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Phase II trial of carboplatin or iproplatin in cervical cancer

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Summary. From July 1984 to November 1987, 89 patients with recurrent measurable squamous-cell cancer of the uterine cervix were randomized in a single institution to receive treatment with either carboplatin (CBDCA) or iproplatin (CHIP). Objective response rates were similar: 2 complete regressions (CRs) and 10 partial regressions (PRs) were recorded both in the 46 evaluable patients treated with CBDCA (response rate, 26.1%; 95% confidence interval, 15–41%) and in the 40 evaluable patients treated with CHIP (response rate, 30%; 95% confidence interval, 17–47%). The median duration of response was 5.5 months for CBDCA and 6 months for CHIP; the median survival was 7.5 and 7.6 months, respectively. Both drugs were given in an outpatient setting and myelosuppression (thrombocytopenia) was the predominant toxicity. Analysis of all toxic events yielded additional interesting observations: the occurrence of moderate to severe platelet nadirs beyond cycle 1 was confined to CHIP, a higher incidence of gastrointestinal toxicity during treatment with CHIP, and five moderate to severe complaints of asthenia (recorded as neurologic events) during CHIP therapy versus only one during treatment with CBDCA. Because of its antitumor activity and its toxicologic advantage, a future role for CBDCA in the treatment of cervical cancer appears likely.

Introduction

In spite of nearly two decades of trials reporting "active" drug combinations against metastatic cervical neoplasia (usually including 100% squamous histologies), there is considerable uncertainty as to their value in achieving durable remissions and long-term benefit. Accordingly, we have opted to treat patients with metastatic or recurrent squamous carcinoma of the uterine cervix in studies using promising single agents. In previous phase II trials, we established the activity of dibromodulcitol [8] and the equivalent efficacy and tolerance of two dose schedules for cisplatin (100 mg/m^2 × 1 day every 4 weeks or 20 mg/m^2 × 5 days every 4 weeks) [9]. One patient achieved a durable complete remission that lasted for >1 year; however, for the majority of responders and for patients exhibiting progressive disease, there was no apparent impact on the median survival, which was 8.5 months for the overall population. Nevertheless, because platinum drugs may play a role in combined-modality therapy with radiation [14] or hyperthermia [6] and because several less toxic analogs were available for clinical testing, we initiated a phase II study of the analogs carboplatin and iproplatin in July 1984. Both carboplatin (CBDCA) and iproplatin (CHIP) were advanced into clinical trials because they exhibited preclinical spectra of activity similar to those shown by cisplatin but produced less nephrotoxicity; in addition, superior gastrointestinal tolerance of CBDCA had been noted in the ferret [16]. Phase I studies generally confirmed the preclinical expectations. As the study was closed to patient entry in November 1987, this report represents the final analysis. Aspects of these trials have been presented either at a symposium [13] or as an abstract [10].

Materials and methods

The present study was initiated as part of the collaborative Cancer Treatment Research Program activities sponsored by the National Cancer Institute (NCI) and including the participation of Latin American and United States cancer centers working under the aegis of the Pan-American Health Organization (PAHO). Parallel randomized phase II studies of carboplatin versus iproplatin were planned and activated in three institutions: Hospital de Oncologia, Instituto Mexicano de Seguro Social (IMSS) in Mexico, Angel Roffo Institute in Buenos Aires, Argentina, and New York University. On the termination of support, accrual was suspended in the latter two institutions and an insufficient number of patients (10 and 5, respectively) were entered for independent analysis. Accrual was continued at the Hospital de Oncologia, with drug being supplied by the Cancer Therapy Evaluation Program, NCI, and with

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Table 1. Patients' characteristics

Prognostic factor	Treatment	
	CHIP	CBDCA
Based on number treated	41	47
Age, median	44 years	48 years
Age, range	30–59 years	26–67 years
ECOG performance status:		
0	7 (17.1%)	9 (19.1%)
1	23 (56.1%)	24 (51.1%)
2	11 (26.8%)	14 (29.8%)
Prior chemotherapy:		
None	39 (95.1%)	42 (89.4%)
Single (S)	0 (0)	0 (0)
Combination (C)	2 (4.9%)	4 (8.5%)
Both S/C	0 (0)	1 (2.1%)
Prior radiotherapy	41 (100%)	47 (100%)
Prior surgery	4 (9.8%)	2 (4.3%)
Prior stage:		
IB	1 (2.4%)	3 (6.4%)
IIA	2 (4.9%)	4 (8.5%)
IIB	10 (24.4%)	12(25.5%)
IIIA	2 (4.9%)	5 (10.6%)
IIIB	9 (22%)	11 (23.4%)
IVA	3 (7.3%)	3 (6.4%)
IVA (bladder)	4 (9.8%)	1 (2.1%)
IVB	1 (2.4%)	0 (0)
Unknown	9 (22%)	8 (17%)
Sites of disease:		
Pelvis	39 (95.1%)	37 (78.7%)
Pelvis only	30 (73.2%)	23 (48.9%)
Lung	1 (2.4%)	7 (14.9%)
Bone	2 (4.9%	2 (4.3%)
Inguinal nodes	6 (14.6%)	8 (17%)
Para-aortic nodes	1 (2.4%)	3 (6.4%)
Distant nodes	4 (9.8%)	9 (19.1%)
Other	3 (7.3%)	4 (8.5%)
Fibrosis only	1 (2.4%)	1 (2.1%)

statistical support being provided by the University of Southern California (USC) Cancer Center. Study entry, tumor measurements, and treatment flow sheets were prospectively collected at the institution, which used Eastern Cooperative Oncology Group (ECOG)-adapted forms that had been translated into Spanish and ECOG toxicity criteria [15]. Selection of patients, part of the follow-up, and review of all forms were the responsibility of the first author (V. L.-P.). Special attention was paid to patient assessability and to the performance status (≤ 2 ECOG scale) enabling outpatient treatment.

Bidimensional measurable disease was required, and for pelvic disease the indicator lesion had to have shown progression (growth of 25% in cross-sectional area or the new appearance of disease) as recorded by periodic joint examination by medical and gynecologic oncologists in a combined clinic. Prior chemotherapy that did not include cisplatin was allowed, but 6 weeks had to have elapsed since prior treatment of any kind; chemotherapy was rarely employed in the institution except as part of the aforementioned studies. Normal serum creatinine levels (<1.5 mg/100 ml) and acceptable hematologic parameters (WBC, >3,000/mm^3; platelets, >100,000/mm^3) were required. Pretreatment liver-function values should not have exceeded twice the normal range. A 24-h creatinine clearance was obtained only after the initial 30 patients had been entered. Most tumor assessment was carried out by physical examination supplemented with ultrasound; occasionally, computerized tomographic (CT) scanning was used, as was a chest X-ray when pertinent. Blood counts were done weekly and blood chemistries, every 4 weeks.

One dose escalation amounting to 25% of the previous level % was built in if hematologic toxicity of grade 1 or less was observed. Dose de-escalations based on grade 3 or 4 toxicities were prescribed (25% or 50% de-escalation, respectively). The initial dose of CHIP was 300 mg/m^2 and that of carboplatin was 400 mg/m^2; both drugs were given by i. v. infusion over 15 min as recommended from phase I trials [3, 5, 12] after being mixed with small volumes of 5% dextrose and water. No hydration was needed, but antiemetics (prochlorperazine and chlorpromazine) were frequently used. All study forms and flow sheets were forwarded to USC for review and analysis.

Methods of analysis. Outcome measures of interest were the tumor response to therapy, duration of response, survival, and the qualitative and quantitative toxicity experiences. A patient was classified as being a responder if she experienced either a complete response (CR) or a partial response (PR). A CR was defined as the complete disappearance of all clinical evidence of tumor and symptoms for two consecutive measurements made at least 4 weeks apart. A PR was defined as a decrease of at least 50% in the sum of products of the perpendicular diameters of all index lesions for at least two consecutive measurements (separated by at least 4 weeks), no increase in any existing lesions, and no appearance of new lesions. For pelvic disease, a response had to be verified by two baseline examiners that always included the gynecologic oncologist (F. T.).

Response duration was calculated as the number of months from the date of randomization until the first evidence of tumor growth or the development of new lesions. Survival was computed as the number of months from randomization until death or until the last follow-up examination. All deaths were considered to be failures, regardless of the cause. Toxicity was evaluated prior to each administration of drug and, when indicated, according to ECOG criteria. Events were classified as being protocol (drug)-related or non-protocol (probably disease)-related. The response rate was calculated as the ratio of the number of patients achieving a CR or PR divided by the number of patients evaluable for response. The Kaplan-Meier product-limit method [7] was used to construct survival and response curves. The median survival and the median response duration were based on the Kaplan-Meier curves.

For investigations of the similarities and differences in outcome obtained for CBDCA vs CHIP, P values were computed based on Pearson's chi-square test or Fisher's exact test for 2×2 tables [17] (for the response rate) and on the log-rank test [7] (for survival and response duration); all P-values were two-sided.

Results

Patients' characteristics

In all 48 patients were randomized to CBDCA and 41, to CHIP; 1 subject randomized to CBDCA refused all therapy prior to the first infusion and was excluded from all analyses. Characteristics of the remaining 47 and 41 treated patients, respectively, are shown in Table 1. These were relatively well balanced, with some predominance of pelvic disease occurring only in the CHIP arm and excess extrapelvic disease, particularly of the lung, occurring in the CBDCA arm. Bone was an uncommon area of involvement, since osseous lesions are not usually assessable.

Exclusions and number of courses

Of the CHIP-treated patients, one subject who received two courses was inevaluable for response because her disease was deemed to be fibrosis on review; i.e. no tumor was seen. In the CBDCA arm, one additional patient who

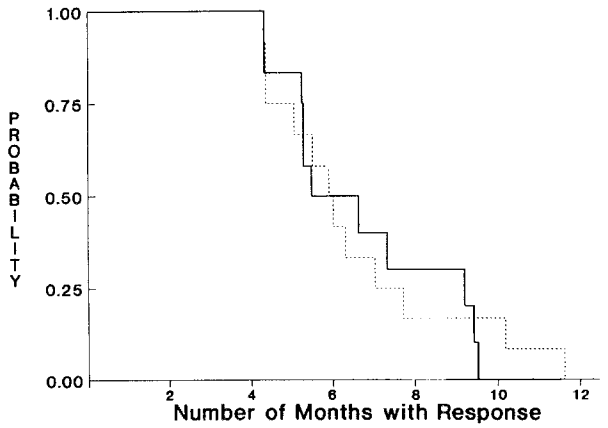

Fig. 1. Response duration in patients achieving a complete or partial response. – – – –,CHIP (median, 6 months; n = 12); ———, CBDCA (median, 5.5 months; n = 12)

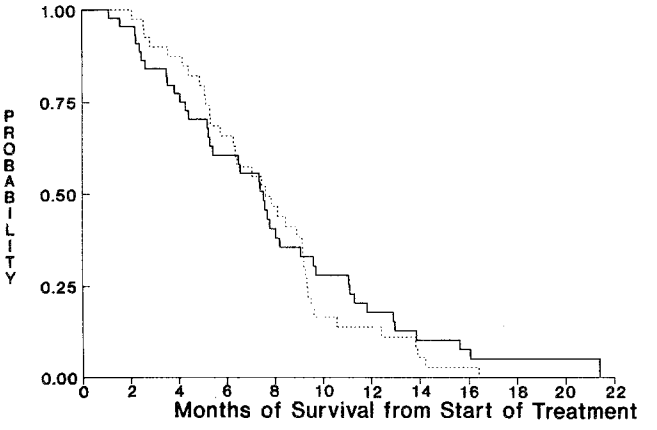

Fig. 2. Survival of patients from the start of treatment. – – – –, CHIP (median, 7.6 months; n = 40); ———,CBDCA (median, 7.5 months; n = 46). P = 0.965 (log-rank test)

Table 2. Treatment courses and doses

Treatment factor	Treatment	
	CHIP (n = 41)	CBDCA (n = 47)
Total dose, median	1,320 mg/m^2	1,800 mg/m^2
Total dose, range	390–4,610	550–6,800 mg/m^2
Courses received (n):		
1	4 (9.8%)	8 (17%)
2	12 (29.3%)	13 (27.7%)
3	9 (22%)	7 (14.9%)
4	4 (9.8%)	3 (6.4%)
5	5 (12.2%)	6 (12.8%)
6	2 (4.9%)	3 (6.4%)
7	2 (4.9%)	3 (6.4%)
8	2 (4.9%)	2 (4.3%)
9	1 (2.4%)	0 (0)
10	0 (0)	2 (4.3%)

received one course was not evaluable for response for the same reason. Both of these patients were excluded from the survival and response analyses but were included in the toxicity assessment. Observations for toxicity were made after 1 course in 41 patients receiving CHIP and in 47 subjects receiving CBDCA. A 2nd course was given to 37 patients on CHIP and 39 subjects on CBDCA. For both drugs, the median number of cycles given was 3 and the maximal number of cycles were 9 and 10, respectively. Doses for 13 (31.7%) of the 41 assessable CHIP patients were escalated, whereas in 3 cases they were decreased (7.3%). For CBDCA, there was no de-escalation, whereas doses were escalated for 14 (29.8%) of the 47 evaluable patients. The treatment courses and dose levels given are shown in Table 2.

Response characteristics and survival

Administration of CHIP resulted in 2 CRs and 10 PRs among 40 evaluable responses, yielding a total of 12 objective responses (response rate, 30%; 95% confidence interval, 17%–47%). Following CBDCA administration, there were again 2 CRs and 10 PRs among 46 evaluable responses, yielding a response rate of 26.1% (95% confidence interval, 15%–41%). Disease confined to the pelvis responded in 37% (11 of 30) of patients on CHIP, whereas an objective response of extrapelvic disease occurred in 10% (1 of 10). The reverse was seen with CBDCA: disease confined to the pelvis responded in 13% (3 of 23) of cases and extrapelvic disease responded in 39% (9 of 23). These patterns of response were not significantly different (P = 0.066 vs P = 0.123; Fisher's exact test). CRs received a median of 7.5 courses (mean, 7), whereas PRs received a median of 6 cycles (mean, 6.4). Four patients with stable disease received a median of 5.5 courses, whereas the 58 patients whose disease progressed during administration of either drug received a median of 2 cycles. The duration of response obtained was 6 months for CHIP and 5.5 months for CBDCA (Fig. 1); relapses occurred during therapy in sites of prior disease. The median survival was 7.6 and 7.5 months, respectively (Fig. 2). No patient was subsequently crossed over to other treatments including cisplatin.

Toxicity

As expected, both platinum analogs were myelosuppressive, with maximal platelet toxicity at 3 weeks into the cycle being most characteristic. In one patient on CBDCA, hematologic toxicity contributed to death from renal failure after gentamycin had also been given. One additional subject in each arm developed grade 4 hematologic toxicities after the first course of therapy; both of these patients were probably predisposed to hematologic toxicities due to their borderline renal function at study entry. In Table 3 toxicities are further categorized as to whether they were drug (protocol)-related or probably disease (non-protocol)-related.

Of the toxicities that were not attributed to treatment, 10 of the 41 (24%) patients on CHIP who were evaluable for toxicity developed moderate or worse toxicity (ECOG grade 2 of more) in any category, whereas 14 of the 47

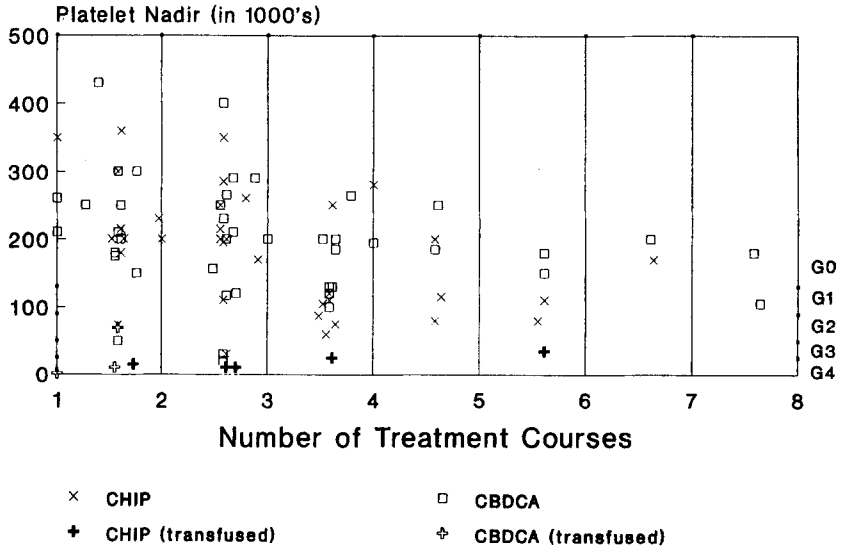

Fig. 3. Grading of platelet nadir in relation to treatment course. After course 2, patients treated with CHIP exhibited more severe toxicity

(30%) subjects on CBDCA had a similar experience. These data do not suggest a trend for greater non-protocol-related toxicity in either treatment arm ($P = 0.636$). Five patients in each arm experienced renal complications that were disease (non-protocol)-related; these ten subjects also manifested more hematologic toxicities as well as edema.

The incidence of leukopenia over all courses, subdivided into grade 0–1 vs 2 or more, was similar following the administration of CHIP or CBDCA, whereas that of thrombocytopenia of grade 2 or more was significantly higher and more severe during treatment with CHIP vs CBDCA (13 vs 6; $P = 0.039$). Both drugs caused moderate to severe anemia in from 22% to 26% of patients. Six subjects on CHIP and four on CBDCA experienced treatment-related bleeding. Although the CHIP dose was de-escalated more often, it appeared to produce lower platelet nadirs after the first two courses (Fig. 3). This could have been attributable to either cumulative marrow toxicity or a change in clearance. On the other hand, during CBDCA administration, platelets were lowest after cycle 1 and nadirs were less severe in subsequent courses.

Nonhematologic toxicity yielded interesting, divergent findings among CHIP- vs CBDCA-treated patients (Table 3). Vomiting occurred in 93% of subjects treated with CHIP, reaching grade 2 or 3 in 46.3% or 29.3% of cases, respectively. For CBDCA, the respective findings were 81%, 38.3%, and 4.3%. Diarrhea occurred in 36.6% of CHIP-treated patients and in 25.5% of CBDCA-treated subjects. When either vomiting or all gastrointestinal toxicities are taken into account, CBDCA is less toxic ($P = 0.001$). Neurotoxicity (weakness, paresthesia) was observed in one patient on CBDCA, whereas six patients on CHIP developed moderate or worse neurotoxicity. Only one of these in each arm was attributable to pelvic nerve

Table 3. The incidence of protocol- and non-protocol-related toxicity of ECOG grade 2 or more

Toxicity	CHIP ($n = 41$)					CBDCA ($n = 47$)				
	Non-prot	Protocol		Prot & non-prot		Non-prot	Protocol		Prot & non-prot	
	n^a	n^a	(%)	n^a	(%)	n^a	n^a	(%)	n^a	(%)
Vomiting	1	31	(76%)	32	(78%)	0	20	(43%)	20	(43%)
Gastrointestinal	0	31	(76%)	31	(76%)	0	20	(43%)	20	(43%)
Diarrhea	0	3	(7%)	3	(7%)	0	5	(11%)	5	(11%)
Infection	0	1	(2%)	1	(2%)	1	2	(4%)	3	(6%)
Bleeding	2	4	(10%)	6	(15%)	2	3	(6%)	5	(11%)
Skin/mucosa	0	2	(5%)	2	(5%)	0	0	(0)	0	(0)
GU	5	0	(0)	5	(12%)	5	0	(0)	5	(11%)
Hematologic	2	17	(41%)	19	(46%)	5	13	(28%)	18	(38%)
Liver	0	0	(0)	0	(0)	1	0	(0)	1	(2%)
Neurologic	1	5	(12%)	6	(15%)	0	1	(2%)	1	(2%)
Respiratory	0	0	(0)	0	(0)	1	3	(6%)	4	(9%)
Other	4	0	(0)	4	(10%)	3	0	(0)	3	(6%)
Any mod$^+$ tox	10	36	(88%)	37	(90%)	14	30	(64%)	33	(70%)

[a] Number of patients who experienced moderate or worse toxicity. Figures in parentheses represent the percentage of patients in that treatment group

Within the individual categories, a single maximal toxicity that was graded as being both protocol- and non-protocol-related was included only in the protocol related side effects. Non-prot, Non-protocol-related; Prot & non-prot, protocol- and non-protocol-related; mod$^+$ tox, moderate or worse toxicity; GU, genitourinary (renal)

involvement; the other five neurotoxic events observed in the CHIP arm consisted of only asthenia. Mucosal and skin toxicities were rare in both arms, as were liver and lung derangements. One episode of infection due to CHIP and two due to CBDCA were reported.

Discussion

Phase II and III studies in ovarian cancer and in a number of other tumors have suggested an equivalent spectrum of activity for cisplatin and carboplatin [5]. In cervical cancer, cisplatin has become established as an important drug because of its activity in advanced cases [2] and its potential in improving the results of radiation when given simultaneously with this modality in localized stages [1]. Although a dose of 100 mg/m^2 cisplatin achieved a significantly higher response rate, the resulting survival was not significantly better than that obtained using 50 mg/m^2 every 4 weeks [2]. Therefore, it appeared justifiable to explore the usefulness of a platinum analog that may be less toxic in this disease. It was reasoned that their similar activity and lower toxicity might encourage wider application of these compounds at earlier stages and in combination with radiation.

In the current study, both analogs demonstrated similar activity. Moreover, the therapeutic results are comparable with those achieved using cisplatin in our preceding study [9]. Similarly, we found no difference in the duration of response, survival, or patterns of response by sites. However, carboplatin's activity was more apparent in extrapelvic than in pelvic disease, whereas iproplatin was more active against pelvic disease. In a series of similarly designed studies, the Gynecologic Oncology Group (GOG) [11] observed response rates of 15.4% (95% confidence intervals, 10.8%–21.4%) for carboplatin and 10.8% (95% confidence intervals, 7%–16.2%) for iproplatin at identical doses in the good-risk patients tested. Subjects who had received prior radiation were given the lower doses of 340 and 270 mg/m^2, respectively. Another feature of that trial involved crossover to cisplatin; 4 of 22 patients exhibited objective responses following such treatment. Based on these observations, the authors concluded that the analogs are probably inferior to the parent drug cisplatin [11]. Unfortunately, crossovers to cisplatin were not carried out in the present study.

Carboplatin has also been studied in cervical cancer by the Southwest Oncology Group as part of a phase II study randomizing patients either to cisplatin plus 5-fluorouracil or to CBDCA. The results have not yet been published, but antitumor activity has been observed in both arms (D. Alberts, personal communication). No phase III comparison of cisplatin and CBDCA exists.

We report toxicities similar to those found by the GOG. In the GOG study, patients completed an evaluation form for determination of gastrointestinal tolerance that was identical to the one used in the cisplatin trials. In terms of gastrointestinal intolerance, carboplatin was the least toxic drug, followed by infusional cisplatin, bolus cisplatin, and, finally, iproplatin. As in other studies, most nonhematologic toxicities were minor. Drug-related neurotoxicity was recorded in five patients on iproplatin; since this involved asthenia, it may represent nonspecific intolerance rather than neurologic disease. Finally, we did note a tendency for some cumulative hematologic toxicity during iproplatin administration but not during treatment with carboplatin.

An exception to the satisfactory tolerance of carboplatin was the finding of severe toxicity during the first cycle in a few patients who had preexisting renal abnormalities. This is not unexpected, in view of the clear relationship that has been described between the AUC (concentration $\times$ time) and glomerular filtration rate for a given dose of carboplatin. The dose-limiting hematologic toxicity was predictably related to the above pharmacokinetic parameters [4].

In spite of the modest activity shown in these trials, in our view, carboplatin's advantage in terms of toxicity establishes a future role for this drug in the treatment of cervical cancer. Presently, there is no evidence that combination therapy is superior in terms of response and survival to single-agent treatment with platinum compounds. Carboplatin may thus provide superior tolerance in terms of nausea and vomiting while obviating the need for hydration. Moreover, interactions with radiation may be more readily exploitable without requiring hospitalization of patients, and practical combination schedules have been developed. Although the hematologic toxicities associated with carboplatin may pose greater problems in the development of combinations with this drug than are encountered with cisplatin, future trials are required to explore this point.

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