Pergamon

Oral Oncol, Eur J Cancer, Vol. 32B, No. 4, pp. 278–279, 1996
Copyright © 1996 Elsevier Science Ltd. All rights reserved
Printed in Great Britain
0964-1955/96 $15.00 + 0.00

0964-1955(95)00082-8

Letter

Phase II Trial of Oxaliplatin (L-OHP) in Advanced, Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck

M. Degardin,[1] P. Cappelaere,[1] I. Krakowski,[1] P. Fargeot,[1] D. Cupissol[1] and S. Brienza[2]

[1]G.T.M.C., National Federation of Anti-Cancer Centers; and [2]Debiopharm, France

Oxaliplatin (L-OHP) or *trans*-1-diaminocyclohexane oxalatoplatinum is a new diaminocyclohexane (DACH) platinum complex with similar antitumour activity as cisplatin against several transplanted murine tumours [1]. L-OHP differs from the currently commercially available platinum complexes, cisplatin and carboplatin, particularly in toxicity profile with the absence of renal and auditory toxicities and minimal myelosuppression. The dose-limiting toxicity of L-OHP is peripheral sensory neuropathy [2–5]. The antitumoral activity of L-OHP has been observed in breast, lung, bladder, oesophagus, ovarian and colorectal cancers and in lymphoma, malignant melanoma and glioblastoma, in numerous phase I–II studies [3, 4, 6–8].

We evaluated the safety/tolerability and antitumour activity of L-OHP in 44 patients with squamous cell carcinoma of the head and neck (SCCHN). All patients had histologically proven advanced, recurrent and/or metastatic SCCHN, not assessable for curative locoregional treatment by surgery and/or radiotherapy. All patients had at least one measurable lesion and signed informed consent. Measurable and assessable lesions were determined by physical examination, endoscopy, chest and bone X-rays, computed tomography and echotomography. Tumour lesions in irradiated fields were not excluded. Normal initial blood count (granulocyte count $\geqslant 2000/\mu l$, platelets $\geqslant 100\,000/\mu l$) hepatic and renal functions (bilirubin, ASAT, ALAT, alkaline phosphatases $\leqslant 1, 25 \times N$, creatinine $\leqslant 120$ umol/l or clearance of creatinine $\geqslant 60$ ml/min) and clinically normal auditory and neurological functions were required. The pretreatment characteristics of all patients are shown in Table 1.

L-OHP was administered every 3 weeks at a dose of 130 mg/sqm by i.v. infusion with 250 ml of dextrose 5% over 2 h. Patients received this treatment until there was evidence of disease progression and/or unacceptable toxicity. Blood cell count and biochemistry, clinical examination and evaluations of neurological and auditory function were performed every 3 weeks (on day 21) and evaluation of disease every two cycles. If a haematological toxicity WHO grade $\geqslant 2$, or neurotoxicity WHO grade $\geqslant 3$ or renal toxicity WHO grade $\geqslant 1$ was observed on day 21, treatment was postponed for a week or until recovery.

Table 1. Patient characteristics

Number of patients (eligible)	44 males
Age (years), median (range)	58 (33–72)
Performance status (WHO)	
0	6
1	24
2	14
Tumour sites	
primary tumour/recurrence	17 (10*)
lymph node	28 (14*)
lung metastases	22
hepatic metastases	3
skin metastases	4 (4*)
others†	8
Prior treatment	
surgery	23
radiotherapy	38
chemotherapy	18
– 17 with cisplatin, median: 300 mg/m^2	(100–600)
– 1 with carboplatin 1200 mg/m^2	
no prior treatment	6

*In irradiated field.
†Pleura, pericardium, bone.

Response and toxicity were defined according to WHO criteria [9]. All 44 patients included in the study were eligible. 10 patients received only one cycle of L-OHP: 6 patients for rapid progression of disease, 2 for refusal after the first administration and 2 patients for early death not related to either progressive disease or toxicity. Therefore, 40 patients were evaluable for response: 17 patients pretreated by chemotherapy and 23 without prior chemotherapy. We observed four partial responses: 3/23 in chemotherapy naïve patients and 1/17 in patients pretreated with chemotherapy. The overall response rate for all 40 evaluable patients was thus

Correspondence to M. Degardin, Centre Oscar Lambret, 1 rue F. Combemale, B.P. 307, 59020 Lille, Cedex, France.
Received 12 Oct. 1995; provisionally accepted 30 Oct. 1995; revised manuscript received 14 Nov. 1995.

10% (IC 95: 1–19%), 13% (IC 95: 0–26%) for patients without prior chemotherapy and 6% for those with prior chemotherapy (IC 95: 0–17%). The responses were seen in primary tumours, lymph nodes and in lung metastases. A response rate of 17% (IC 95: 0–36%) was observed in the group of 18 patients who had received at least two cycles of L-OHP. The duration of responses were 2, 2, 3 and 4 months. Disease stabilisation was observed in 3 patients for 6, 8 and 12 months. The median survival for all 44 eligible patients was 5 months.

Overall, 105 cycles of L-OHP were administered, for a median of two cycles (range: 1–10) and the median dose was 260 mg/sqm (130–1300) of L-OHP per patient. The projected dose of 130 mg/sqm per cycle was delivered in 103 (98%) cycles and in 42 (95%) patients. All 44 eligible patients were evaluable for toxicity. The tolerability of L-OHP was excellent. The main toxic effect was peripheral sensory acute neuropathy. These dysesthesias (WHO grade $\leqslant 2$) occurred in 20 patients (47%) receiving a mean of 1.6 cycles of L-OHP. Only one patient, with neurotoxicity WHO grade 3, after 10 cycles of L-OHP, stopped the treatment. Gastrointestinal toxicity was frequent but mild and haematotoxicity was minimal: neutropenia WHO grade $\leqslant 2$ in 9% of patients and in 5% of cycles. We have observed neither renal toxicity nor ototoxicity. There were no treatment-related deaths.

In conclusion, an analysis of our results reveals that L-OHP at the dose of 130 mg/sqm, every 3 weeks, has a good safety/tolerability and a moderate activity in advanced, recurrent and/or metastatic SCCHN [10]. Excellent renal and haematological tolerance and synergy with fluorouracil [6] suggests the possibility of combination chemotherapy, particularly with carboplatin or fluorouracil in SCCHN and other platinum-sensitive tumours. Given the patient characteristics and the disease-specific setting, these results are comparable to phase II activity data with cisplatin at standard doses (100 mg/sqm), with much better tolerance and no life-threatening toxicity. The preclinical data, suggesting no cross-resistance between these two agents, make the possibility of comparison or combination studies an interesting prospect.

1. Mathe G, Kidani Y, Noji M, *et al.* Antitumour activity of L-OHP in mice. *Cancer Lett* 1985, **27**, 135–143.
2. Mathe G, Kidani Y, Eriguchi M, *et al.* Oxalato-platinum or L-OHP, a third generation platinum complex: an experimental and clinical appraisal and preliminary comparison with cisplatinum and carboplatinum. *Biomed Pharmacother* 1989, **43**, 237–250.
3. Extra JM, Espie M, Calvo F, *et al.* Phase I study of oxaliplatin in patients with advanced cancer. *Cancer Chemother Pharmacol* 1990, **25**, 299–303.
4. Misset JL, Brienza S, Burki F, *et al.* Early phase II trial of trans-l-diammino-cyclohexane oxaloplatin (L-OHP) in malignant melanoma, ovarian carcinoma and non-Hodgkin's lymphoma (NHL). *Eur J Cancer* 1991, **27** (suppl 2), S 196 (abstr 1196).
5. Brienza S, Gastiaburu J, Cvitkovic E, *et al.* Clinical characteristics and reversibility of neurological signs after long term oxaliplatin (L-OHP) therapy. *Ann Oncol* 1994, **5** (suppl 5), 128 (abstr 225).
6. Levi F, Perpoint B, Garufi C, *et al.* Oxaliplatin activity against metastatic colorectal cancer. A phase II study of 5 day continuous venous infusion at circadian rhythm nodulated rate. *Eur J Cancer* 1993, **29A**, 1280–1284.
7. Monnet I, Brienza S, Voisin S, *et al.* Phase II of oxaliplatin (L-OHP) in patients with advanced non-small cell lung cancer (NSCLC). Preliminary results. *Ann Oncol* 1994, **5** (suppl 5), 128 (abstr 224).
8. Chollet P, Bensmaine MA, Deloche C, *et al.* Preliminary results of phase II study of oxaliplatin (L-OHP): a new active agent in platinum pretreated ovarian cancer. *Ann Oncol* 1994, **5** (suppl 8), 110 (abstr 554).
9. Miller AB, Hoogstraten B, Staquet M, *et al.* Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
10. Recondo G, Armand JP, Tellez Bernal E, *et al.* Recurrent and/or metastatic head and neck squamous cell carcinoma: A clinical univariate and multivariate analysis of response and survival with cisplatin based chemotherapy. *Laryngoscope* 1991, **101**, 494–501.