# Vinorelbine, Cisplatin, and 5-Fluorouracil as Initial Treatment for Previously Untreated, Unresectable Squamous Cell Carcinoma of the Head and Neck

## *Results of a Phase II Multicenter Study*

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**BACKGROUND.** The combination of vinorelbine (VNR), cisplatin (CDDP), and 5-fluorouracil (5-FU) has previously been shown to be active in recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCHNC). This multicenter Phase II study was carried out with the aim of evaluating the effectiveness of this combination in patients with previously untreated, unresectable locally advanced SCHNC.

**METHODS.** Sixty patients with previously untreated, unresectable SCHNC were treated with CDDP 80 mg/m$^2$ on Days 1, 5-FU 600 mg/m$^2$ as a 4-hour infusion on Days 2–5, and VNR 25 mg/m$^2$ iv bolus on Days 2 and 8. There were 15 patients with laryngeal carcinoma, 19 patients with oropharyngeal carcinoma, 15 with carcinoma in the oral cavity, 5 with carcinoma in the hypopharynx, and 4 with carcinoma in the maxillary sinus. Most patients (78%) had Stage IV disease. After achievement of the best possible objective response, patients were subjected to definitive locoregional treatment, i.e., radiotherapy and/or surgery, as appropriate.

**RESULTS.** All patients completed the induction chemotherapy. After a mean of 3.86 cycles per patient, the overall response rate was 88% (95% confidence interval [CI], 82–94%), with a complete response rate of 23% (95% CI, 14–26%). Complete responses were more frequently seen in patients with N0-1 disease than in those with N2–3 disease ($P = 0.037$). No other statistically significant correlation between type of response and extent of disease was noted. Toxicity consisted mainly of myelosuppression and gastrointestinal side effects. After definitive locoregional treatment, 58% of patients were clinically free of disease. These patients included those who had complete response after induction chemotherapy, 19 of 39 patients who had partial response, and 2 with stable disease. Median disease free survival was 16 months, and median overall survival was 23 months.

**CONCLUSIONS.** The combination regimen of CDDP, 5-FU, and VNR was very active in previously untreated SCHNC. It was well tolerated in most cases, and neurotoxicity was not a major side effect. This regimen, which does not require hospitalization, should be compared with standard chemotherapy, such as the combination of CDDP and continuous-infusion 5-FU. ***Cancer* 1997;79:1394–400.**


**KEYWORDS: vinorelbine, cisplatin, 5-fluorouracil, head and neck carcinoma, chemotherapy.**

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Although classically confined to the palliation of recurrent squamous cell head and neck carcinoma (SCHNC), systemic chemotherapy has recently been employed as a part of a multidisciplinary therapeutic strategy for treating SCHNC before definitive locoregional treatment, i.e., surgery and/or radiotherapy.[1,2] Antineoplastic drugs shown to be effective as single agents in the treatment of SCHNC include, among others, cisplatin (CDDP), carboplatin, 5-fluorouracil (5-FU), methotrexate, bleomycin, and vinca alkaloids.[1] Most chemotherapeutic regimens currently employed in the management of advanced SCHNC include moderate to high dose CDDP, usually in combination with other antineoplastic drugs.[1–3] Among these regimens, the combination of CDDP and 5-FU, without[4,5] or with[6–8] folinic acid, is considered by many oncologists to be the optimal treatment for advanced SCHNC. This combination is also based on experimental investigations that have demonstrated a marked synergism between 5-FU and CDDP.[4,5,9]

In the last decade, initial treatment with aggressive chemotherapy has frequently been associated with an overall response rate often exceeding 75%,[1–8] and the achievement of a complete tumor regression has been associated with a better prognosis.[1,2] However, despite promising objective tumor regressions and successful organ preservation after locoregional treatment,[10] the prognosis of patients with advanced SCHNC is still dismal.[11] For this reason, finding new and active antineoplastic drugs and chemotherapeutic schedules is still a major goal for most oncologists.

The vinca alkaloid vinorelbine (VNR, 5′-nor-anydrovinblastine) is a new semisynthetic derivative of vinblastine.[12] It has been shown to be active against squamous cell lung carcinoma,[13] bronchial adenocarcinoma,[13] breast carcinoma,[14] and SCHNC.[15] VNR has been reported to damage mitotic microtubules at concentrations shown to be ineffective on other classes of microtubules, and this may account for the low neurotoxicity reported in initial clinical studies.[13–15,17] On the other hand, its lower neurotoxicity is balanced by myelosuppression, which may represent the dose-limiting toxicity of VNR.[12,13]

On the basis of the significant activity shown by VNR against SCHNC, as well as that of other vinca alkaloids alone[15–20] or in combination with CDDP,[21,22] we tested the combination of VNR and CDDP plus 5-FU in a multicenter study involving a series of 80 patients with recurrent and/or metastatic SCHNC.[23] The 55% overall response rate, with a 13% complete response rate achieved in the latter study, prompted us to test the combination of VNR, CDDP, and 5-FU as initial treatment in a series of patients with previously untreated SCHNC. In this article we report the clinical efficacy and toxicity of such a regimen in a series of 60 patients with advanced, previously untreated, unresectable SCHNC.

## MATERIALS AND METHODS

After giving written informed consent, 60 consecutive elegible patients with previously untreated SCHNC were included in the study. The following elegibility criteria had to fulfilled prior to entry: histologic diagnosis of SCHNC; neoplasm not susceptible to radical surgery; age $\leq$ 75 years; performance status $\leq$ 2, according to Eastern Cooperative Oncology Group criteria; measurable disease, according to World Health Organization (WHO) criteria[24]; adequate liver function (serum bilirubin $\leq$ 1.2 mg%, serum transaminases $<$ 2 times normal value) and renal tests (serum creatinine $\leq$ 1.2 mg%, blood urea nitrogen $\leq$ 50 mg%, creatinine clearance $>$ 60 mL/min); adequate bone marrow function (white blood cell count $\leq$ 4000/mm$^3$, platelets $\leq$ 120,000/mm$^3$, hemoglobin $\geq$ 12 gr%); no history of severe and uncontrolled liver, renal, cardiovascular, metabolic, or neurologic diseases; no sign of brain metastases; no second malignant neoplasm except adequately treated cutaneous basalioma; and geographic accessibility, to guarantee adequate follow-up. Before receiving chemotherapy, patients were extensively staged according to medical history, physical examination, otorhinolaryngology (ORL) examination, chest X-ray, skull X-ray, abdominal sonogram, 99Tc bone scan, computed tomography (CT) scan of the involved areas, electrocardiography, and routine chemistry and hematologic tests. CT scan, general, and ORL examinations were employed for definition of objective response. The other staging tools were employed for definition of objective response as needed. The treatment schedule was as follows: CDDP 80 mg/m$^2$ diluted in 500 mL of normal saline over 90-minute infusion on Day 1, preceded by a hydration protocol with 2000 mL of normal saline and 5% glucose with KCl, and followed by 250 mL of 18% mannitole plus 1000 mL of 5% glucose as posthydration; 5-FU 600 mg/m$^2$ diluted in 500 mL of normal saline over 4-hour infusion on Days 2–5; and VNR 25 mg/m$^2$ intravenous (i.v.) push on Days 2 and 8. VNR dosage was chosen on the basis of a previous Phase I–II study, in which it was shown that 25 mg/m$^2$ week was the optimal VNR dosage that could be reliably given to patients with SCHNC.[9] This regimen was recycled every 21–28 days, if possible. If myelosuppression occurred, therapy was delayed by 1 week or until recovery; but granulocyte-colony stimulating factor (G-CSF) 5 mg/kg/day, given subcutaneously, was employed as needed. A complete blood cell count was obtained before Day 1 and 8 of each cycle to assess bone marrow toxicity. Granisetron

3 mg i.v. or ondansetron 24 mg i.v. was employed to help prevent vomiting on the day of CDDP administration. In the subsequent days of chemotherapy, granisetron or ondansetron were given orally.[25]

Objective tumor response and chemotherapy-related toxicity were evaluated according to WHO. criteria.[24] Briefly, a complete response (CR) was defined as the complete disappearance of all signs and symptoms of disease for at least 4 weeks; a partial response (PR) was defined as a ≥50% decrease 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 tumors; no change (NC) was defined as a <25% increase or <50% decrease in the size of tumors; and progressive disease (PD) was defined as a ≥25% increase in the dimensions of tumors or the appearance of new metastases. Responses were reported as relative rates with 95% confidence intervals (CI).

Patients were first restaged after three cycles to assess objective response. Patients with CR received definitive locoregional therapy as soon as they recovered from toxicity. The same therapeutic strategy applied to patients with PD. Patients with PR or NC received two more cycles of chemotherapy, up to five cycles; then patients with ''stable'' PR or those who showed an amelioration of response (PR converted to CR or NC converted to PR) received definitive locoregional treatment. Patients still in NC after five cycles of chemotherapy received two more cycles, up to a maximum of seven cycles, then shifted to locoregional therapy.

In other words, enrolled patients were given definitive locoregional therapy when the ''best response'' to chemotherapy was obtained. Thus, patients showing clinical CR received definitive locoregional therapy. Patients with PR after the first three cycles were given two more cycles of chemotherapy in the hope that quality of response would improve, then chemotherapy was withdrawn and locoregional treatment was given. Patients who showed PD at first evaluation did not receive further chemotherapy and were offered locoregional treatment. Patients who had NC after the first three cycles received two more cycles; in cases of PR, patients were given locoregional therapy, whereas in cases of stabilization, they had more chemotherapy up to a maximum of seven courses and were then subjected to radiotherapy.

The occurence of ≥Grade 2 cardiotoxicity, an adverse neurologic event, or Grade 4 toxicity of any kind (with the exception of alopecia and leukopenia) led to patients' withdrawal from chemotherapeutic treatment. Protocol violation also led to patients' withdrawal from the study. Analysis of disease free and overall survival was carried out according to the Kaplan–Meyer product limit test. These data were calculated from the first day of chemotherapy. Comparison between rates was carried out with Fisher's exact test. Comparison of survival curves was performed with the log rank test.

**TABLE 1**
**Patient Characteristics**

| Characteristic | No. of patients (%) | | | | |
|---|---|---|---|---|---|
| No. of enrolled patients | 60 (100%) | | | | |
| Mean age (yrs) | 58.9 | | | | |
| Sex | | | | | |
| Male | 54 (90%) | | | | |
| Female | 06 (10%) | | | | |
| ECOG performance status | | | | | |
| 0 | 23 (38%) | | | | |
| 1 | 26 (43%) | | | | |
| 2 | 11 (18%) | | | | |
| Histology | | | | | |
| Squamous cell carcinoma | 60 (100%) | | | | |
| Well differentiated | 24 (40%) | | | | |
| Moderately differentiated | 20 (33%) | | | | |
| Poorly differentiated | 16 (27%) | | | | |
| Site of disease | | | | | |
| Oral cavity | 15 | | | | |
| Oropharynx | 19 | | | | |
| Hypopharynx | 05 | | | | |
| Larynx | 15 | | | | |
| Maxillary sinus | 04 | | | | |
| Extent of disease | | | | | |
| Stage II | 04 (07%) | | | | |
| Stage III | 09 (15%) | | | | |
| Stage IV | 47 (78%) | | | | |
| | N0 | N1 | N2 | N3 | Total (%) |
| T and N classification | | | | | |
| T1 | 0 | 0 | 1 | 1 | 02 (04%) |
| T2 | 4 | 0 | 0 | 1 | 05 (08%) |
| T3 | 5 | 4 | 4 | 0 | 13 (22%) |
| T4 | 9 | 10 | 18 | 3 | 40 (67%) |
| Total | 18 | 14 | 23 | 5 | 60 (100%) |
| (%) | (30%) | (23%) | (38%) | (08%) | |

ECOG: Eastern Cooperative Oncology Group.

## RESULTS

### Patient Population

The main clinical and demographic characteristics of enrolled patients are shown in Table 1. There were 60 enrolled patients, with a mean age of 58.9 years (range, 44–75) and a mean ECOG performance status of 0.76 (range, 0–1). There were 54 males (90%) and 6 females (10%). Sites of primary neoplasm included the following: oral cavity 15 patients; larynx, 15; oropharynx, 19; hypopharynx, 5; and maxillary sinus, 4. Histologically, 24 patients (40%) had well-differentiated SCHNC, 20

(33%) moderately differentiated SCHNC, and 16 (27%) poorly differentiated SCHNC. Four patients had Stage II SCHNC, 9 patients had Stage III disease, and 47 (78%) had Stage IV disease. Staging by tumor size and lymph node status is also shown in Table 1. Forty-seven percent of patients had N2 or N3 disease, 22% of patients had T3 tumors and 67% had T4 head and neck carcinoma.

### Induction Chemotherapy

All enrolled patients were evaluable for response after induction chemotherapy. The overall response rate (ORR) of the whole series, independent of the number of cycles received, was 88% (95% CI, 82–94%), with 14 patients (23%; 95% CI, 14–26%) showing a clinical CR and 39 patients (65%; 95% CI, 42–58%) a PR. Six patients (10%) had stabilization of disease (SD), and only 1 patient (2%) had PD. Overall, patients received a mean of 4.9 cycles each. Type and rate of objective responses were analyzed according to the number of cycles received. After their first 3 cycles of chemotherapy, 10 patients had a clinical CR and were given definitive locoregional therapy as needed, 28 patients a PR of ≥50%, and 21 had NC. One patient had PD and was given locoregional therapy. The 28 patients with PR after the first 3 cycles received 2 more cycles of chemotherapy; after a total of 5 cycles, 4 of these patients achieved a clinical CR and 24 showed a stable PR. All of these patients were subjected to definitive locoregional therapy. The 21 patients with NC after the first 3 cycles received 2 more cycles of chemotherapy, after which 13 patients had a PR of ≥50% and received locoregional therapy. Eight patients with NC received further therapy up to 7 cycles; two had a PR of ≥50%, and six had SD. All received locoregional therapy. Thus, overall, clinical CR was achieved after 3 cycles of chemotherapy in 10 patients and after 5 cycles in 4 patients. Similarly, a PR of ≥50% was obtained after 3 cycles of chemotherapy in 24 patients, after 5 cycles in 13 patients and after 7 cycles in 2 patients.

CRs were more frequently seen in patients with N0–1 disease (11 CRs among 32 patients) than in patients with N2–3 disease. This difference was statistically significant ($P = 0.037$). No other statistically significant correlation was seen between CR rate and clinical parameters such as site of primary disease, T classification, age, or gender.

### Toxicity from Chemotherapy

The types and degrees of adverse reactions are shown in Table 2. Over a total of 294 cycles administered (4.9 cycles/patient), the main toxicities were represented by myelosuppression and gastrointestinal side-effects.

**TABLE 2**
**Numbers and Percentages of Patients with Treatment-Related Toxicity**

| | WHO score | | | |
|---|---|---|---|---|
| **Type of toxicity** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Gastrointestinal | | | | |
| Nausea/vomiting | 22 (37%) | 09 (15%) | 08 (14%) | 00 |
| Stomatitis | 16 (27%) | 08 (14%) | 07 (12%) | 00 |
| Diarrhea | 07 (12%) | 08 (14%) | 02 (03%) | 00 |
| Hematologic | | | | |
| Leukopenia | 21 (35%) | 12 (20%) | 07 (12%) | 03 (05%) |
| PTL | 12 (20%) | 07 (12%) | 04 (07%) | 00 |
| Anemia | 07 (12%) | 05 (08%) | 00 | 00 |
| Neurologic | 07 (12%) | 07 (12%) | 00 | 00 |
| Alopecia | 05 (08%) | 04 (07%) | 00 | 00 |
| Phlebitis | 06 (10%) | 00 | 00 | 00 |
| Renal | | | | |
| BUN | 04 (07%) | 00 | 00 | 00 |
| Creatinine | 03 (05%) | 00 | 00 | 00 |

WHO: World Health Organization; BUN: blood urea nitrogen.

Twenty-one patients (35%) experienced Grade 1 leukopenia, and 12 patients (20%) Grade 2 leukopenia. Grade 3 and Grade 4 leukopenia were observed in 7 (12%) and 3 (5%) patients, respectively. Twelve patients (20%) had Grade 1 thrombocytopenia. Grade 2 and Grade 3 thrombocytopenia were observed in 7 (12%) and 4 patients (7%), respectively. Grade 1–2 anemia in 11 cases (18%). Short term administration of G-CSF was given in 35 cycles (18% of cycles) to allow for administration of the second full dose/cycle of VNR.

Grade 1–2 nausea/vomiting was observed in 31 cases (52%), but 8 cases (14%) of Grade 3 vomiting were seen. Phlebitis at the injection vein was recorded in 6 cases (10%). Grade 1–2 oral mucositis was recorded in 24 cases (40%). Grade 3 stomatitis was observed in 12% of patients. Despite the use of a combination of potentially neurotoxic drugs, neurotoxicity was not a major side-effect. Seven patients (12%) had Grade 1 neurotoxicity and 7 more patients had Grade 2 neurotoxicity, but no case of severe neuromotor toxicity occurred.

### Locoregional Treatments

All patients completed induction chemotherapy and received locoregional therapy with radiotherapy and/or surgery when indicated. Overall, 34 patients (57%) were subjected to radiotherapy immediately after induction chemotherapy. Radiotherapy was delivered at a dose of 1.8 gray (Gy)/day 5 times/week with bilaterally opposed fields, which included tumor primary site

and upper neck. Spinal cord shielding was applied at 45–46 Gy and a tumor boost was given up to 65 Gy. No patients with cancer in the maxillary sinus or the hypopharynx underwent surgery. On the other hand, 26 patients (43%), including patients with laryngeal, oropharyngeal, and oral carcinomas, underwent surgery and subsequent radiotherapy. Surgery included resection of primary tumor plus lymph node dissection of the neck in 24 cases. In 2 patients with oropharyngeal carcinoma, the only surgery performed was residual lymph node dissection followed by radiotherapy.

All patients with laryngeal carcinoma responded to induction chemotherapy. Among these patients, 8 patients underwent radical surgery. Two patients had pathologically confirmed CR, whereas 6 had microscopic residual disease in the surgical specimen. Two patients with laryngeal carcinoma who achieved a major tumor regression refused surgery, even a conservative procedure, and received only radiotherapy. The remaining 5 patients did not undergo surgery because their physicians decided against it. Voice preservation was thus achieved in 7 of 15 patients with laryngeal carcinoma. No chemotherapy-related complications were noted after surgery.

Overall, 35 of 60 patients (58%) were rendered clinically free of disease after completion of locoregional treatments. This group included the 14 patients with clinical CR after induction chemotherapy, 19 of 39 patients (49%) who had PR, and 2 patients who had SD.

### Survival

Median disease free survival was 16 months. Most patients showed recurrent disease at locoregional sites, but two patients developed lung metastases. Median overall survival was 23 months. Most patients were given second-line chemotherapy with methotrexate and bleomycin on a weekly schedule. A major response (CR) to chemotherapy was correlated to a significantly longer disease free ($P < 0.01$) and overall survival ($P < 0.05$) when compared with the survival of patients who had PR, NC, or PD after induction chemotherapy (Figs. 1 and 2). No statistically significant relationship was observed between response and N status (N1–2 vs. N3–4).

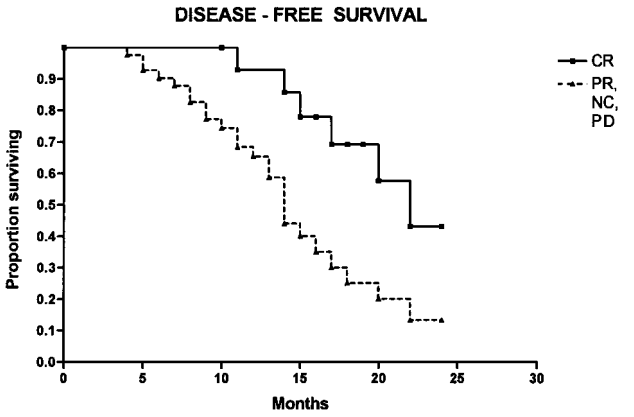


**FIGURE 1.** Disease free survival is shown according to type of response to systemic chemotherapy. CR: complete response; PR: partial response; NC: no change; PD: progressive disease.

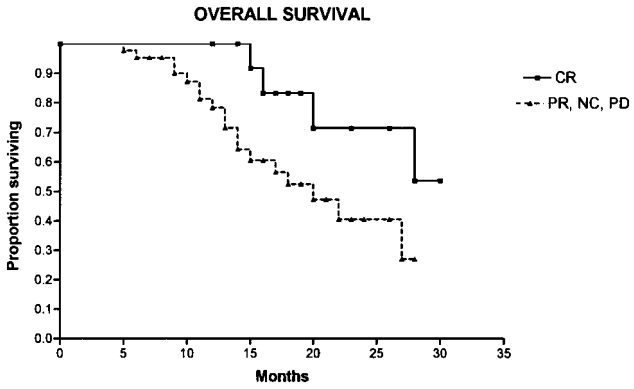


**FIGURE 2.** Overall survival is shown according to type of response to systemic chemotherapy. CR: complete response; PR: partial response; NC: no change; PD: progressive disease.

## DISCUSSION

On the basis of the promising activity shown by VNR in SCHNC when employed either as a single agent or in association with other drugs,[6,7,9] we tested the combination of CDDP 80 mg/m$^2$ on Day 1 and 5-FU on Days 2–5 plus VNR 25 mg/m$^2$ on Days 1 and 8 in a multicenter study involving a series of 60 patients with advanced, unresectable SCHNC. This three-drug combination regimen has been previously tested in a multicenter Phase II investigation, carried out by several of us (the authors of this article), involving 80 patients with recurrent and/or metastatic SCHNC. In this study, an overall response rate of 55% with a 13% CR rate was achieved on an intent-to-treat basis.[23] In the current study, we achieved an 88% overall response rate (95% CI, 82–94%), with a 23% CR rate (95% Cl, 18–28%) after induction chemotherapy. Most patients (63%) achieved a major response after 3 cycles of chemotherapy. Twenty-two patients obtained a major response after 5 cycles, and only 3% of patients achieved such a response after 7 cycles. The overall response rate obtained in the current study is roughly comparable to that reported in medical literature with other polychemotherapeutic regimens, such as the

combination of CDDP and prolonged i.v. infusion 5-FU.[1,4,24] However, the CR rate (23%) does not seem better than CR rates obtained with other aggressive regimens, such as PFL, which has been reported to induce a very high complete response rate.[7] Moreover, these data are very similar to those achieved by some of us in a previous Phase II study with the combination of CDDP and 5-FU plus levofolinic acid, for which a 30% CR rate was reported.[8] This comparative issue can be addressed only in a prospective ''head-to-head'' trial, and no firm conclusions can be drawn from retrospective Phase II study analysis. However, the multicentric nature of this study should be stressed in evaluating clinical results. It also should be noted that the CDDP, 5-FU, and VNR regimen can be easily given on an outpatient basis. The ease of administration may give this regimen an advantage over regimens that require hospitalization.

After induction chemotherapy, all patients received definitive locoregional therapy. Overall, 58% of enrolled patients were rendered free of disease after completion of both chemotherapy and radiotherapy with or without surgery. The use of induction chemotherapy did not seem to influence negatively the feasibility of locoregional treatments and the outcome of patients. On the other hand, patients who achieved a clinical CR after induction chemotherapy had a statistically significant longer disease free and overall survival. The 2-year overall survival of this group of patients was quite significant (even though, at least in our opinion, it was far from satisfying).

The CDDP, 5-FU, and VNR regimen was quite well tolerated and easily accepted by most patients. Myelosuppression was the most frequent toxicity, and severe stomatitis, which may very distressing for patients with head and neck carcinoma, was recorded in a minority of cases (12%). Mild chemical phlebitis at the injection vein was recorded in 10% of cases. Although this regimen included potentially neurotoxic drugs, neurologic adverse events were quite mild and rather infrequent. However, a careful evaluation of benefits versus chemotherapy-related side-effects should be made for every patient before induction chemotherapy is given.

In conclusion, the combination of CDDP, 5-FU, and VNR is certainly active, at least in terms of clinically objective tumor regression, in previously untreated patients with unresectable SCHNC. These data confirm our previous experience in treating recurrent and/or metastatic SCHNC with the same combination.[23] This polychemotherapeutic regimen is well tolerated by most patients and may be safely given on an outpatient basis with less psychological and physical distress as compared with other multiday regimens that require hospitalization. Evaluating the possible superiority of this regimen over standard CDDP and 5-FU regimen was beyond the parameters of this study, and this issue could be settled only in a carefully designed prospective trial.

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