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Short communication

Phase II trial of carboplatin and vinblastine in advanced squamous-cell carcinoma of the head and neck

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Summary. A chemotherapy regimen consisting of carboplatin and vinblastine was given to 30 patients with recurrent or previously untreated, locally advanced squamous carcinoma of the head and neck region. The main aim of the study was to assess the toxicity of this regimen, the feasibility of its out-patient administration and the tumour response. A total of ten patients (33%) achieved an objective response, including two who achieved a complete response. The combination offered useful palliation for patients with recurrent disease; it was well tolerated and can be given on an out-patient basis. This regimen could be combined with other active agents such as methotrexate or bleomycin.

Introduction

It is far from clear as to which chemotherapy is best for treating advanced or recurrent squamous carcinoma of the head and neck. In a randomised setting, cisplatin-based combinations have not been shown to be superior to single-agent methotrexate [6]. A combination of cisplatin and 5-fluorouracil given by infusion is associated with some of the highest reported response rates (89%), but the median survival of responders was rather short (36 weeks) [10]. The risk of toxicity associated with this regimen is significant, and patients require 1 week of hospitalisation every 3 weeks whilst on treatment.

The aim of this study was to assess the toxicity and efficacy of a combination of vinblastine and carboplatin; this combination offered the prospect of effective, low-toxicity treatment that could be given on an out-patient basis. Carboplatin, an analogue of cisplatin, has potential advantages over the parent compound in the treatment of this disease. Carboplatin has been successfully substituted for cisplatin in the treatment of ovarian cancer, resulting in no loss of efficacy and in reduced toxicity. Less nausea and vomiting was seen after carboplatin, and nephrotoxicity was very uncommon [1, 12]. The single-agent activity of these two compounds against head and neck cancer may be similar; the published range (24%–26%) of response rates [2, 4, 7] achieved using carboplatin are very similar to the 28% response rate observed for cisplatin by Hong and colleagues [9]. Vinblastine is also active against this disease, with a response rate of 29% [5]; its toxicity is low apart from mild myelotoxicity, which is quantitively and temporally different from the effect of carboplatin upon bone marrow.

Two groups of patients were treated. The first included patients who had symptomatic loco-regional disease or distant metastases after undergoing potentially curable radiotherapy with or without surgery. The second group presented with stage IV tumours [3], usually with fixed and inoperable cervical lymph node metastases; these patients had received chemotherapy before definitive treatment.

Patients and methods

A total of 30 patients comprising 6 women and 24 men entered this study between January 1986 and February 1988. All had a creatinine clearance of >50 ml/min and a WHO performance status of ≤2. The mean age was 54 years (range, 19–70 years). All subjects suffered from squamous tumours; the frequency of the site of origin is listed in Table 1.

Vinblastine (6 mg/m^2) was given i.v. as a bolus, followed by a 1-h infusion of 300 mg/m^2 carboplatin in 500 ml 5% dextrose. The carboplatin dose was not titrated against creatinine clearance. Metoclopramide (10 mg) was given i.v. simultaneously with the infusion and was subsequently given p.o. every 6 h for at least the next 24 h. This regimen was repeated every 4 weeks. Response was assessed by standard WHO criteria [11], usually by direct clinical measurement, as most patients had at least one lesion that could easily be measured using callipers. Patients with recurrent disease who achieved a complete (CR) or partial response (PR) continued to receive chemotherapy for a maximum of six cycles. After two courses, previously untreated patients received radical radiotherapy to the primary tumour and neck nodes, the final tumour dose being 60–70 Gy in 6–7 weeks.

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Table 1. Site of origin of stage IV squamous carcinoma

Site of primary tumour	Number of patients
Larynx	9
Oral cavity	4
Pharynx:	
Naso	5
Oro	6
Hypo	5
Bulky, fixed neck nodes from unknown primary	1

Table 2. Response rate to chemotherapy

	No previous treatment ($n = 13$)	Previous radiotherapy ($n = 17$)
Complete response	1	1
Partial response	6	2
Stable disease	3	2
Progressive disease	3	12
Response rate	54%	18%

All responses assessed by WHO criteria; response duration, >1 month

Results

The overall response rate was 33% (2 CRs and 8 PRs; 95% confidence interval, 15%–50%). Previously irradiated patients showed a worse response than did untreated patients (18% vs 54%; Table 2). This difference did not quite reach the conventional level of statistical significance ($P = 0.06$, Fischer's exact test).

Two previously irradiated patients with stable disease obtained marked symptomatic relief; chemotherapy provided good palliation, although tumour shrinkage was insufficient to represent a PR. Response duration in the previously treated group was short, being 8 months for the complete responder and 5 months for the two partial responders. It was difficult to judge the impact of initial response in the ten patients (including one CR and six PRs) among previously untreated subjects who proceeded to radiotherapy. The median survival was 44 weeks (95% confidence limit, 36–78 weeks) and the estimated percentage of patients surviving for 1 year was 43% (95% confidence limits, 17%–69%). All five patients with distant metastases showed no response to treatment.

Toxicity was mild, taking the form of nausea and vomiting and bone marrow suppression: 50% of patients ($n = 15$) suffered some nausea or vomiting, but transient vomiting (WHO grade 2) was the most severe side effect. A total of 74 cycles of chemotherapy were given; nausea (WHO grade 1) was recorded in 21 instances and transient vomiting, in 14 (WHO grade 2). The lowest WBC counts were seen between day 7 and day 14; the mean nadir count was 3.6×10^9/l, the lowest recorded value being 1×10^9/l. The lowest platelet count was observed 14–28 days after chemotherapy; the mean nadir value was 190×10^9/l, the lowest recorded value being 72×10^9/l. Apart from grade 1 alopecia in two patients, no other side effects were seen.

Discussion

This regimen is certainly suitable for out-patient administration its toxicity is low. The mild to moderate gastrointestinal toxicity of the combination is particularly advantageous to patients with advanced head and neck cancer. The upper airways and digestive tract may be disrupted as a consequence of disease or previous treatment; eating may be difficult and vomit is more likely to be aspirated.

The response rate of this combination is similar to that of methotrexate given on various dosing schedules [13]. Most combination regimens are empirical amalgamations of active agents with differing toxicities. As marrow suppression was mild, vinblastine and carboplatin at the doses used in this study could be combined with other active agents, particularly methotrexate, which has long been regarded as "standard therapy" [8]. It is difficult to know the extent to which vinblastine contributed to the efficacy of this regimen, as its overall response rate is little better than that obtained using single-agent carboplatin; the previously mentioned 29% response rate to the former drug [5] was derived from old pooled data, to which only few recent data have been added. As this combination of carboplatin and vinblastine showed some activity with low toxicity, further evaluation with other active drugs seems to be indicated.

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