Phase II Randomized Trial Comparing Vinorelbine versus Vinorelbine plus Cisplatin in Patients with Recurrent Salivary Gland Malignancies

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Received March 3, 2000; revision received August 18, 2000; accepted October 2, 2000.

BACKGROUND. Some previous studies have shown that vinorelbine (VNB) is active in recurrent salivary gland tumors.

METHODS. Between April 1993 and April 1997, 36 patients in a Phase II randomized trial received either cisplatin, 80 mg/m^2, on Day 1 plus VNB, 25 mg/m^2, on Days 1 and 8 (every 3 weeks) (for a minimum of 3 cycles (Arm A [16 patients]), or VNB, 30 mg/m^2/week, (for a minimum of 9 wks) (Arm B [20 patients]). There were 23 males and 13 females with a median age of 59 years (range, 20–74 years) and a median Eastern Cooperative Oncology Group performance status of 1 (range, 0–2). Four patients had been treated with prior surgery (S) or radiotherapy (RT), 27 patients had been treated with S plus RT, and 5 patients had been treated with S plus RT plus mitoxantrone. Eighteen patients had major salivary gland tumors, and 18 patients had minor salivary gland tumors; 9 patients had adenocarcinoma, 22 patients had adenoid cystic carcinoma, 1 patient had a malignant mixed carcinoma, 3 patients had undifferentiated carcinoma, and 1 patient had a mucoepidermoid carcinoma. The site of recurrence was local in (16 patients), local plus metastatic in 5 patients, and metastatic only in 15 patients. These characteristics were well balanced between the 2 arms.

RESULTS. In Arms A and B a complete response (CR) was noted in 3 patients (19%) and no patients, respectively; a partial response (PR) was noted in 4 patients (25%) and 4 patients (20%), respectively; no change was noted in 6 patients (37.5%) and 9 patients (45%), respectively; and progressive disease was noted in 3 patients (19%) and 7 patients (35%), respectively. The median duration of the CR was 15+ months (range, 6–27+ months) and for PR the median duration was 7.5 months (range, 3–11+ months) and 6 months (range, 3–9 months) in Arms A and B, respectively. Number of patients surviving $>$ 12 months was 6 versus 1 in Arms A and B, respectively ($P < 0.05$). Grade 2–3 nausea and emesis was statistically higher ($P < 0.001$) in Arm A; there was no significant difference with regard to other side-effects between the two treatment arms.

CONCLUSIONS. VNB is a drug with moderate activity in salivary gland malignancies. The combination of cisplatin plus VNB was found to be more active than VNB alone, with a good number of CRs and long-term survivors reported in the current study. ***Cancer* 2001;91:541–7.** © *2001 American Cancer Society.*

KEYWORDS: salivary gland carcinoma, cisplatin, vinorelbine, chemotherapy, adenoid cystic carcinoma, recurrence, metastasis.

In contrast to the other head and neck neoplasms in which the primary site and the cervical lymph nodes are common sites of recurrences, carcinoma of the major and minor salivary glands most often recurs at the primary and/or distant metastatic sites.[1] In se-

lected cases, locoregional recurrences, may be managed with additional surgery or radiotherapy. However, the majority of patients with recurrent, metastatic or unresectable salivary gland carcinoma are not amenable to the usual treatment with surgery and postoperative radiation. The lungs are favored sites of metastases, although bone, liver, central nervous system, and other organs may become involved.[1]

The use of chemotherapy for recurrent salivary gland carcinoma currently is under investigation. Cisplatin, doxorubicin, and 5-fluorouracil (5-FU) are the most active agents against adenocarcinoma-like salivary gland tumors (adenoid cystic carcinoma, malignant mixed tumor, adenocarcinoma, and acinous cell carcinoma).[2,3] Combination chemotherapy including the aforementioned drugs as well mitomycin-C, cyclophosphamide (CYC), methotrexate, bleomycin, and vincristine (VCR) also may achieve tumor regression.[2–4]

Vinorelbine (VNB) has proven to be effective in nonsmall-cell lung carcinoma, breast carcinoma, cisplatin-resistant ovarian carcinoma, and Hodgkin disease. In patients with recurrent squamous cell head and neck carcinoma VNB has shown moderate activity as first-line therapy[5] and very low efficacy in heavily pretreated patients.[6]

In a pilot study using VNB alone in 20 patients with recurrent adenocarcinoma-like salivary gland malignancies, we observed 4 partial responses (PR) (20%) and 9 cases of no change (NC) (stable disease), (45%) which demonstrates moderate activity for this drug despite the high percentage of cases of adenoid cystic carcinoma histology (13 patients) and the high number of patients (11 of 20) with distant metastases.[7,8] Cisplatin is the most effective drug in these tumors and can induce complete responses (CRs) in adenoid cystic carcinoma;[9] moreover, cisplatin and VNB have been shown to have a synergistic activity both in vitro and in vivo.[10,11]

In the current study we report a randomized Phase II trial of the use of VNB alone versus the combination of cisplatin plus VNB in patients with recurrent salivary gland malignancies.

MATERIALS AND METHODS

Patient Population

Between April 1993 and February 1997, 36 patients were entered into the study. Eligibility criteria included the presence of a biopsy-proven recurrent malignancy of major (parotid, submandibular, sublingual) or minor (hard palate, buccal mucosa, base of tongue, floor of mouth, paranasal sinus, nasopharynx, retromolar trigone, or other) salivary gland origin and one of the following histologies: adenoid cystic carcinoma, malignant mixed carcinoma, adenocarcinoma, or poorly differentiated mucoepidermoid carcinoma. Pretreatment evaluation included a complete history and physical examination; a complete blood count with platelet and differential counts; blood chemistries; chest-X-ray; computed tomography scan, and ear, nose and throat examination.

Disease that was measurable and in clear progression at the start of chemotherapy was required as was an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

Other eligibility criteria included the following: neutrophil count $> 1500/\mu L$, platelet count $> 100{,}000/\mu L$, hemoglobin level > 9 g/dL, serum creatinine concentration < 1.5 mg/dL, bilirubin level < 2.0 mg/dL, and aspartate aminotransferase $<$ twice the upper limits of normal. Patients with a history of congestive heart failure or brain metastases were excluded.

Written informed consent was obtained from all patients in accordance with institutional and state regulations.

Twenty patients randomly were assigned to receive VNB alone and 16 to receive the combination of VNB and cisplatin. The follow-up procedure, imposed by the Ethics Committee, was comprised of a team examination every 15 days for 6 months, every month for up to 1 year, and every 2 months thereafter.

Treatment Schedule

Patients were randomized to one of two study arms. Arm A was comprised of cisplatin, 80 mg/m^2, on Day 1 plus VNB, 25 mg/m^2, on Days 1 and 8 every 3 weeks. Arm B was comprised of VNB, 30 mg/m^2, intravenously weekly. In Arm A the patients received an intravenous push of cisplatin after 2 hours of prehydration with 0.9% NaCl and mannitol, followed by 2 hours of posthydratation with 5% glucose plus 10 meq/L of KCl; VNB was given as shown in Arm B.

Methylprednisolone and granisetron were given on Day 1 to control nausea and emesis.

The study is based on a maximum of six cycles. Only patients who achieved either a response or NC after the third cycle reached the sixth course of treatment. In patients with progressive disease treatment was interrupted after at least three cycles.

In Arm B, VNB, diluted with 100 mL of normal saline, was administered intravenously and infused over 10 minutes. This was followed for the next 10 minutes by another 100 mL of normal saline.

Patients received treatment for at least 9 weeks unless disease progression was documented after at least 4 weeks of treatment. Patients with NC continued

treatment for at least 18 weeks. Patients who achieved an objective response continued treatment until disease progression or toxicity.

Treatment interruption was permitted in case of disease progression, severe toxicity, or patient refusal to continue. No crossover or second-line treatment was scheduled; patients with progressive disease received palliative treatment only.

Drug Schedule Modification

On the day of treatment, the granulocyte count had to be $> 1500/\mu L$ and the platelet count $> 100{,}000/\mu L$ for administration of full dose VNB with or without cisplatin. Doses of both drugs were reduced by 50% for granulocyte counts of $1000–1499/\mu L$ and platelet counts $< 75{,}000/\mu L$ to $99{,}999/\mu L$ on the day of treatment; both drugs were withheld when the granulocyte and/or platelet counts were below these levels. There was a 50% reduction for both drugs if there was a delay in therapy of > 2 weeks but ≤ 3 weeks, or if granulocytopenic fever occurred during the previous cycle. There was 50% dose reduction of cisplatin if a nadir of < 500 granulocytes/μL and/or $< 50{,}000$ platelets/μL occurred during the previous cycle, but a dose reduction of VNB was based on the weekly complete blood count as outlined earlier.

Granulocyte–colony-stimulating factor (G-CSF; Neupogen, Amgen, Thousand Oaks, CA) (5 μg/kg/day) was permitted only after the first course of treatment for patients who experienced Grade 3 or 4 granulocytopenia or developed neutropenic fever between cycles of chemotherapy. G-CSF was not given prophylactically to maintain the weekly VNB schedule.

In Arm A before each cycle, serum creatinine, calculated creatinine clearance, and serum electrolytes (including magnesium) were determined. If the serum creatinine concentration was > 1.6 mg/dL but the calculated creatinine clearance was > 50 mL/minute, the cisplatin dose was reduced by 50%; cisplatin was withheld if the calculated creatinine clearance was < 50 mL/minute. If cisplatin was held for any length of time, retreatment was at a 50% dose level.

There were dose modifications for VNB if hyperbilirubinemia developed (50% dose for a serum bilirubin level of 2.1–3.0 mg/dL and 25% dose for a bilirubin level > 3.0 mg/dL).

Response and Toxicity Criteria

Standard International Union Against Cancer criteria[12] were used for response determination and toxicity grading. Criteria for the removal of patients from the study included disease progression, unacceptable toxicity, a delay in treatment of > 4 weeks, requirement for palliative radiotherapy (bone lesions), or patient refusal to continue.

Statistical Analysis

Survival curves were estimated by the product-limit method and compared using the log-rank test. Cox regression was used to explore the influence of prognostic factors on survival and to assess treatment-by-factor interactions. All reported P values are two-tailed.

RESULTS

Response and Survival

Patients characteristics are listed in Table 1. The two groups were balanced evenly for age, gender, ECOG performance status, prior therapy, site of primary tumor, histology, site of recurrence, and metastases. All patients were evaluable for response and toxicity. Overall, 74 courses of VNB plus cisplatin were given; the median number of chemotherapy cycles per patient was 5 (range, 2–6 cycles); 174 courses of VNB alone were given with a median number of 9 chemotherapy cycles per patient (range, 6–19 cycles). The median delivered VNB dose intensities in Arm A and Arm B were 85.7 and 91.2, respectively; the median cisplatin dose intensity was 90.5%. The overall response rate for patients randomized to Arm A was 44% (7 of 16 patients) and was 20% for those patients randomized to Arm B (4 of 20 patients) (Table 2). There were 3 (19%) and 0 CRs in the VNB plus cisplatin and VNB arms, respectively. Two patients with adenoid cystic carcinoma achieved a CR; the first patient was affected by lung metastases and the second by one lung and one osteolytic tibial lesion. Another patient with a recurrent T4 parotid undifferentiated carcinoma achieved a CR after treatment with cisplatin plus VNB.

The median CR duration was 15+ months (range, 6–27+ months).

In the VNB arm, two patients with adenoid cystic carcinoma achieved a PR; the first patient developed a local recurrence in the palate and the second patient developed lung metastases. In this case, at the time of disease progression retreatment with VNB was effective, with a second response lasting 7 months.

The median durations of PR for the VNB plus cisplatin and VNB alone arms were 7.5 months (range, 3–11+ months) and 6 months (range, 3–9 months), respectively. The median NC duration was 5 months (range, 3–8 months) and 3.5 months (range, 2–10+ months) in Arms A and B, respectively.

The median time to disease progression was 7 months for Arm A and 5 months for VNB alone (Arm B) ($P = 0.06$). Patients with an ECOG performance

TABLE 1
Patient Characteristics

	Cisplatin + VNB	VNB
No.	16	20
Age (yrs)		
Median	58	61
Range	20–68	27–74
Gender		
Male	10	13
Female	6	7
ECOG PS		
0	4	5
1	10	11
2	2	4
Prior therapy		
Surgery	1	0
Radiotherapy	2	1
Surgery + radiation	11	16
Surgery + radiation + mitoxantrone	2	3
Site of primary tumor		
Parotid gland	5	8
Submandibular gland	3	2
Hard palate	2	4
Buccal mucosa	3	3
Base of tongue	0	1
Maxillary sinus	3	2
Histology		
Adenocarcinoma	4	5
Adenoid cystic carcinoma	9	13
Malignant mixed tumor	0	1
Undifferentiated carcinoma	2	1
Mucoepidermoid carcinoma	1	0
Site of recurrence		
Local	7	9
Local + mets	3	2
Mets only	6	9
Site of metastases		
Lung	6	7
Bone	1	1
Lung + bone	2	2
Lung + bone + LN + skin	0	1

VNB: vinorelbine; ECOG PS: Eastern Cooperative Oncology Group performance status; mets: metastases; LN: lymph node.

TABLE 2
Results

	Cisplatin + VNB	VNB
Response		
CR	3 (19%)	0
PR	4 (25%)	4 (20%)
NC	6 (37.5%)	9 (45%)
PD	3 (19%)	7 (35%)
Median CR duration (mos) (range)	15+ (6–27+)	—
Median PR duration (mos) (range)	7.5 (3–11+)	6 (3–9)
Median NC duration (mos) (range)	5 (3–8)	3.5 (2–10+)
Median survival (mos) (range)		
Overall	10 (3–29+)	8.5 (2.5–16)
CR	19+ (12+/29+)	—
PR	12.5	9
NC	9.5	7
PD	5	4
No. of patients surviving > 12 mos	6 [a]	1

VNB: vinorelbine; CR: complete response; PR: partial response; NC: no change (stable disease); PD: progressive disease.
[a] $P < 0.05$.

status of 0–1 had a better response rate (10 of 30 patients; 33.3%) than patients with an ECOG performance status of 2 (1 of 6 patients; 16.6%).

Patients with adenocarcinoma showed a response rate (3 of 9 patients; 33.3%) that was comparable to that for patients with adenoid cystic carcinoma (6 of 22 patients; 27.3%). No response was noted in the patient with a mixed malignant tumor. There was a nonstatistically significant prevalence of adenoid cystic carcinoma in Arm B; there were 4/9 (44.4%) and 2/13 (15.4%) responses in Arm A and B, respectively.

Patients who developed a local recurrence had approximately the same response rate (5 of 16 patients; 31.2%) as that observed in patients with distant metastases (6 of 20 patients; 30%).

Patients previously treated with mitoxantrone had no response.

The median overall survival durations for Arms A and B were 11 months (range, 3–29+ months) and 8.5 months (range, 2.5–16 months), respectively; a significant difference in survival > 12 months was noted in Arm A ($P < 0.05$). At 2 years 19% of patients treated with the combination were alive whereas in the VNB alone arm no patient still was alive at 2 years.

The survival curve analysis showed a trend ($P = 0.058$) toward better survival in the cisplatin plus VNB arm (Fig. 1). The median survival for patients achieving CR was 19+ months; the median survival of patients achieving a PR was 12.5 months for the cisplatin plus VNB arm and 9 months for the VNB alone arm. Patients with an ECOG performance status of 0–1 had a median survival of 10.5 months, which was statistically better ($P < 0.05$) than patients with an ECOG performance status of 2 (median survival time, 4.5 months).

Twenty-one patients (58.3%) had pain before chemotherapy; results with regard to pain were constant in responders; analgesic consumption was reduced. Among nonresponders a reduction in pain was achieved in 7 of 14 patients; nevertheless, this improvement was found to be transient.

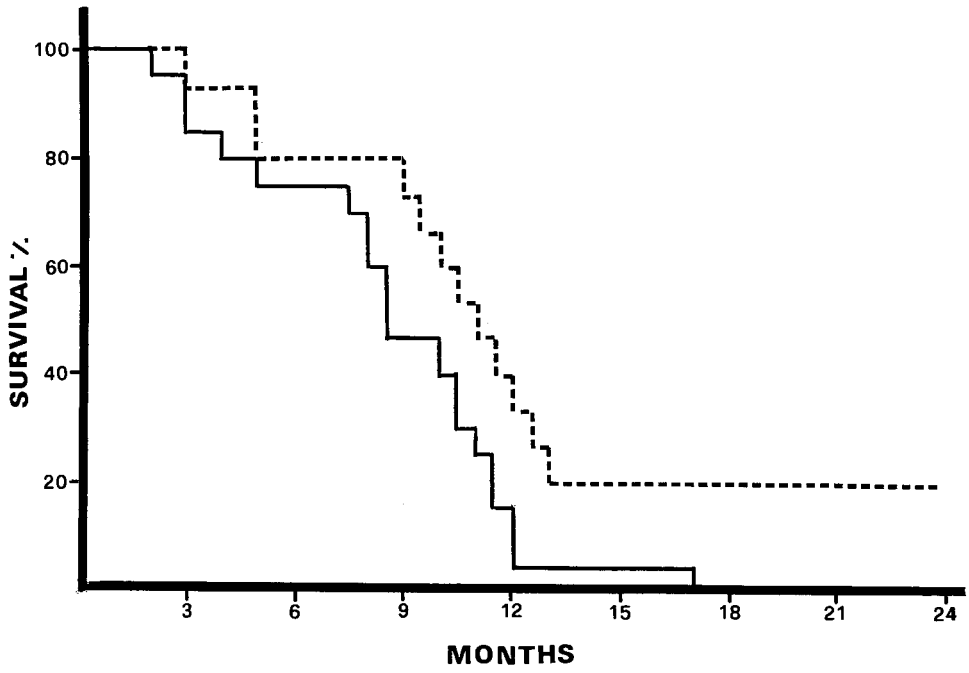

FIGURE 1. Overall survival. Solid line: vinorelbine alone; dashed line: vinorelbine plus cisplatin ($P = 0.058$).

TABLE 3
Toxicity

	Cisplatin + VNB	VNB
Nausea/emesis		
Grade 1	7 (44%)	2 (10%)
Grade 2	8 (50%)	—
Grade 3	1 (6%)	—
Leukopenia		
Grade 1	4 (25%)	5 (25%)
Grade 2	3 (19%)	3 (15%)
Grade 3	2 (12.5%)	2 (10%)
Thrombocytopenia		
Grade 1	2 (12.5%)	2 (10%)
Grade 2	1 (6%)	—
Anemia		
Grade 1	2 (12.5%)	1 (5%)
Grade 2	1 (6%)	—
Peripheral neurotoxicity		
Grade 1	1 (6%)	1 (5%)
Grade 2	1 (6%)	—
Alopecia		
Grade 1	1 (6%)	1 (5%)
Local phlebitis	2 (12.5%)	3 (15%)

VNB: vinorelbine.
Grade 2–3 nausea/emesis: cisplatin + vinorelbine vs. vinorelbine = $P < 0.001$.

Toxicity

No drug-related death and no Grade 4 toxicity were observed in either treatment arm. Leukopenia was the most frequent toxicity in the two arms; it was distributed equally and with a low percentage (12.5% and 10%) of Grade 3 intensity (Table 3).

There was a statistically significant ($P < 0.05$) prevalence of Grade 2–3 nausea/emesis in the combination arm (Arm A). No genitourinary toxicity was observed in either arm. There was a trend toward a higher incidence of anemia, thrombocytopenia, and peripheral neurotoxicity in the cisplatin plus VNB arm, even if these toxicities were never > Grade 2 (Table 3).

Local phlebitis and alopecia occurred at a similar rate in the two arms.

DISCUSSION

With regard to advanced locoregional or metastatic salivary gland carcinomas, to our knowledge only a small series of patients treated uniformly with single agent chemotherapy have been reported to date.[2–4,9,13,14] Three drugs with demonstrable activity in adenocarcinoma-like tumors are cisplatin, 5-FU, and doxorubicin, with CRs ranging from 7–18 months in duration and with locoregional disease more likely to respond than distant metastases.[2–4,9] Chemotherapy regimens combining CYC, doxorubicin, and cisplatin (CAP) have shown significant activity in patients with advanced disease. In published data, the overall response rate to CAP was reported to be 64% (23 of 36 patients) with 28% of patients (10 patients) achieving a CR; the response duration usually is short.[15–18]

The response to CAP is decreased in patients pre-

viously treated with chemotherapy or patients with adenoid cystic tumors. Adenoid cystic carcinoma is the most common salivary gland tumor treated with chemotherapy; distant metastases occur in at least 40–50% of patients.[19,20]

As a single agent, cisplatin is reported to result in CRs in patients with adenoid cystic carcinoma.[9] CRs were observed with the combination of VCR and doxorubicin,[2] VCR + doxorubicin + CYC,[21] doxorubicin + 5-FU + mitomycin-C,[22] VCR + CYC + 5-FU,[23] cisplatin + doxorubicin + 5-FU,[24] and cisplatin + epirubicin + 5-FU.[25]

In the current randomized clinical study all patients had been previously treated heavily and all tumor recurrences were bulky and progressive. Chemotherapy was administered in an outpatient setting with the goal of palliation.

The conclusions of this study can be summarized as follows.

VNB is a drug with moderate activity in these histologies (6 of 34 PRs; 17.6% in the pilot study, and in the VNB arm of the current trial). The activity of VNB is similar to that reported for cisplatin, 5-FU, and anthracycline/mitoxantrone. The drug is very well tolerated. The poor results reported most likely are due to the high percentage of adenoid cystic carcinoma with distant metastases occurring.

The combination of cisplatin plus VNB is more active than VNB alone with a 19% CR rate and some long-term survivors. This scheme also has shown good activity (CR + PR, 44.4%) in adenoid cystic carcinoma, which generally is a chemoinsensitive illness.

The addition of cisplatin to VNB statistically increased moderate emesis even if the other side effects were comparable in the two arms; the toxicity of our combination appears less clinically relevant than that previously observed for CAP e PEF (cisplatin, epirubicin, and 5-FU) schemes.[15–18,25]

Despite the absence of an apparent survival benefit, palliation of pain and local disease frequently was pronounced. With regard to pain, results were constant in responders. Among nonresponders, a transient reduction was observed in 50% of cases despite the absence of objective tumor regression.

The results observed with the combination of cisplatin plus VNB are nearly comparable to those reported in the best series of patients treated with the CAP scheme[15–18] and are better than those reported by our team using monochemotherapy (cisplatin or doxorubicin)[14] and the PEF combination.[25]

To our knowledge, the optimal drug combination and the delivery method remain undefined in these tumors. There is a strong need for new active drugs. Patients with bulky disease, impaired ECOG performance status, or marginal nutritional status might be best treated by supportive care.

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