapy and six died after only one cycle. There were no side effects save alopecia.

At this dose ifosfamide was ineffective in advanced squamous carcinoma of the lung, in contrast to the results of other studies [2, 3, 5, 6]. Although the number of patients in the present series was small, it is unlikely that a useful therapeutic effect was missed; if the drug were effective in $>20\%$ of patients, the chance of a negative response in the first 14 patients would be 0.04 [4]. The discrepancy between these results and those of other workers probably arises from differences in prognostic factors, particularly the extent of disease, together with the practice of excluding as unevaluable those patients failing to complete several cycles of chemotherapy [5, 6]. In our opinion, clinical response should be assessed and not the number of chemotherapeutic cycles that patients can survive, and all patients entering studies should be evaluated.

It might be argued that the dose of ifosfamide was suboptimal, but a response rate of 27% has been claimed for a similar regimen [3]. Pharmokinetic studies show that smaller fractionated doses of ifosfamide (1.0–1.5 g/m$^2$) given over 0.5 h for 5 days are associated with a time-dependent increase in metabolism (personal communication, L. Lewis et al., Department of Pharmacology, Guy's Hospital, London), whereas higher levels of unchanged are recovered from urine after large single doses than after smaller doses given over 3 days, suggesting a dose-dependent saturable metabolism [1]. These findings suggest that the smaller fractionated doses of ifosfamide might have a theoretical advantage.

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