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Original article

Treatment of recurrent and/or metastatic squamous cell head and neck carcinoma with a combination of vinorelbine, cisplatin, and 5-fluorouracil: A multicenter phase II trial

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Summary

Purpose: Vinorelbine has been demonstrated to be active against squamous cell carcinomas of the head/neck (SCHNC) and lung. This multicenter phase II trial was carried out to evaluate the activity and tolerability of the combination of vinorelbine, cisplatin, and 5-fluorouracil given on an outpatient schedule in a series of 80 patients with recurrent SCHNC.

Patients and methods: Eighty patients with recurrent and/or metastatic SCHNC were treated with a combination of CDDP 80 mg/m^2 on day 1, 5-FU 600 mg/m^2 as a 4-hour infusion on days 2–5, and vinorelbine 25 mg/m^2 on days 2+8. This cycle was repeated every 28 days. Most patients had oral cavity, larynx, or oropharynx carcinoma (88%). Forty-seven had previously received surgery alone, two radiotherapy alone, and 31 surgery plus radiotherapy. Seventy-two patients had locoregional recurrency, and eight had distant metastases.

Results: According to an intent-to-treat analysis, complete response (CR) of a mean duration of 12.7+ months was achieved in 13% of cases (95% CI 5%–21%), and partial response of 8.3+ months in 45% of patients (95% CI 33%–56%), for an overall response rate of 55% (95% CI 43%–65%). Nine patients (11%) showed no change, and 22 (28%) progressed. Five patients were not evaluable for response and toxicity. CR were seen more frequently in patients pretreated with only surgery than in those who had also received radiotherapy (15% vs. 9%; p = 0.7). No statistically significant differences in response rate according to site of primary tumor were found (p = 0.8, NS). The received dose intensities of 5-FU, CDDP, and VNR were 90%, 92%, and 82%, respectively. The overall survival of the series as a whole was 9.7+ months (range 4–27). Toxicity was generally acceptable. Grades 3 and 4 leukopenia were recorded in 11% and 5% of patients, respectively. Noteworthy was the occurrence of pain at the tumor site after vinorelbine administration in 5 patients.

Conclusion: The combination regimen of CDDP, 5-FU and vinorelbine is quite active in the treatment of metastatic and/or recurrent SCHNC. This regimen should be tested as initial treatment in previously untreated patients and compared to a standard regimen in recurrent SCHNC.

Key words: head/neck cancer, vinorelbine, cisplatin, 5-fluorouracil, chemotherapy

Introduction

A high proportion of patients with stage III–IV squamous cell carcinoma of the head and neck (SCHNC) at diagnosis will eventually recur even after optimal locoregional treatment with surgery and/or radiation therapy [1]. These patients are potential candidates for palliative chemotherapy [1].

Several multidrug combination regimens have been tested in patients with recurrent and/or metastatic SCHNC. The drugs most commonly employed, alone or in various combinations, include methotrexate, bleomycin, vinca alkaloids, 5-fluorouracil (5-FU), and cisplatin (CDDP) [2]. In particular, the combination of CDDP plus infusional 5-FU seems to be very effective [3, 4, 5]. The use of this combination is based on both experimental [6, 7] and clinical [3, 4] data which have shown a remarkable synergism between CDDP and 5-FU.

Vinca alkaloids, such as vinblastine, have also been successfully employed in advanced SCHNC, alone [8] or in combination with other drugs [9–13]. Recently, vinorelbine (5'-nor-anydrovinblastine, VNR), a new semisynthetic vinca alkaloid, has been demonstrated to be quite active in the treatment of squamous cell carcinoma of the lung and the head/neck region [14, 15]. Although it has been suggested that VNR is less neurotoxic than other vinca alkaloids, it is quite myelosup-

pressive, with granulocytopenia as its dose-limiting toxicity [14, 15]. Preclinical experiments on P388 murine leukemia have shown that VNR and CDDP may act synergistically [16], and clinical studies have demonstrated a good antineoplastic activity of the combination of CDDP and vinca alkaloids in advanced squamous cell HNC [17, 18]. Moreover, the combination of CDDP, VNR, and 5-fluorouracil with folinic acid has been tested in advanced non-small-cell lung cancer with interesting results [19].

On the basis of these observations we carried out a clinical trial on the combination of CDDP, 5-FU and VNR to test the activity and toxicity of the regimen in SCHNC. In the present paper we report the results of this multicenter study in a series of 80 patients with recurrent and/or metastatic SCHNC.

Materials and methods

After the approval of the Ethical Committees of the participating Institutions was obtained, a multicenter phase II trial was started in July 1991. All eligible cases were centrally registered by phone call or fax to the coordinating center (Service of Chemotherapy, University of Palermo).

Entry criteria

Prior to their entry into the study patients had to fulfill the following eligibility criteria: histological diagnosis of recurrent and/or metastatic SCHNC; measurable disease according to the WHO criteria [16]; written informed consent; age ≤ 75 years; life-expectancy > 2 months; adequate bone marrow function (WBC ≥ 4,000/mmc; Plt ≥ 120,000/mmc; Hb > 10 gr%); adequate renal test results (BUN ≤ 50 mg%; serum creatinine ≤ 1.2 mg%; creatinine clearance > 60 ml/min); adequate liver chemistries (serum bilirubin < 1.2 mg%; serum transaminases < 2 times normal value); no previous chemotherapy; no other malignant neoplasm except in situ cervical carcinoma of the uterus or cutaneous basal cell carcinoma; absence of brain metastases; no major concomitant or uncontrolled cardiovascular, metabolic, renal, respiratory or neurological diseases; geographical accessibility to the oncological center.

Treatment plan

The treatment plan was: CDDP 80 mg/m^2 diluted in 500 cc of normal saline over 1 hour with a standard pre- and post-hydration protocol with forced diuresis with 250 cc of 18% mannitol on day 1; 5-FU 600 mg/m^2 diluted in 500 cc of normal saline over a 4-hour infusion on days 2–5; and VNR 25 mg/m^2 on days 2 and 8. This regimen was tentatively repeated every 28 days depending on recovery from toxicity. This chemotherapeutic schedule was designed on the basis of literature data on non-small-cell lung cancer and SCHNC [18, 19], and on a previous feasibility dose-finding study carried out by some of us (VG and NG, unpublished results) whereby it was not possible to increase the 5FU dose over 600 mg/m^2/day in combination with CDDP and VNR without the occurrence of severe mucositis and leukopenia. Antiemetic therapy consisted of ondansetron 24 mg i.v. on the CDDP day, followed by 8 mg p.o. b.i.d. on the 5-FU day [20]. The occurrence of progressive disease, protocol violations, ≥ grade 2 cardiotoxicity or neurological side effects, or grade 4 toxicity of any kind except for leukopenia and alopecia led to patients' withdrawal from the study. In instances of leukopenia grade ≥ 2 and/or thrombocytopenia grade 1 before each new cycle or before VNR on day 8, chemotherapy administration was delayed for one week.

Clinical efficacy and toxicity evaluation

Before starting chemotherapy patients were staged by history, physical examination, otorhinolaryngology examination, chest X-ray, skull X-ray, 99Tc bone scan, CT scan of the involved areas, abdominal sonograms, ECG, hemocromocytometric analysis, and routine chemistry tests. These tests were also employed for response evaluation as needed.

Objective tumor regression, as well as toxicity, were evaluated according to the WHO criteria [21]. Briefly, a complete response (CR) was defined as the disappearance of all signs of disease for at least 4 weeks; a partial response (PR) was defined as a > 50% reduction in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 4 weeks without the appearance of any new lesion; no change (NC) as a < 50% decrease or < 25% increase in the size of tumor deposits; and progressive disease (PD) as a > 25% increase in the size of tumoral lesions or the appearance of any new lesion. The duration of both complete and partial responses was calculated from the beginning of chemotherapy until relapse, progression, or death.

The first evaluation of response was performed after 3 cycles. In case of progressive disease patients were given second-line chemotherapy or were offered radiotherapy if not received before. In case of CR a total of 6 cycles were given; in case of PR or NC chemotherapy was given until progression or unacceptable toxicity.

Statistics

Objective responses are reported as relative rates with 95% confidence limits (95% CL). Comparison of response rates among different subgroups of patients was carried out employing the chi-square test. Duration of response and survival analysis were carried out according to the Kaplan-Meyer product-limit method. Analysis of dose-intensity was performed for all cycles according to the method previously described by Hryniuk [22].

Results

Patient population

The main clinical and demographic characteristics of enrolled patients are depicted in Table 1. There were 75 males and 5 females with a mean age of 62 years and a mean Karnofsky Index of 76. All patients had recurrent and/or metastatic disease after locoregional treatment: 47 patients (59%) had previous surgery, 31 (39%) had surgery plus radiotherapy, and only 2 had previous radiotherapy alone. The median disease-free interval from the initial treatment to the diagnosis of recurrent disease was 20.3 months (range 5.0/43.5). Sites of primary tumor were: oral cavity (25%), larynx (37.5%), oropharynx (25%), hypopharynx (2.5%), maxillary sinus (5%), and other (5%). Most patients (n = 72; 90%) had locoregional recurrency, but 8 (10%) had metastatic disease in lungs, nodes, liver, bone, or subcutaneous tissues. Of 72 patients with locoregional recurrence 32 (44%) had nodal disease, 8 (11%) recurrence only at tumor site and 32 (44%) had recurrent disease at both tumor site and nodes. Skin was infiltrated in 11 (15%) cases.

Objective responses

Type and duration of objective tumor response, as well as survival, are depicted in Table 2. Response rates

Table 4. Main toxicities.

Type of toxicity	No. of patients (%) Grade (WHO scoring system)			
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	27 (36%)	28 (37%)	20 (27%)	–
Diarrhoea	10 (13%)	7 (9%)	3 (4%)	–
Stomatitis	16 (21%)	10 (13%)	10 (13%)	–
Leukopenia	19 (25%)	18 (24%)	8 (11%)	4 (5%)
Thrombocytopenia	14 (19%)	5 (7%)	1 (1%)	–
Anemia	12 (16%)	8 (11%)	2 (3%)	–
Constipation	8 (11%)	9 (12%)	–	–
Phlebitis	8 (11%)	–	–	–
Pain at injection site	6 (8%)	–	–	–
Pain at tumor site	5 (7%)	–	–	–

effects were myelosuppression and gastrointestinal toxicity. Leukopenia was recorded in 59 patients (78%), but grades 3 and 4 leukopenia was only seen in 8 (11%) and 4 (5%) patients, respectively. Twenty patients had thrombocytopenia of any grade; among these patients five (7%) reported grade 2 thrombocytopenia. Moderate to severe anemia was observed in 10 patients (14%).

Almost all patients suffered from gastrointestinal side effects. However, diarrhea was recorded less frequently than expected: 20 patients had liquid stools of any grade, with only 3 patients suffering from grades 3 diarrhea. Grade 3 nausea/vomiting was seen in 27% of patients, and grades 1 and 2 in 36% and 37% of cases, respectively. Severe stomatitis (grade 3) was observed in only 13% of cases.

Despite the use of a combination of potentially neurotoxic drugs, neurotoxicity was not a major complaint. Transient mild-to-moderate constipation was recorded in 17 patients (23%), while grade 1 neuromotor toxicity (paresthesias) was seen in only 1 patient. Pain at the injection venous site was observed in 6 patients (8%), and chemical phlebitis in 8 (11%). Previously described acute pain syndrome at the tumor site (18) was seen in 5 patients (7%).

Discussion

The result of chemotherapeutic treatment for recurrent and/or metastatic squamous cell head and neck carcinoma (SCHNC) are still unsatisfactory, since in most series patients show a median survival of 6–10 months despite some dramatic shrinkage in tumor size and improvement in performance status [2–5]. Several studies have shown that 5-FU and CDDP have synergistic antineoplastic activity.

On the basis of the promising activity shown by vinorelbine alone or in combination with other drugs in SCHNC [15, 20] and in other squamous cell carcinomas [14, 19], the combination of CDDP, 5-FU and VNR has been tested in a multicenter phase II trial involving 80 HNC patients.

In our hands this regimen induced a 55% (95% CI 43%–65%) overall response rate (intent-to-treat analysis) with a 13% (95% CI 5%–21%) complete response rate and a 42% (95% CI 31%–53%) partial response rate. The mean duration of CR and PR were 13.7+ and 8.3+ months, respectively. Achievement of an objective response was somewhat easier in patients (15%) with recurrent disease after surgery-only than in those who were pretreated also with radiotherapy (9%). There was only an occasional objective response in patients with distant metastatic disease.

No statistically significant differences were observed when response rates were analyzed according to site of primary neoplasm.

The 58% overall response rate achieved in the present study is within the range reported by other authors with combination regimens shown to be active in advanced SCHNC [4, 24–26], although our data are slightly superior to the 49% average response rate achieved in several trials with the combination of CDDP plus continuous venous infusion 5-FU (CVI 5-FU), [25, 27].

Our current data with the CDDP/5-FU/VNR regimen are better, at least in terms of response rate, than those which we reported in a previous study using the combination of CDDP 100 mg/m^2 plus 120-hour CVI 5-FU (1 g/m^2/day) in a series of patients with recurrent and/or metastatic SCHNC with a 42% ORR and a mean duration of 8.0+ months [27]. Moreover, in most studies, patients receiving 120-hour CVI 5-FU required hospitalization both in order to receive chemotherapy and to treat chemotherapy-related side effects, while the CDDP/5-FU/VNR schedule was given altogether on an outpatient schedule, and hospitalization because of toxic effects was required only occasionally.

The treatment was well tolerated, since all patients were treated on an outpatient basis, and treatment-related hospitalization was required in only 4 cases. Although leukopenia and gastrointestinal toxicity were the most frequently observed side effects, noteworthy is the occurrence of pain at tumor site following VNR administration in 5 patients [23]. Neurotoxicity was not a major clinical problem in this series despite the use of a combination regimen comprising different potentially neurotoxic drugs. Analysis of both received dose-intensity and cumulative delivered dose showed that it is feasible to give this regimen to patients with advanced SCHNC at an acceptable dose intensity.

In conclusion, clinical data reported in the present study suggest that the combination of CDDP, 5-FU and VNR is active in recurrent and/or metastatic SCHNC. This regimen may be safely given on an outpatient basis. Although the response rate is high, we cannot as yet recommend its use as standard therapy for recurrent and/or metastatic SCHNC. However, clinical results are good enough to prompt clinical investigators

to compare the combination of CDDP, VNR and 5-FU to a standard regimen, such as CDDP plus CVI 5-FU. Whether this combination regimen is superior to CDDP plus CVI 5-FU can be determined only by a prospective randomized study. The good activity shown in this trial also suggests the testing of this regimen as neoadjuvant chemotherapy for previously untreated, unresectable SCHNC. Such trials are currently ongoing at our Institutions.

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