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A Phase II Study of Piritrexim in Patients with Advanced Squamous Cell Carcinoma of the Head and Neck

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PIRITREXIM (PTX) is a new lipid-soluble antifolate which, like methotrexate (MTX), is a potent inhibitor of dihydrofolate reductase.The entry of PTX into cells is rapid and carrier independent. Unlike MTX, PTX cannot be polyglutamated [1, 2]. PTX administered orally is rapidly and well absorbed; its bioavailability is 64–75% [3–5]. Previous phase II trials using different schedules showed that PTX is an active drug in squamous cell carcinoma of the head and neck (SCCHN) [6, 7]. We evaluated the activity and toxicity of PTX administered orally, with escalating doses, in two institutions, in 33 previously pretreated patients with recurrent and/or metastatic SCCHN.

All patients had histologically confirmed SCCHN, a normal initial haemogramme, hepatic and renal functions and signed informed consent. Patients' characteristics are shown in Table 1. PTX was administered orally at a starting dose of 25 mg three times a day for 4 days weekly (300 mg/cycle). If no significant toxicity (WHO grade > 1) occurred, the dose was escalated after four cycles to 375 mg, and then to 500 mg weekly. If any WHO grade ≥ 2 toxicity occurred within the first three cycles, or WHO grade ≥ 3 toxicity at any time, the dose was reduced to 225 mg, and further to 150 mg weekly. The total number of cycles was 228 (starting dose 126 cycles; dose escalation 44 cycles; doses reduction 58 cycles; median six cycles, range 1–24) and the median total dose received per patient was 1650 mg of PTX (range 300–5200).

The criteria for response and toxicities followed the WHO standard criteria [8]. In case of a tumour response, patients continued therapy until progression; in case of progression or no change at 12 weeks, patients were taken off study. Tumour response was assessed every four cycles (4 weeks). 8 patients were not evaluable because PTX was stopped before four cycles for myelotoxicity (3 patients), dysphagia (3 patients) and refusal (2 patients). 6 of 25 patients evaluable achieved a partial response. The overall response rate was, therefore, 24% (95% confidence interval 7–41%) for 25 assessable patients, or 18% for all 33 eligible patients. A stabilisation of disease was observed in 60%, and progression in 16% of evaluable patients. Responses persisted for 13, 15, 15, 17, 19 and 29 weeks, but all responders later relapsed. Four of 6 responders had previously received chemotherapy, including platinum, as palliative treatment. Responses according to sites of disease were primary tumours 2/9, lymph nodes 3/6, lung metastases 5/13 and skin metastases 1/6. All 33 patients were evaluable for toxicity. The dose limiting toxicities (WHO grade ≥ 2) were neutropenia in 39% and thrombocytopenia in 21% of patients received the starting dose. Recovery from low counts was achieved within a few days after withdrawal of PTX. Neutropenia, thrombocytopenia and anaemia (WHO grade ≥ 2) for all cycles of PTX occurred in 39, 24 and 33% of patients, respectively. Other toxicities including nausea, vomiting, mucositis, skin rash and fatigue were mild or moderate. There were no treatment-related deaths. There seems to be no correlation between dose and response, or toxicity of PTX and response.

In conclusion, PTX at the dose of 25 mg three times daily for 4 days weekly seems moderately efficient in heavily pretreated patients with SCCHN; the dose limiting toxicity was haematological.

Table 1. Patients' characteristics

	No. of patients
Total no. of patients entered	33
Male	32
Female	1
Age (years)	
Median	53
Range	35–78
Performance status (WHO grade)	
Median	1
Range	0–2
Prior treatment	
Surgery	20
Radiation	28
Chemotherapy	26
Sites of disease	
Primary tumour only	8
Lymph nodes only	4
Lung metastases only	9
Multiple sites	12

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Prognostic Significance of Epstein-Barr Virus Association in Hodgkin's Disease

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THERE IS now strong evidence to suggest that Epstein-Barr virus (EBV) is involved in a proportion of cases of Hodgkin's disease (HD) [1–4]. Mixed cellularity HD (HDMC) is more likely to be EBV-positive compared with nodular sclerosis HD (HDNS), and, in addition, our data suggest that paediatric and older cases are more likely to be EBV-positive than young adult cases [2–4].

Despite improvements in the treatment of HD, there are still a number of cases with poor clinical outcome. In order to identify these cases and initiate alternative treatment regimes early in disease, we have previously devised a prognostic index. Since older age and HDMC as compared to HDNS have been associated with poor prognosis [6], we assessed the relationship between EBV-positivity and clinical outcome. The use of EBV-positivity in the prognostic index was also evaluated.

Paraffin-embedded sections from 59 HD cases (35 males, 24 females) diagnosed over a 13-year period (1976–1989) were investigated for the presence of EBV using immunohistochemical and *in situ* methods, as described previously [7, 8]. Cases of HD were considered EBV-associated if Reed-Sternberg (RS) cells expressed the EBV LMP-1 protein or EBER-1 RNA. We have found EBER-1 RNA *in situ* hybridisation to be the most reliable method of detecting EBV in HD tumours [7]. The series included 27 HDNS, 28 HDMC, 3 lymphocyte-predominant HD cases and 1 case of lymphocyte-depleted HD. 16 patients had stage I, 13 stage II, 19 stage III and 11 stage IV disease. The prognostic indices were calculated on prospectively collected data, but do not include additional weighting for bulk disease, as this information was not available. Early stage disease was treated with radiotherapy alone. Later stage or bulky disease was treated with a four-drug regimen (chlorambucil, vinblastine, procarbazine and prednisolone), plus or minus radiotherapy. Minimum follow-up is 48 months.

21 cases were categorised as EBV-associated. The age distribution and histological subtype of the EBV-associated cases were in agreement with those of previous studies [2–4]. Using standard survival analysis techniques, there was no evidence of an association between EBV status and survival (hazard ratio = 0.56, 95% confidence limits 0.11–2.68) (Figure 1a, b).

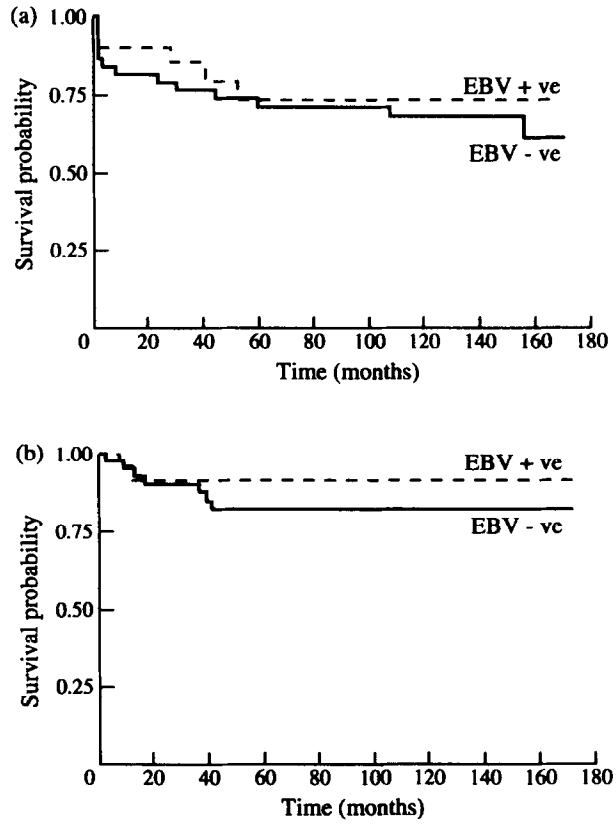

Figure 1. (a) Disease-free survival by EBV status. (b) Total survival by EBV status.

This observation applies to unadjusted analyses of the entire data set and was confirmed by analyses stratified by age and by age plus histological subtype. In addition, EBV status did not provide an improvement to the prognostic index in explaining survival. Our results are consistent with two recent studies which investigated the association between EBV status and clinical outcome, using immunohistochemical techniques and the polymerase chain reaction, respectively [9, 10].

This study provides no evidence to support the hypothesis that EBV-associated cases of HD have a less favourable clinical outcome than EBV-negative cases. We can conclude that the detection of EBV within RS cells in individual HD cases is not a clinically useful prognostic marker.

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