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Letters

Phase II Study of Cystemustine in Advanced Head and Neck Cancer. A Trial of the EORTC Clinical Screening Group

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CYSTEMUSTINE is a new cysteamine (2-chloro-ethyl) nitrosourea, with a strong alkylating activity and a pharmacokinetic advantage for membrane diffusion [1, 2]. This drug has previously shown some efficacy in malignant glioma, melanoma, soft tissue sarcoma and renal adenocarcinoma phase II trials [3–6]. However, the antitumoral activity of cystemustine in squamous cell head and neck cancer is unknown until now. Therefore, the EORTC Clinical Screening Group performed a phase II trial in order to investigate the efficacy and tolerance of cystemustine in these patients.

Patient eligibility was defined by a squamous cell carcinoma of the head and neck, locally advanced and/or metastatic, at least one measurable target, and no radio- or chemotherapy 4 weeks before the start of the study. Previous chemotherapy with nitrosourea was a criterion for exclusion. All patients provided written informed consent.

Cystemustine was given intravenously at a dose of 60 mg/m^2, infused in 100 ml 5% dextrose, over 15 min, according to the regimen utilised in a phase I trial conducted by Mathé *et al.* [7]. Treatment was repeated every 2 weeks and efficacy was determined after four cycles or sooner in the case of progressive disease. For patients with response, the schedule was continued until progression or excessive toxicity. Administration of cystemustine was postponed for 1 week in case of grade 2 neutropenia (WHO) and/or grade 1 thrombocytopenia at day 15. The dose was reduced to 45 mg/m^2 after thrombocytopenia with a grade >3. If treatment had to be delayed for more than 3 weeks, the patient was considered off the study. When progression occurred before the end of the 8 weeks of treatment, this was considered as a therapeutic failure.

28 patients (all males, median age: 56 years, range 37–70, mean WHO performance status: 1(0–2), were included in this study. Out of these, 2 patients were considered ineligible because they had received previous chemotherapy a little before the start of the study. 26 patients were fully evaluable. The median number of cycles administered were three (range 1–11 cycles).

A partial response was observed for 2 patients (response and confidence limits: 7.69; 0.9–25.1%). The time to response was 4 and 17 weeks and the duration of response was 26 weeks. The two responses occurred in lung cancer (one complete response and one partial response).

Haematological toxicity is shown in Table 1 and was infrequent and mild. Non-haematological toxicity was rare, with only 4 patients experiencing a nausea–vomiting WHO grade larger than two (15.4%).

Cystemustine has a minor haematological toxicity, at the dose of 60 mg/m^2 by cycle, for head and neck cancer patients.

The Clinical Screening Cooperative Group, with the same schedule, for other solid tumours, has observed a grade >2 toxicity for leukocytes, granulocytes and platelets in 21.7, 14.5 and 17.5% of patients, respectively (unpublished data). For some patients, thrombocytopenia was of a long duration; moreover, the non-haematological toxicity was gastro-intestinal, with a WHO grade >2 in 15.4% of patients.

With the schedule chosen, cystemustine shows an antitumoral activity as mild as the other nitrosoureas given for these carcinomas. Perhaps, a higher response rate could be obtained with a dose of 90 mg/m^2, which was given for melanoma or renal carcinoma in other phase II trials.

Table 1. Haematological toxicity (26 evaluable patients)

	Median of nadirs	Range	Grade >2 (number of pts)
White blood cells ($\times 10^9$/l)	6.20	2.2–18.4	2
Neutrophils ($\times 10^9$/l)	4.44	1.25–11.51	1
Platelets ($\times 10^9$/l)	217	43–432	4

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However, head and neck cancer patients have generally unfavourable performance status and haematological tolerance. Moreover, thrombocytopenia may increase the risk of major haemorrhage. Also, nitrosoureas were rarely used for the treatment of these patients. Cystemustine should not, therefore, be used at a dose of 60 mg/m^2 every 2 weeks in the treatment of advanced head and neck carcinomas.

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