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Carboplatin in Combination with Raltitrexed in Recurrent and Metastatic Head and Neck Squamous Cell Carcinoma: A Multicentre Phase II Study of the Gruppo Oncologico Dell'Italia Meridionale (G.O.I.M.)

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Abstract. *Background: The combination of cisplatin (CDDP) and 5-Fluorouracil (5-FU) is a standard regimen for the treatment of recurrent and metastatic head and neck squamous cell carcinoma (HNSCC). This combination shows a relevant toxicity and new chemotherapy associations with a more favourable toxicity profile are awaited. Carboplatin (CB) is a platinum derivative with less toxicity than CDDP. Raltitrexed (R) is a potent and specific thymidylate synthase inhibitor with activity comparable to that of 5-FU in colorectal cancer; moreover, it showed activity as a single agent in HNSCC. Materials and Methods: Since 2001, a multicentre, phase II trial has been underway to evaluate the efficacy and toxicity of the CB+R combination in untreated patients with recurrent or metastatic HNSCC. Thirty-two patients were enrolled and included in an intent-to-treat analysis. Toxicity was graded according to NCI criteria. Patients had a histo/cytologically proven recurrent or metastatic HNSCC; patients with locally advanced disease not amenable to CDDP+5-FU treatment were also included. Patients had to be >18 years old with ECOG PS of 0-2 and adequate bone marrow, renal and liver functions. CB (AUC 5) and R (3 mg/m^2) were administered intravenously every 3 weeks. The median age was 62 years (range 43-71), 29 M/3 F. The median PS was 1 (0-2). Twelve patients were staged III and 20 were metastatic (10 recurrent). The oral cavity/oropharynx were the primary site in 20 patients and the larynx in 10 patients. The median number of cycles delivered was 3, while globally 115 cycles were administered. The median time to progression was 4.2 months and median duration of survival was 9.8 months. Results: Seven patients achieved a partial response (22%), 10 patients showed a stable disease (31%), while 13 patients (48%) had progressive disease. Eight patients (25%) had a G 3-4 neutropenia, while G 3-4 anaemia was observed in 2 patients and thrombocytopenia in 1 patient. No extra-haematological G 3-4 toxicities were observed. A persistent G 2 hepatic toxicity led a patient to drop out from the study. Conclusion: In our phase II trial, CB in combination with R showed a moderate activity with safe administration on an outpatient basis.*

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Head and neck cancer represents 3% to 4% of all cancer with more than 500,000 new cases diagnosed annually worldwide, thus representing a significant international health problem (1).

The incidence of locoregional failures and distant metastasis is high after primary surgery of head and neck squamous cell carcinomas (HNSCC), especially in patients with unfavourable prognostic factors such as residual disease, histological evidence of extranodal spread and/or multiple nodes in the neck.

Current treatment of recurrent disease is palliative at best and there is no long-term benefit. The two randomised trials (2, 3) that established cisplatin and 5-Fluorouracil (5-FU) as a reference regimen in the treatment of recurrent or metastatic HNSCC were reported in 1992 and have been reviewed recently (4-6). In

both trials, each enrolling approximately 250 patients into one of the 3 arms, the response rate for cisplatin and 5-FU was significantly better (32%), but there were no observed differences in median survival (about 6 months) across the treatments tested. Furthermore, this combination is associated with significant mucosal toxicity and prolonged administration time, factors that are problematic in this patient population and that detract from the palliative intent of the therapy. These data clearly point to the need for new approaches in this setting (7).

The spectrum of antitumour activity of carboplatin is very wide and, in general, efficacy has been observed in tumour types known to be responsive to the parent compound. Carboplatin has been actively tested in head and neck cancer. Response rates were in the range of 14 to 30% with an average of 26% (8). As it induces significantly less renal, otologic, gastrointestinal and neurologic toxicity, it can be used as out-patient treatment without hyper-hydration.

Raltitrexed is a folate-based quinazoline-selective specific thymidylate synthase inhibitor that undergoes extensive polyglutamation within cells. Unlike 5-FU, raltitrexed inhibits thymidylate synthase directly and does not require the presence of a second agent; furthermore, the drug is specific for thymidylate synthase (TS) and does not appear to affect other cellular pathways. Raltitrexed is taken up into cells by the reduced folate carrier system in the cell membrane. This carrier is found more frequently on some tumour cells, an observation that may help to explain the selectivity of raltitrexed. While raltitrexed is active in its parent form, once inside the cell it is rapidly converted into polyglutamated forms. These polyglutamates are more potent inhibitors of TS than the parent drug, are retained within cells for longer and cause enhanced and extended inhibition of TS, which permits a more convenient (once every 3 weeks) dosing schedule than is possible for regimens based on 5-FU (9, 10).

Raltitrexed has been shown to be equivalent, in terms of survival, to 5-FU in 2 of 3 large randomised phase III studies in patients with advanced colon cancer (11). Raltitrexed may have a broad range of activity in tumour types other than colorectal cancer (9, 12). Platinum compounds and raltitrexed act by different mechanisms: platinum compounds by damaging DNA and raltitrexed by interfering with DNA synthesis and repair. The results of *in vitro* cell line work indicate a synergy between raltitrexed and cisplatin (13).

The primary aim of new combination chemotherapy is to increase activity while maintaining tolerability by combining optimal dosage of single, active and non cross-resistant drugs which have no overlapping toxicities. On the basis of these considerations, carboplatin and raltitrexed appear to be ideal drugs for combination chemotherapy.

Materials and Methods

Patient selection. From August 2001 to June 2003, 32 patients with unresectable/advanced HNSCC (stage III-IV) were treated. Patients between 18 and 75 years of age were enrolled if they met the following criteria: i) pathologically confirmed, unresectable or metastatic HNSCC disease not amenable to definitive locoregional treatment; ii) bi-dimensionally measurable disease, at least one area of which had not been subject to prior irradiation; iii) no previous chemotherapy or immunotherapy; iv) performance status of 0,1 or 2 according to the ECOG scale; v) adequate bone marrow reserve (WBC≥4,000/mL, neutrophils≥2,000/mL, platelets≥100,000/mL and haemoglobin level≥10 g/dL), normal hepatic and renal function; vi) written informed consent.

Patients were not eligible for the study if they met any of the following criteria: presence or history of symptomatic central nervous system (CNS) metastases, prior malignancies, except for basal cell or squamous cell skin cancer, *in situ* cervical cancer, or other cancer for which the patient had been disease-free for 5 years and bone marrow metastasis as the only site of disease.

The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki. The study was approved by the local ethic committee, and all patients were required to provide written informed consent as approved by the local institutional review board before initiation of any study procedures.

Treatment plan and dose modifications. Prior to treatment, a medical history was taken, and patients underwent a physical examination (including clinical tumour assessment, ECOG performance status, vital signs, concomitant medications, baseline signs and symptoms), laboratory evaluation (white blood cell, neutrophil count, platelet count, haemoglobin) and serum chemistry evaluation (alkaline phosphatases, bilirubin ASAT, ALAT, serum creatinine, creatinine clearance, sodium, calcium, potassium). Patients had an ECG and radiological examinations to document all lesions including a chest X-ray, upper abdominal ultrasound, TC or NMR of measurable disease. Whole brain TC or bone scan were done only if clinically indicated.

These procedures were performed as needed after the second and sixth cycle of therapy in order to assess the objective response according to WHO criteria (14). Haemochromocytometric parameters were performed weekly and serum chemistry every 3 weeks to closely monitor potential toxicity.

A tumour was defined as unresectable if it was fixed to either a bone structure or lymph nodes or if it was too invasive to allow for radical surgical removal. Relapsing disease was considered as metastatic disease (stage IV).

Carboplatin was administered intravenously over 1 h at the dosage of AUC 5 (Calvert formula, 15); raltitrexed was administered intravenously as a 15-min infusion after carboplatin at the dosage of 3 mg/m^2. Chemotherapy was given on a 3-weekly basis. All patients were premedicated, receiving anti-HT3 drugs and dexamethasone as antiemetic support. Granulocyte colony stimulating factors (G-CSFs) were not recommended for standard prophylaxis, but could be given if needed. The restaging procedure were performed after the second course of therapy and then after the sixth in responders. Tumour response was assessed according to the WHO criteria.

Patients were discontinued from the study if they withdrew consent, had disease progression or experienced unacceptable drug toxicity.

Table I. *Patient characteristics.*

Enrolled	32
Evaluable	32
Sex (M/F)	29/3
Age	
Median	62
Range	43-71
ECOG performance status	
0	5 (16%)
1	21 (65%)
2	6 (19%)
Locally advanced	12
Metastatic (including recurrent)	20
Site of primary	
Oral cavity/oropharynx	20
Larynx	10
Maxillary sinus	2

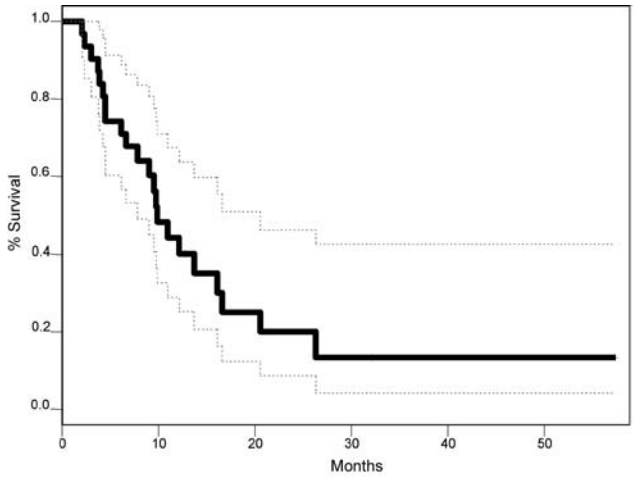

Figure 1. *The Kaplan-Meier survival curve.*

All toxicities were graded according to the NCI Common Toxicity Criteria. If ≥ grade 2 neutropenia occurred, treatment was delayed by 1 week and then, if the recovery from myelosuppression was not complete, a 25% dose-reduction was provided for both carboplatin and raltitrexed. In the case of grade 2 anaemia or platelet toxicity with complete recovery after a week's delay, a dose reduction of 25% for both carboplatin and raltitrexed was provided. If recovery was not achieved after a 2-week delay, the patient was excluded from the study because of toxicity. The occurrence of ≥ grade 2 cardiotoxicity or neurotoxicity, or grade 4 toxicity of any kind (with the exception of neutropenia and alopecia) led to a patient's withdrawal from the study.

Statistics. The primary goal of this study was to estimate the objective response rate according to "intent-to-treat analysis". Objective responses were reported as relative rates with 95% confidence limit (CL). The duration of response was calculated from the first record of response to the date of progression; the time to progression (TTP) was calculated from the date of the first cycle of therapy to the date of progression; and overall survival (OS) from the start of chemotherapy to death or last known follow-up. All data were centrally collected at the Oncology Institute of Bari, Italy.

A univariate analysis of survival data according to the Kaplan-Meier product-limit estimate was performed. Comparisons in survival distribution were made by log-rank test (16).

Results

Patient population. Thirty-two patients entered the study, and their main clinical and demographic characteristics are listed in Table I. Briefly, there were 29 males and 3 females with a median age of 62 years (range 43-71) and a performance status according to the ECOG performance scale of 0 in 5 patients (16%), 1 in 21 patients (65%) and 2 in 6 patients (19%). Disease was locally advanced in 12 patients (37%) and metastatic, including recurrent, in 20 patients (63%). In 20 patients (63%) the oral cavity/oropharynx was the site of primary disease, in 10 patients (31%) the larynx and in 2 patients (6%) the maxillary sinus. No patient had previously received any systemic chemotherapy.

Objective response and survival. Thirty- two enrolled patients were fully evaluable for response, survival and toxicity. In an intent-to-treat analysis, among the 32 evaluable patients, 7 partial responses were observed (22%, 95% CL 7.8%-20.5%), 10 patients showed stable disease (31%) and 13 patients (41%) progressed. Two patients (6%) were not evaluated: 1 patient for early death and 1 for refusal to continue chemotherapy after the first cycle. After a median follow-up of 18 months, the median time to progression was 4.2 months (range 1-15), and the median overall survival was 9.8 months (range 2-57, Figure 1). One and 2-year survival rates were 44.2% and 20.1%, respectively.

Toxicity. The side-effects of the treatment are summarized in Table II. The main observed toxicity was represented by haematological side-effects. No chemotherapy-related toxic death was observed. Haematological grade 3-4 side-effects were: anaemia (6%), neutropenia (25%) and thrombocytopenia (3%). Non-haematological grade 3-4 toxicity was limited to alopecia in 1 patient (3%). The grade 1-2 side-effects were: anaemia (25%), neutropenia (16%), thrombocytopenia (25%), nausea/vomiting (22%), diarrhoea (12%), alopecia (9%), mucositis (22%), transaminases (19%), asthenia (9%), renal, neurotoxicity and fever (3%).

Table II. *Toxicity.*

	G1-2	G 3-4
Anaemia	8 (25%)	2 (6%)
Neutropenia	5 (16%)	8 (25%)
Thrombocytopenia	8 (25%)	1 (3%)
Nausea/vomiting	7 (22%)	-
Diarrhoea	4 (12%)	-
Alopecia	3 (9%)	1 (3%)
Mucositis	7 (22%)	-
Transaminases	6 (19%)	-
Neurotoxicity	1 (3%)	-
Fever	1 (3%)	-
Asthenia	3 (9%)	-
Renal	1 (3%)	-

Discussion

Chemotherapy is considered to have a limited role in terms of survival in head and neck cancer. It is only the standard therapy for recurrent disease with a marginal palliative benefit. The most frequently employed regimen is cisplatin plus 5-FU in recurrent or metastatic head and neck cancer and, despite yielding higher response rates, this regimen has not been shown to produce a survival benefit compared with single agents in randomised comparisons.

The Eastern Cooperative Oncology Group conducted 2 consecutive randomised studies with cisplatin combinations in patients with recurrent or metastatic HNSCC. These 2 randomised trails compared cisplatin doublets (cisplatin and paclitaxel at 2 dose levels, and cisplatin and paclitaxel *versus* cisplatin plus 5-FU), but failed to show statistically significant survival differences between the treatment arms (17, 18). Furthermore, considerable toxicities were observed in both trials.

Other studies have replaced docetaxel with paclitaxel in combinations with cisplatin. In a phase II cooperative study with 46 patients, the combination of docetaxel plus cisplatin at the dosage of 75 mg/m^2 and 100 mg/m^2, respectively, every 3 weeks, was administered; a response rate of 46% was observed with a median survival of 11 months. Six early deaths were considered as possibly treatment-related with neutropenia of grade III-IV in about one-third of the patient population (19).

The search for new active antineoplastic agents against recurrent or metastatic head and neck cancer still represents a major end-point of medical oncology. In a European phase I study, raltitrexed showed antitumour activity in 2 patients with head and neck cancer, prompting several phase II studies employing this new drug as a single agent or in combination (12).

As a single agent in a phase II multicentre Australian study, raltitrexed, given at a dosage of 3 mg/m^2 every 3 weeks in 24 evaluable patients, led to 5 patients with stable disease lasting a median of 188 days, while for all patients the median time to progression was 41 days and the median survival was 101 days. This patient group was heavily pretreated with surgery and radiotherapy (20).

In an open dose-escalation phase I study, ten Bokkel Huinink *et al*. treated cohorts of patients with escalating doses of raltitrexed (2.0 mg/m^2 to 3.5 mg/m^2) immediately followed by cisplatin (80 mg/m^2) every 3 weeks to determine the maximum tolerated dose. The recommended dose for further study was raltitrexed 3.0 mg/m^2 in combination with cisplatin 80 mg/m^2 every 3 weeks. In 15 evaluable patients 9 objective responses (1 complete and 8 partial) were observed. It is worth noting that, in this study, due to cisplatin-induced nephrotoxicity expressed as a creatinine clearance decrease of more than 50% in the first cohort of 3 patients, the cisplatin dose was reduced to 80 mg/m^2 for all subsequent treatment cycles (21).

In a phase II study, patients with inoperable locally advanced or metastatic HNSCC, not preatreated with chemo- or radiotherapy, were randomised to receive cisplatin 60 mg/m^2 and raltitrexed 2.5 mg/m^2 on day 1, and L-folinic acid 250 mg/m^2 + 5-FU 900 mg/m^2 on day 2 (arm A) or cisplatin 65 mg/m^2 and methotrexate 500 mg/m^2 on day 1, and L-folinic acid 250 mg/m^2 + 5-FU 80 mg/m^2 on day 2 (arm B). An overall response rate of 77% was observed in arm A (61 patients), and 42% in arm B in the first 36 patients with a statistically significant difference in both overall response rate and complete response rate. (22).

The present study was undertaken in patients with HNSCC in the attempt to find a useful combination showing the lowest possible toxicity profile. Carboplatin can replace cisplatin because of its significantly reduced non-haematological toxicity (emesis, nephrotoxicity, neurotoxicity), while raltitrexed is reported to cause less grade 3 or 4 neutropenia and stomatitis when compared to 5-FU on the Mayo Clinic schedule.

In our study, 53% of patients showed disease control with a confirmed response seen in 22% of patients; the median time to progression was 4.2 months and the median overall survival was 9.8 months, with a projected 1-year survival of 44%.

In summary, the combination of raltitrexed and carboplatin had a manageable toxicity profile and could be administered with a simple and short administration schedule on an out-patient basis with less psychological and physical distress than other multiday regimens that require hospitalisation. Compared to the standard palliative regimen using cisplatin and 4 to 5-day infusional 5-FU, or to multiple novel agents or combinations, our regimen is more convenient, requires fewer days of treatment and might have similar efficacy in patients with locally advanced or metastatic HNSCC.

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