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Short communication

300 mg/m^2 carboplatin (Cb), adriamycin (A) cyclophosphamide (C) (CACb-300) combination in advanced ovarian carcinoma: a feasibility study

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Summary. Carboplatin (Cb) is an active drug in ovarian carcinoma that has fewer visceral side effects than cisplatin (CDDP) but higher myelotoxicity, which makes it difficult to combine at efficient doses with other myelotoxic drugs. In a preliminary study in advanced ovarian carcinoma, Rosso et al. [4] showed the maximum tolerated dose of Cb given in combination with cyclophosphamide (C) and adriamycin (A) to be 200 mg/m^2. Since the efficacy of Cb may be dose-dependent, as is that of CDDP, we started a feasibility study of a CACb-300 regimen, that is, using Cb at 300 mg/m^2 with lower C and A doses. Our data shows that the CACb-300 combination can safely be given in previously untreated patients for at least six 28-day cycles.

Introduction

Carboplatin (*cis*-diammino-1,1-cyclobutaneplatinum dicarboxylate; Cb) is one of the less toxic platinum derivatives as far as nausea and vomiting as well as nephrologic and neurologic side effects are concerned [1]. However, myelotoxicity is dose-limiting when Cb is given in combination with more than one myelotoxic drug. In a phase I study in advanced ovarian carcinoma using 28-day cycles, Rosso et al. [4] showed the maximum tolerated dose of Cb given with cyclophosphamide (C) (600 mg/m^2) and adriamycin (A) (45 mg/m^2) (CACb-200) to be 200 mg/m^2. In a later phase III trial conducted by the same group [2], preliminary results tended to show that the CACb-200 combination gives a somewhat lower response and survival than the standard cyclophosphamide – adriamycin – (CAP) regimen. However, since the efficacy of Cb and CDDP [3] may be dose-dependent, we decided to carry out a feasibility study of this combination using lower doses of C (500 mg/m^2) and A (40 mg/m^2) and a Cb dose of 300 mg/m^2 (CACb-300).

Materials and methods

A total of 16 consecutive patients with histologically proven (FIGO) stage III-IV ovarian adenocarcinoma were included in a study carried out between July 1986 and January 1987. Inclusion criteria included no previous chemoradiotherapy, an age of <70 years, a WHO performance index of $\leqslant 3$, and the absence of any contraindication to chemotherapy. Exclusion criteria were the presence of another perceptible tumor, low malignancy, brain metastasis, and the impossibility of follow-up. For the first cycle, drugs were given assuming a 1-m^2 body area; the subsequent five cycles were given at full doses, with a compliance of 92%, 95%, and 95% for C, A, and Cb, respectively. Hematologic nadirs were determined at each cycle by weekly blood counts and graded according to the WHO scale.

Results

A total of 14 patients were evaluable (1 died after the first cycle and another was excluded for protocol violation): of these, 8 received the full 6-cycle protocol and 6 had only 3–5 cycles due to tumor progression. Anemia of grade 0–I was observed in 81% of the patients and that of grade II–III, in 19%. Grade 0–I platelet toxicity was reported in 86% of the patients, grade II, in 6% (one patient), and grade IV, in 6% (one patient), the latter without any detectable hemorrhage. Neutropenia was the main concern; grade 0–I was observed in 38% of the patients, whereas grades II, III, and IV were each reported in 21% of the patients. However, grade II, III, and IV toxicities were not associated with infection except in one easily manageable case. As shown in Table 1, some cumulative toxicity for neutrophils occurred during the six-cycle protocol, but chemotherapy was delayed by 1 week at the sixth cycle in two patients and by 2 weeks in only one. Nausea and vomiting of grade I was reported in 30% of the patients, grade II, in 46%, and grade III, in 23%. Neither nephro- nor neurotoxicity occurred. The clinical response rate (WHO criteria) was 57% (8/14). After second-look laparotomy, four patients had a partial response, two of whom had a residuum measuring <2 cm in diameter, and four underwent a complete response, two of whom showed negative cytology and histology.

Discussion

Cb is an active drug in ovarian adenocarcinoma; however, due to myelotoxicity it has as yet rarely been included in three-drug combinations. Our study shows that such a combination can indeed safely be given in previously untreated patients during at least six 28-day cycles using a 300 mg/m^2 Cb dose. The lower (200 mg/m^2) Cb dose pre-

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Table 1. Cumulature toxicity for neutrophils during six-cycle protocol

Number of cycle	1	2	3	4	5	6	After
Hemoglobin (9 g/100 ml)							
Z	11.5 (10.2–13.6)	11.3 (6.9–13.1)	11.8 (10.7–14)	11.3 (10.7–13.2)	11.4 (10.5–12.4)	11.4 (10.4–12.7)	11.1
N	10.8 (9.4–11.8)	10.7 (9.2–12.4)	10.3 (9.6–11.8)	9.7 (6.8–12)	10 (9.2–10.7)	10.3 (10.2–10.5)	(9.9–12.8)
Neutrophils (10^9/ml)							
Z	6.3 (3.2–10.2)	5.2 (3.1–12.1)	3.5 (2.3–8)	3.5 (1.5–6.2)	2.8 (1.6–5.5)	2.9 (1.3–4.4)	3.0
N	3.6 (0.3–15.8)	0.9 (0–1.5)	1.2 (0–6.4)	1.2 (0.1–3.1)	1.1 (0.1–1.3)	1 (0.1–1.6)	(2.5–7.6)
Platelets (10^{-9}/l)							
Z	462 (293–657)	388 (173–564)	380 (261–625)	327 (441–229)	302 (262–423)	253 (152–358)	356
N	320 (110–540)	188 (15–340)	170 (47–483)	128 (13–203)	102 (18–137)	156 (46–242)	(177–764)

Numbers in parentheses represent the range
Z, zenith; N, nadir

viously given in the Conte et al. [2] phase III trial may account for the somewhat lower response and survival achieved by the CACb-200 regimen compared with that obtained using the CAP combination. The preliminary results (in 110 patients) of our ongoing randomized phase III trial comparing the CACb-300 with the CAP regimen confirm its acceptable tolerance and efficacy.

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