Eur J Cancer, Vol. 27, No. 5, pp. 576–579, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00
Pergamon Press plc

Phase I/II Study of Carboplatin and 5-fluorouracil in Patients with Advanced Head and Neck Carcinoma

Stein Kaasa, Erik Thorud, Johan Tausjø, Erik Wist, Jan F. Evensen, Stein Gundersen and Herman Høst

59 patients with histological verified squamous cell carcinoma of the head and neck, 39 with primary disease and 20 with relapse were given carboplatin and 5-fluorouracil (5-FU) in escalated carboplatin doses. The starting dose with carboplatin was 200 mg/m^2 and the dose was escalated to 300 mg/m^2, 350 mg/m^2, 400 mg/m^2 and thereafter by 20 mg/m^2 per step. All patients received a dose of 1000 mg/m^2 5-FU as a continuous infusion for 5 days. The myelotoxicity was moderate. No patients had grade 4 haemoglobin toxicity, while 7 patients had grade 3 toxicity. 2 patients had grade 4 leucocyte toxicity and 1 patient had grade 3. 4 patients were observed with a grade 4 platelet toxicity. 2 early deaths occurred at a dose level of 420 mg/m^2. 18 out of 39 patients in primary treatment responded while 2 out of 20 patients treated for relapse responded. On the basis of the present study the maximum tolerable dose for carboplatin in combination with 5-FU 1000 mg/m^2 is between 350 and 400 mg/m^2.
Eur J Cancer, Vol. 27, No. 5, pp. 576–579, 1991

INTRODUCTION

LOCAL AND regional control is one of the main problems in the treatment of disseminated squamous cell carcinoma of the head and neck. Combination chemotherapy given as neoadjuvant treatment (prior to radiotherapy and/or surgery) has shown response rates ranging from 34% to 84% [1–3] with regimens containing cisplatin and continuous administration of 5-fluorouracil (5-FU) as the most potent [4–6].

A combination of cisplatin and 5-FU has been reported to be poorly tolerated in patients with cardiovascular disease and/or chronic alcoholism [7]. Furthermore, emesis, hearing loss, peripheral neuropathy and anaemia may be considerable.

Carboplatin, a cisplatin analogue, has shown significant antitumour effects in head and neck cancer [8–13] with a reduction in the side-effects of nephrotoxicity and emesis. The response rates are similar to those achieved with cisplatin. In phase I trials the major side-effect of carboplatin was myelosuppression, usually indicated by thrombocytopenia [8–10].

The present study was undertaken in order to establish the maximum tolerated dose and to evaluate the effect on the neoplastic tissue of carboplatin in combination with 5 days of continuous 5-FU. On the basis of results from earlier studies [11] the starting dose of carboplatin was 200 mg/m^2.

MATERIALS AND METHODS

The patients eligible for the study were those with advanced, non-resectable, histologically verified squamous cell carcinoma of the head and neck region, or with recurrent disease after previous primary surgery and/or radiotherapy. Patients who had previously undergone chemotherapy were not included. The patients had to have a WHO performance status of ≤ 2, a pretreatment haemoglobin of >10 g/dl, white blood count (WBC) $\geq 3.5 \times 10^9$/l, platelet count $\geq 125 \times 10^9$/l, 4 hour creatinine clearance ≥ 60 ml/min, and good liver function with AST, ALT, LDH, gamma glutamyl transpeptidase (gamma-GT), alkaline phosphatase and bilirubin <2.5 times the upper limit of normal values.

All patients gave their informed consent in accordance with the guidelines of the institution.

The starting dose for carboplatin was 200 mg/m^2 and the dose was escalated to 300 mg/m^2, 350 mg/^{2}, 400 mg/m^2 and thereafter by 20 mg/m^2 per step. There were no dose escalation within patients. All the patients received a dose of 1000 mg/m^2 5-FU as a continuous infusion for 5 days. Chemotherapy was given every 28 days if the WBC was $\geq 3.0 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l and renal function normal. At least 3 patients were included at each dose level. In order to evaluate the tumour response, 14 patients could be included at each dose level. When response was achieved further patients were included at the given dose level. Gastrointestinal toxicity, stomatitis, diarrhoea and WHO performance status were assessed according to WHO criteria before each treatment cycle and 4 weeks after therapy. Before each course of chemotherapy the patients received a clinical examination. Haematological, renal, and liver toxicity were examined with laboratory methods. In patients who experienced grade 3 or 4 toxicity the next course were given when the leucocyte count reached a value of $\geq 1.0 \times 10^9$/l and/or with thrombocyte count $\geq 100 \times 10^9$/l. Further chemotherapy were only given if these values were reached within 6 weeks. The effect on the neoplastic tissue was measured according to WHO criteria.

The treatment was stopped at a particular dose level if at least 2 patients had a thrombocyte count of $\leq 25 \times 10^9$/l (toxicity grade IV), a leucocyte count of $\leq 1.0 \times 10^9$/l (toxicity grade IV), or a drop in haemoglobin of ≥ 2 g/dl after a course of chemotherapy.

Correspondence to S. Kaasa.
S. Kaasa, E. Thorud, J.F. Evensen, S. Gundersen and H. Høst are at the Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Oslo; J. Tausjø is at the Department of Radium and Diagnostic Radiology, The National Hospital, Oslo; and E. Wist is at the Department of Oncology, Tromsø University Hospital, Tromsø, Norway.
Revised 11 Feb. 1991; accepted 20 Feb. 1991.

Table 1. Patient characteristics

Dose carboplatin (mg/m²)	No. of patients	Men/ women	Age*	Performance status (WHO) 0	1	2	3	Primary treatment/ relapse
200	3	3/0	76(66–81)	0	1	2	0	3/0
300	3	2/1	64(56–84)	0	2	1	0	1/2
350	14	9/5	68(32–78)	1	8	4	1	6/8
400	19	16/3	67(52–85)	1	6	10	2	13/6
420	15	8/7	60(47–80)	1	5	7	2	12/3
440	5	4/1	55(52–70)	0	3	2	0	4/1
Total	59	42/17		3	25	26	5	39/20

* Median (range).

RESULTS

The study comprised 60 patients. 1 patient was excluded after a revised histological diagnosis that showed a non-Hodgkin lymphoma. Thus, 59 patients were actually evaluated. 39 were given carboplatin/5-FU as primary therapy and 20 were given the chemotherapy regimen since they had had relapses after primary surgery and/or radiotherapy. The distribution of patients for each dose size of carboplatin is shown in Table 1. The majority of the patients were men. The age range was 32–84 years. Most patients had WHO performance status 1 and 2.

The primary tumours were located in the oral cavity (19/59), mesopharynx (7), larynx (8), epipharynx (7), hypopharynx (3) maxillary sinus (3), and parotic gland (2). No primary tumour was found in 6 patients.

45 patients received two cycles of chemotherapy and 28 received three. There was no relationship between drug dose and the number of treatment cycles per patient (Table 2). Lack of tumour response was the most common reason for interrupting the treatment after two courses. 5 patients refused more chemotherapy (Table 3). The myelotoxicity was moderate. No patients had grade 4 haemoglobin toxicity, while 7 patients had grade 3 toxicity (Table 4). 2 patients had grade 4 leucocyte toxicity and 1 patient had grade 3 (Table 5). 4 patients were observed with a grade 4 platelet toxicity (Table 6). All of these patients had received a dose of $\geq$400 mg/m² of carboplatin. They all had a platelet count of $\geq 130 \times 10^9$/l 2 weeks later. Patients with grade 3 haemoglobin toxicity had all received a dose of $\geq$400 mg/m². No renal toxicity was found as measured by creatinine clearance, and no liver toxicity was found. 2 patients in primary treatment and 1 treated for relapse had a complete tumour response (Table 7). 16 of the patients with primary treatment and 1 patient treated for relapse had partial remissions. 4 patients received the chemotherapy with a 4–10 days delay while 1 patient had a 17 days delay.

The subjective toxicity was low. 6 patients experienced grade 2 diarrhoea while 2 patients experienced grade 2 stomatitis. Grade 3 emesis was observed in two of a total of 135 courses of chemotherapy. No patient had grade 4 emesis.

2 early deaths occurred. A male patient aged 60 with an initial performance status of 1 developed chest pain and supraventricular arrhythmia, with low-voltage electrocardiogram (ECG), and died the following day. The autopsy report showed coronary and aortic atherosclerosis grade II-III. No sign of recent myocardial infarction was revealed. The other, a woman aged 81, with an inital performance status of 2, had diabetes mellitus. At the end of the third chemotherapy cycle she developed diarrhoea

Table 2. No. of patients per treatment cycle

Dose carboplatin (mg/m²)	Treatment cycle 1	2	3
200	3	2	2
300	3	3	2
350	14	11	6
400	19	12	8
420	15	12	7
440	5	4	3
Total	59	45	28

Table 3. Distribution of patients by reason for not receiving three treatment cycles

Reason for not receiving 2nd and 3rd cycle	2nd course	3rd course
Progressive disease	3	3
No change	—	11
Suicide	1	—
Haemoglobin toxicity	3	1
Leucocyte toxicity	—	1
Thrombocyte toxicity	2	1
Refused more chemotherapy	4	1
Early death	1	1
Total	14	17

Table 4. Haematological toxicity, haemoglobin and WHO toxicity criteria

Dose carboplatin (mg/m²)	No. of courses	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
200	7	0	1	0	0	0
300	8	4	3	1	0	0
350	34	17	10	3	0	0
400	40	19	9	6	5	0
420	34	11	14	6	2	0
440	12	9	1	1	0	0

No. of courses: first, second and third courses added.

Table 5. Haematological toxicity, white blood cells and WHO toxicity criteria

Dose carboplatin (mg/m²)	No. of courses	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
200	7	0	0	0	0	0
300	8	0	0	4	0	0
350	34	12	9	5	4	0
400	40	8	7	12	2	1
420	34	7	13	8	4	1
440	12	9	2	0	1	0

Table 6. Haematological toxicity, platelet count and WHO toxicity criteria

Dose carboplatin (mg/m²)	No. of courses	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
200	7	5	0	2	0	0
300	8	5	0	1	2	0
350	34	20	5	1	0	0
400	40	22	3	8	1	3
420	34	17	7	4	2	1
440	12	2	6	2	1	0

followed by septicaemia and renal failure. Autopsy revealed a generalised atherosclerosis, grade III-IV. The 2 early deaths occurred at a dose level of 420 mg/m². 5 patients had received a carboplatin dose of 440 mg/m² prior to the death of the 81-year-old woman. Further escalation of the dose was stopped after the 2 deaths, in accordance with the protocol.

DISCUSSION

Neoadjuvant combination chemotherapy with carboplatin and 5-FU was well tolerated in the present study. A small minority of the patients experienced nausea and vomiting when traditional antiemetic regimens with low dose metoclopramide and neuroleptics were given. Carboplatin in doses from 200 to 440 mg/m² seems to be much better tolerated than cisplatin in doses of 100 mg/m². Leucocytopenia and thrombocytopenia (grade 3) were only seen in patients receiving carboplatin doses of 350 mg/m² or more. However, none of these patients developed serious infections. 5 patients refused more chemotherapy due to minor emesis and infections. These patients would probably have continued their treatment if it was the primary curative treatment modality.

The protocol criteria state that the given dose level should not be continued if at least 2 patients developed grade 4 toxicity, so that the highest tolerable dose in this study was 350 mg/m². The dose escalation was stopped at 440 mg/m² after 2 early deaths at a dose level of 420 mg/m². Other phase I/II studies in head and neck cancer have shown similar toxicity. In a phase I study of patients with various advanced cancers, including head and neck, lung, and breast carcinomas, the recommended starting dose in good risk patients was 400 mg/m² carboplatin [12]. In ovarian cancer, carboplatin doses of 350 mg/m² have been recommended in combination with doxorubicin, hexamethylmelanine and cyclophosphamide [13]. Carboplatin has been recommended for oesophagus cancer at a dose of 480 mg/m² given as single agent therapy [14]. A dose of 300 mg/m² has been recommended as a starting dose for dose escalation therapy [15, 16]. Large interpatient variations in toxicity have been seen [15]. On the basis of the present study and these results it seems that the maximum tolerable dose is between 350 and 400 mg/m². Toxicity should be monitored carefully with nadir values. Further studies will have to be done to establish the optimal dose.

Table 7. Tumour response (WHO criteria)

Dose carboplatin (mg/m²)	Primary						Secondary (relapse)					
	CR	PR	NC	PD	NE	Total	CR	PR	NC	PD	NE	Total
200	0	1	1	1	0	3	0	0	0	0	0	0
300	0	1	0	0	0	1	0	0	2	0	0	2
350	0	3	2	0	1	6	0	0	5	3	0	8
400	1	5	5	1	1	13	1	0	4	0	1	6
420	0	5	5	0	2	12	0	1	1	0	1	3
440	1	1	1	2	0	4	0	0	1	0	0	1
Total	2	16	14	4	4	39	1	1	13	3	2	20

CR = complete response, PR = partial response, NC = no change, PD = progressive disease, NE = not evaluable.

The response rates in our study were comparable or somewhat lower than those published by others [15, 16]. The latter may be explained by the selection of patients with better prognoses in earlier studies than the patients in our study. Furthermore, 14 patients did not receive their second or third cycle of chemotherapy due to several reasons (Table 3); this may also reduce the response rate. The majority of responding patients received radiotherapy; thus duration of response to chemotherapy was not evaluable.

It is still a controversial issue whether chemotherapy should be used as standard neoadjuvant treatment in patients with advanced head and neck cancer. Only large randomised trials may answer this question, and several randomised studies have been started. A Scandinavian randomised trial using cisplatin 100 mg/m² and 5-FU will soon be completed.

If the effect of the tumour (response rate) of carboplatin is similar to that of cisplatin, carboplatin should be preferred due to the lower incidence of gastrointestinal, hearing and renal side-effects. Furthermore, carboplatin and 5-FU are easy to administer in outpatients.

Combination chemotherapy that produces only minor side-effects will be a useful supplement for reducing the tumour volume in patients suffering a relapse in previously irradiated areas. A combination of carboplatin and 5-FU may be preferable for this group of patients.

1. Taylor SG, Applebaum E, Showel JL, *et al.* A randomised trial of adjuvant chemotherapy in head and neck cancer. *J Clin Oncol* 1985, **3**, 672–679.
2. Dasmahapatra KS, Citrin P, Hill GJ, Yee R, Mohit-Tabatabai MA, Rush BF, Jr. A prospective evaluation of 5-fluorouracil plus cisplatin in advnaced squamous-cell cancer of the head and neck. *J Clin Oncol* 1985, **3**, 1486–1489.
3. Holoye PY, Grassman TW, *et al.* Randomised study of adjuvant chemotherapy for head and neck cancer. *Otolaryngol Head Neck Surg* 1985, **93**, 712.
4. Vogl SE, Shoenfeld DA, Kaplan BH, Lerner HJ, Engstrom PF, Horton J. A randomized prospective comparison of methotrexate with a combination of methotrexate, bleomycin and cisplatin in head and neck cancer. *Cancer* 1985, **56**, 432–442.
5. Williams SD, Velez-Garcia E, Essessee I, Ratkin G, Birch R, Einhorn LH. Chemotherapy for head and neck cancer. Comparison of cisplatin + vinblastine + bleomycin versus methotrexate. *Cancer* 1986, **57**, 18–23.
6. Kish JA, Ensley JF, Jacobs J, Weaver A, Cummings G, Al-Sarraf M. A randomized trial of cisplatin (CACP) + 5-fluorouracil (6-FU) infusion and CACP + 5-FU bolus for recurrent and advanced squamous cell carcinoma of the head and neck. *Cancer* 1985, **56**, 2740–2744.
7. Thorud E, *et al.* High acute toxicity of pre-irradiation chemotherapy (cisplatin + 5-FU) in head and neck carcinomas is related to concomitant cardiovascular disease (abstr.) 14th Int Cancer Congress, Budapest, 1986.
8. Eisenberger M, Hornedo J, Silva H, Donehower R, Spaulding M, van Echo D. carboplatin (NSC-241-240): an active platinum analog for the treatment of squamous-cell carcinoma of the head and neck. *J Clin Oncol* 1986, **4**, 1506–1509.

9. Al-Sarraf M, Metch B, Kish J, *et al.* Platinum analogs in recurrent and advanced head and neck cancer: a Southwest Oncology Group and Wayne State University Study. *Cancer Treat Rep* 1987, **71**, 723–726.
10. de Andres Basauri L, Lopez Pousa A, Sampedro F. Carboplatin, an active drug in advanced head and neck cancer. *Cancer Treat Rep* 1986, **70**, 1173–1176.
11. Forastière AA, Natale RB, Vogel WC, *et al.* Carboplatin (CBDCA) and 5-Fluorouracil (5-FU) combination chemotherapy in advanced head and neck cancer. *Proc. ASCO* 1986, **5**, 545.
12. Leyvraz S, Ohnuma T, Lassus M, Holland JF. Phase I study of carboplatin in patients with advanced cancer, intermittent intravenous bolus, and 24-hour infusion. *J Clin Oncol* 1985, **3**, 1385–1392.
13. ten Bokkel Huinink WW, van der Burg MEL, van Oosterom AT, *et al.* Carboplatin in combination therapy for ovarian cancer. *Cancer Treat Rev* 1985, **15**, 9–15.
14. Sternberg C, Kelsen D, Dukeman M, Leichman L, Heelan R. Carboplatin: a new platinum analog in the treatment of epidermoid carcinoma of the esophagus. *Cancer Treat Rep* 1985, **69**, 1305–1307.
15. Forastière AA, Natale RB, Takasugi BJ, Goren MP, Vogel WC, Kudla-Hatch V. 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.
16. Volling P, Schröder M, Rauschning W, Achterrath W, Stennert E. Carboplatin. The better platinum in head and neck cancer? *Arch Otolaryngol Head Neck Surg* 1989, **115**, 695–698.

Eur J Cancer, Vol. 27, No. 5, pp. 579–582, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Treatment of Breast Cancer in Two Teaching Hospitals: a Comparison with Consensus Guidelines

Mark McCarthy and Jo Bore

We compared the initial treatment of 383 patients with breast cancer in two central London teaching hospitals during 1986 with the guidelines of the King's Fund Consensus Conference for breast cancer treatment held in London the same year. The majority of patients (68%) received lumpectomy and 18% received mastectomy. Lumpectomy was followed by radiotherapy for 95% of cases but 30% of mastectomy patients also received radiotherapy. Only 42% of the patients had surgical sampling of the axillary nodes. Cytotoxic chemotherapy was recorded for 27% women under 50, but also for 16% women age 50 or more. Tamoxifen was given to 58% of women aged 50 or more, but also to 26% of women under 50. We conclude that there are discrepancies between consensus guidelines and clinical practice. Further study is needed to determine whether these variations are clinically important, and whether similar variations exist elsewhere in Europe.
Eur J Cancer, Vol. 27, No. 5, pp. 579–582, 1991

INTRODUCTION

BREAST CANCER is the most common malignancy of women in Western industrialised countries. Neither the cause nor a means of primary prevention of breast cancer are known; therefore, management depends on early diagnosis (including screening) and treatment.

Three consensus developing conferences have been held on the management of breast cancer. The 1980 National Institutes of Health (NIH) conference [1] in the USA covered the initial treatment of breast cancer, and described the trend towards more conservative surgery and the use of primary radiotherapy with or without minimum surgery. A second NIH conference [2], held in 1985, looked at the role of cytotoxic drugs and endocrine therapy. In 1986, the King's Fund held a conference [3] in London, which differed in including lay members in the panel. The conference addressed a broad range of issues on breast cancer management and presented guidelines on local and systemic treatment.

Correspondence to M. McCarthy.
The authors are at the Department of Community Medicine and Middlesex School of Medicine, University College London, 66–72 Gower Street, London WC1E 6EA, U.K.
Revised and accepted 28 Jan. 1991.

This study compares the initial treatment of patients with breast cancer in two central London teaching hospitals in the same year as the King's Fund consensus statement. The two hospitals, Middlesex Hospital and University College Hospital, both provide radiotherapy and oncology services. Patients are referred directly by general practitioners, and also by other hospitals in surrounding districts. We used the consensus conference statement as our criterion for quality assessment.

METHODS

Four sources were available from which names of patients could be identified: the regional cancer register (held at the Thames Cancer Registry); a register of cancer patients held locally in University College Hospital; histopathology laboratory records; and the routine hospital discharge information system (Hospital Activity Analysis). We wrote to all 18 consultants who had treated patients with breast cancer identified from these sources, explaining the study and seeking their permission to review patient case notes: no consultant refused. The study was approved by the Bloomsbury district ethical committee.

We included in the study patients diagnosed with primary breast cancer. We excluded patients who were male (2), treated privately outside the NHS (21), bilateral (8), referred for a second opinion (1) or having non-carcinomatous breast disease