Eur J Cancer Clin Oncol, Vol. 25, No. 2, pp. 173–176, 1989.
Printed in Great Britain

0277–5379/89$3.00 + 0.00

Carboplatin and Continuous Infusion 5-Fluorouracil for Advanced Head and Neck Cancer

IAN N. OLVER,* DAVID DALLEY,† ROBERT WOODS,‡ RODNEY ARONEY,§ PETER HUGHES,* JAMES F. BISHOP* and DEBORAH CRUICKSHANK*

Peter MacCallum Cancer Institute, Melbourne, †St. Vincents Hospital, Sydney, ‡Royal North Shore Hospital, Sydney and §Repatriation General Hospital, Sydney, Australia

Abstract—*Fifty-one patients with recurrent or advanced squamous cell carcinoma of the head and neck received carboplatin* 70 mg/m^2/*day bolus* × 5 *days i.v. and 5-fluorouracil* (*5-FU*) 1000 mg/m^2/*day by continuous infusion i.v. for* 5 *days as initial chemotherapy. There were four complete responders* (*CR*) *and* 12 *partial responders* (*PR*). *Durations of CR were* 6.8 *months*, 7.2+ *months and* 14.8+ *months with one patient lost to follow up after achieving CR. For objective responders the median relapse-free survival from the time of response was* 5.3 *months and survival from registration* 11.7 *months. The median survival for all patients was* 4.8 *months. The major toxicities were myelosuppression and mucositis. Neutropenia* (<1.0 × 10^9/l) *occurred in* 19% *of patients, thrombocytopenia* (<50 × 10^9/l) *in* 17% *and severe* (*WHO grade three or four*) *mucositis was experienced by* 28% *patients. This combination had less gastrointestinal and nephrotoxicity than platinum containing combinations and can be used in patients with a poorer performance status.*

INTRODUCTION

COMBINATION CHEMOTHERAPY in recurrent or metastatic squamous cell carcinoma of the head and neck has been disappointing because responding patients rarely have a survival advantage. One of the most promising combinations, *cis*-platinum and continuous infusion 5-FU, produces response rates in up to 70% of patients with improvement in performance status and survival in some cases [1].

The value of *cis*-platinum in combination chemotherapy for head and neck cancer has been demonstrated in randomized studies by the EORTC and SAKK groups [2, 3]. However, the severe gastrointestinal toxicity and nephrotoxicity and the required fluid loading with *cis*-platinum limits the use of such combinations to patients with a good performance status and normal renal function.

Carboplatin is an analogue of *cis*-platinum which in phase I trials showed markedly less gastrointestinal toxicity and less nephrotoxicity and did not require fluid loading. Its dose-limiting toxicity was myelosuppression [4, 5]. Moreover, a linear relationship between creatinine clearance and platelet nadir was established allowing for accurate dosage reduction in the presence of renal impairment [6, 7]. Rozencweig *et al.* suggested that a daily for 5 day schedule for carboplatin was associated with less nausea and vomiting than a single bolus dose although there was no advantage shown for any particular schedule in NCI studies [4, 5]. The single agent activity of carboplatin in both schedules is similar to *cis*-platinum in phase II studies in head and neck cancer [8, 9].

This phase II trial of carboplatin and continuous infusion 5-FU was undertaken to investigate the efficacy and toxicity of this combination for treating recurrent or metastatic squamous cell carcinoma of the head and neck.

MATERIALS AND METHODS

Eligible patients had histologically confirmed incurable recurrent advanced or metastatic squamous cell carcinoma of the head and neck with measurable or evaluable disease. Other eligibility requirements were no prior chemotherapy, no radiotherapy within 4 weeks prior to entering the study, a performance status of ECOG 0–3, adequate bone marrow reserve with WBC >3.5 × 10^9/l and platelets >100 × 10^9/l, and a creatinine clearance of 0.4 ml/s or above. Written informed consent was required.

Treatment consisted of carboplatin (David Bull Laboratories, Australia) 70 mg/m^2 i.v. over 1 h

Accepted 3 August 1988.
Address for correspondence: I.N. Olver, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne, Vic. 3000, Australia.

daily for 5 days and 5-FU 1 g/m^2/day by continuous infusion for 5 days commencing on day 1. Cycles were repeated every 28 days if the WCC $>3.5 \times 10^9$/l and the platelets $>100 \times 10^9$/l.

If the pretreatment creatinine clearance was between 0.6 and 0.8 ml/s carboplatin dose was reduced by 75% and between 0.4 and 0.6 by 50%. If grade 3 or 4 toxicity occurred the doses of carboplatin and 5-FU were reduced by 20% for subsequent courses. Standard World Health Organization criteria for response and toxicity were used [10].

All analyses were performed using the BMDP Statistical Software Package [11].

Survival was calculated from the day of entry onto the study whilst relapse-free survival for responders was calculated from the date of documented response until progression. The product limit (Kaplan–Meier) method was used to estimate survival and relapse from survival distributions and the log-rank test used to assess the effect of pretreatment characteristics on survival. Response rates were compared using chi-square tests or tests for linear trend where levels of the independent variable were ordinal. The effect of pretreatment characteristics on response and survival was addressed using chi-square and log-rank tests respectively.

RESULTS

Fifty-one patients previously untreated with chemotherapy received 142 courses of carboplatin and continuous infusion 5-FU (median number of courses 2, range 1–6). The patients were predominantly in their sixth or seventh decade and most had a performance status of ECOG 0–2 (Table 1).

Twelve patients had received no prior treatment having presented with advanced disease, 12 had relapsed after surgery, 10 after radical radiation therapy and 16 after treatment with both modalities. Most patients had locoregional disease but one had presented with distant disease and four had relapsed with distance disease.

There were four CRs and 12 PRs. Nine patients died within the first month, seven of rapidly progressive disease, one with myocardial infarct and one of asthma unrelated to disease or treatment. None of the patients were considered toxic deaths and none were myelosuppressed at the time of death. The maximum response was achieved in one to six courses of chemotherapy (median 2). Chemotherapy for responders was discontinued after six courses.

The median relapse-free survival for responders was 5.3 months (6.8+ months for CR, 4 months for PR). The durations of response for patients achieving CR were 6.8 months, 7.2+ months and 14.8+ months with one patient lost to follow-up after achieving CR. The median survival for objective responders was 11.7 months (19.4 CR and 11.7 for PR) while for non-responders who lived for more than 1 month it was 4.6 months with nine patients dying within 1 month. The median survival for all patients was 4.8 months (Fig. 1).

Table 1. Patient characteristics

	Number of patients	Number responding	Median survival (months)
No. entered	51		
Median No. courses (range)	2 (1–6)		
Median age (range)	57.5 (19–72)		
Male:female	44:7		
Performance status (ECOG)			
0	19	4	5.4
1	17	8	7.2
2	11	3	2.9
3	4	1	0.5
Primary site			
Oral cavity	17	3	4.6
Nasopharynx	11	4	>11.7
Oropharynx	13	5	4.7
Hypopharynx	5	1	1.4
Larynx	3	2	†
Multiple	2	1	—
Prior treatment			
None	12	6	11.7
Surgery only	12	3	4.6
Radiation only	10	4	4.7
Both	16	3	4.0
Unknown	1	—	†
Disease at study entry			
Untreated:			
Stage III*	1	1	†
Stage IV	7	3	11.7
Multicentre	2	1	†
Multisite	1	1	†
Stage unknown	1	0	†
Relapsed:			
Locoregional	34	8	4.5
Locoregional and distant	4	2	4.7
Unknown	1	0	†

*UICC stage.
†Insufficient cases.

The influence of pretreatment characteristics on response and survival was tested, but with small numbers the power to detect even quite large differences is small. There was a trend for improved survival in better performance status patients (P trend = 0.02) but with no other characteristics listed in Table 1 was a significant effect on response or survival demonstrable.

The major toxicities were haematological and gastrointestinal (Table 2). There were no septic episodes in the 19% of patients who had grade 3 or 4 neutropenia and only three episodes of minor bleeding with 17% of patients experiencing grade 3 or 4 thrombocytopenia. Patients with grade 3 or 4

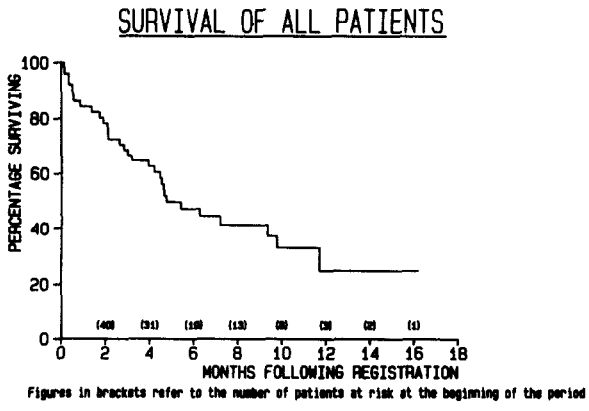

Fig. 1. Overall survival from study entry for all patients. Median was 4.8 months.

mucositis had the doses of carboplatin and 5-FU reduced by 20%.

The only evidence for cumulative toxicity was with haemoglobin and creatinine clearance where there were significant trends for lower values as the number of courses increased (P for trend = 0.0004 and 0.014 respectively).

Phlebitis was a frequent problem but only five patients required central venous access devices for subsequent courses. Alopecia was partial and only occurred in 9% of patients while no severe renal toxicity or neuropathy was seen.

Since the toxicity was acceptable, the planned drug doses were able to be delivered to most patients over their course of treatment (Table 3). There was no correlation between dose and response, however, if patients who received greater or less than 95% of the planned dose were compared. Only one patient withdrew from the study because of toxicity when he developed mucositis after his 5th course.

Table 2. Haematological and gastrointestinal toxicity

Toxicity	WHO grade (%) [10] 0	1	2	3	4
Hb					
% patients	43	36	19	2	0
% courses	65	23	11	1	0
Neutrophils					
% patients	42	15	24	12	7
% courses	44	24	18	8	7
Platelets					
% patients	55	24	4	15	2
% courses	24	15	3	7	1
Mucositis					
% patients	49	13	9	22	6
% courses	68	12	9	9	2
Nausea and vomiting					
% patients	39	33	22	5	0
% courses	56	22	19	3	0
Diarrhoea					
% patients	91	2	2	4	0
% courses	97	1	1	1	0

Table 3. Percentage of planned dose delivered per patient for all courses while on study

	Patient
CBDCA (% dose)	
>95	32
80–94	13
<80	5
Unknown	1
[median 98% (54–107)]	
5-FU (% dose)	
>95	32
80–94	14
<80	4
Unknown	1
[median 100% (8–106)]	

Twenty-one patients received further treatment with radiation or chemotherapy following protocol therapy or upon relapse. In no case did added radiotherapy improve the response category achieved by chemotherapy. The only relapsed patient who responded to further therapy was a patient who had achieved a CR to carboplatin and 5-FU and again responded to this regimen.

There were no documented treatment related deaths. Of the 31 recorded deaths, 27 were due to tumour, three of causes unrelated to tumour or treatment and the cause was unknown in one patient.

DISCUSSION

This study shows that the combination of carboplatin and 5-FU is active in advanced head and neck cancer and well tolerated. Forastiere *et al.* reported a response rate of 48% for this combination in head and neck cancer but gave the carboplatin as a single bolus dose of 300 mg/m^2 on day 1 [13]. They excluded two patients who had an inadequate trial of therapy from the denominator in reporting response. Using the same exclusion criteria the response rate in the current study is 38% (24–54% for 95% confidence interval). The median duration of response in Forastiere's series at 4.7 months is similar to ours.

There is a wide variation in response rates in such phase II studies depending on patient characteristics and selection as well as sample size [1,12,14]. Our study included some poor performance status patients and the majority of our early deaths were due to relentless and rapid progression of disease.

The advantage of substituting carboplatin for *cis*-platinum in combination with 5-FU was demonstrated in this study by the lack of gastrointestinal

toxicity, nephrotoxicity or neurotoxicity. The lower incidence of nausea and vomiting (72% of patients WHO grade 0 or 1) is characteristic of carboplatin as compared to *cis*-platinum but may further be attributed to the divided rather than single bolus doses of carboplatin as suggested by Rozencweig from the phase I studies of the 5-day schedule of carboplatin [4]. The spectrum of toxicities in this study is similar to that reported by Forastiere *et al.*, with myelosuppression dose limiting and mucositis the major gastrointestinal toxicity [13]. The phlebitis was predominantly due to the continuous infusion 5-FU since it appeared similar in both studies. The cumulative toxicity demonstrated by the trend toward falling haemoglobin values with repeated courses of carboplatin/5-FU has previously been reported in a phase II study of carboplatin as a single agent in head and neck cancer [8]. A similar trend for creatinine clearance is surprising, although no acute nephrotoxicity was apparent.

Patients with a ECOG performance status tolerated this treatment well with one of four such patients achieving a partial response. We were able to treat patients with impaired renal function who would have been excluded from receiving *cis*-platinum. Since dose modification of carboplatin can be accurately performed due to the linear relationship between platelet nadir and creatinine clerance, carboplatin can be safely given in this setting [7].

Carboplatin and 5-FU is a useful alternative to cisplatin combinations for patients with renal impairment or who could not tolerate the gastrointestinal toxicity of the platinum or the fluid load required for prehydration.

Acknowledgements—The authors wish to acknowledge the contributions of Drs B.L. Hillcoat, J. Zalcberg, A. Zimet, M. Byrne, R. Snyder, I. Burns and J. Paige to the study and David Bull Laboratories Australia and the Anti-Cancer Council of Victoria for partial funding of the trial.

REFERENCES

1. Kish JA, Weaver A, Jacobs J *et al.* Cisplatin and 5-fluorouracil infusion in patients with recurrent and disseminated epidermoid cancer of the head and neck. *Cancer* 1984, **53**, 1819–1824.
2. Clavel M, Cognetti F, Dodion P *et al.* Combination chemotherapy with methotrexate, bleomycin and vincristine with or without cisplatin in advanced squamous cell carcinoma of the head and neck. *Cancer* 1987, **60**, 1172–1177.
3. Abele R, Honegger HP, Grossenbacker R *et al.* A randomized study of methotrexate, bleomycin, hydroxyurea with versus without cisplatin in patients with previously untreated and recurrent squamous cell carcinoma of the head and neck. *Eur J Cancer Clin Oncol* 1987, **23**, 47–53.
4. Rozencweig M, Nicaise C, Beer M *et al.* Phase I study of carboplatin given on a five day intravenous schedule. *J Clin Oncol* 1983, **1**, 621–626.
5. Foster BJ, Clagett-Carr K, Leyland-Jones B *et al.* Results of NCI-sponsored phase I trials. *Cancer Treat Rev* 1985, **12**(Suppl A), 43–49.
6. Egorin MJ, Van Echo DA, Tipping SJ *et al.* Pharmacokinetics and dosage reduction of *cis*-diammine(1,1-cyclobutane dicarboxylato)platinum in patients with impaired renal function. *Cancer Res* 1984, **44**, 5432–5438.
7. Egorin MJ, Van Echo DA, Olman EA *et al.* Prospective validation of a pharmacologically based dosing scheme for the *cis*-diamminedichloroplatinum(II) analogue diammine-cyclobutane dicarboxylato platinum. *Cancer Res* 1985, **45**, 6502–6506.
8. Eisenberger M, Hornedo J, Silva H *et al.* Carboplatin (NSC 241-240): an active platinum analogue for the treatment of squamous cell carcinoma of the head and neck. *J Clin Oncol* 1986, **4**, 1506–1509.
9. de Andres Basauri L, Lopez Pousa A, Alba E *et al.* Carboplatin, an active drug in advanced head and neck cancer. *Cancer Treat Rep* 1986, **70**, 1175–1176.
10. Miller AB, Hoogstraten B, Staquet M *et al.* Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
11. Dixon WG ed. *BMDP Statistical Software.* University of California Press, 1985.
12. Al-Sarraf M. Chemotherapeutic management of head and neck cancer. *Cancer Metast Rev* 1987, **6**, 181–189.
13. Forastiere AA, Natale RB, Takasugi BJ *et al.* A phase I–II trial of carboplatin and 5-fluorouracil combination chemotherapy in advanced carcinoma of the head and neck. *J Clin Oncol* 1987, **5**, 190–196.
14. Creagan ET, Ingle JN, Schutt AJ *et al.* A phase II study of *cis*-diamminedichloroplatinum and 5-fluorouracil in advanced upper aerodigestive neoplasms. *Head Neck Surg* 1984, **6**, 1020–1023.