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Carboplatin and Cyclophosphamide Salvage Therapy for Ovarian Cancer Patients Relapsing after Cisplatin Combination Chemotherapy

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30 ovarian cancer patients with a relapse after prior cisplatin combination chemotherapy were treated in a phase II study with cyclophosphamide 100 mg/m² orally on days 1–7 and carboplatin 300 mg/m² intravenously on day 8. Treatment was well tolerated. The major side-effect was thrombocytopenia. 28 patients were evaluable for response. The response was 5 CRs (18%), 4 PRs (14%) 15 SDs (53%) and 4 PDs (14%), for an overall response rate of 32%. The overall progression-free survival lasted from 2 to 23 months, median 8 months. Overall survival ranged from 2 to 35+ months, median 12 months. Patients with a therapy-free interval of more than 1 year showed a higher response rate (46%) than patients with a shorter therapy-free interval (20%). It is concluded that platinum containing second-line chemotherapy, after treatment that already contained cisplatin, is only warranted to palliate symptoms.
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INTRODUCTION

OVARIAN CANCER causes about 6% of all cancer deaths in Europe and the United States [1, 2]. The introduction of cisplatin combination chemotherapy in the treatment of advanced ovarian cancer has significantly improved the response rate, progression-free and overall survival [3–8]. However, even patients with a histologically proven complete response have a relapse rate of approximately 50% [3, 7, 9–15].

In patients with primary chemotherapy resistance salvage chemotherapy is ineffective [16]. Patients who respond to cisplatin and relapse after a therapy-free interval have a more favorable prognosis. Response rates up to 70% can be achieved with cisplatin retreatment in complete responders to first-line cisplatin combination chemotherapy once they relapse [17].

Carboplatin has almost the same activity as cisplatin in the treatment of ovarian cancer, but is significantly less neuro- and nephrotoxic [18 19]. Since the majority of the patients who relapse after cisplatin chemotherapy have a decreased renal function and some degree of neurotoxicity, salvage chemotherapy with carboplatin appears to be more attractive than that with cisplatin. We have investigated the value of salvage combination chemotherapy with carboplatin and cyclophosphamide.

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PATIENTS AND METHODS

Patient eligibility criteria included: histologically proven epithelial ovarian carcinoma, progressive and measurable disease, prior treatment with cisplatin combination chemotherapy, a therapy-free interval of at least 3 months, white blood cells (WBC) $> 3.0 \times 10^9$/l, platelets $> 75 \times 10^9$/l.

30 patients were entered in the study. Histological tumour type was endometrioid adenocarcinoma in 2 patients, serous

Table 1. Patients' characteristics at the start of carboplatin and cyclophosphamide (n = 30)

Age; median (range)	56	(42–71)
Creatinine (μmol/l); median (range)	96	(59–156)
Tumour size:		
< 2 cm		2
2–5 cm		16
> 5 cm		12
Ascites		16
Response to prior therapy		
Pathological complete response		10
Microscopic disease		1
Clinical complete response		10
Partial response		1
Progressive disease		1
Adjuvant chemotherapy		7
Prior chemotherapy; median (range)		
Total dose cisplatin (mg)	675	(350–1200)
No. of cycles	9	(3–15)
Therapy duration (mos)	12	(4–29)
Therapy-free interval (mos)	12	(3–60)

Table 2. Response in relation to therapy-free interval

Response	TFI < 1 year	TFI > 1 year	All patients
Complete response	1	4	5
Partial response	2	2	4
Stable disease	9	6	15
Progressive disease	3	1	4
Total	15	13	28
Response rate	20%	46%	32%

TFI = therapy-free interval.

cystadenocarcinoma in 8, mucinous cystadenocarcinoma in 1 and adenocarcinoma in 19. Tumour grade was grade 2 in 7 patients, grade 3 in 19, and unknown in 4 patients. The patient characteristics at the start of salvage chemotherapy are shown in Table 1. Of note, 28 patients had bulky disease.

Treatment consisted of cyclophosphamide 100 mg/m^2 orally day 1–7, carboplatin 300 mg/m^2 intravenously day 8, once every 4 weeks. The doses of cyclophosphamide and carboplatin were reduced by 50% and 25%, respectively, if at the day of retreatment WBC was between 3–4 × 10^9/l and/or platelets between 75–120 × 10^9/l. If WBC was < 3 x 10^9/l and/or platelets < 75 × 10^9/l treatment was delayed until recovery. If the creatinine clearance fell to 20–50 ml/min carboplatin was reduced by 50%. Response was evaluated by computed tomography, gynaecological and complete physical examination after the first 2 cycles. Responses were defined according to the WHO response criteria [20]. The therapy-free interval is the interval between the last day of the prior therapy and the start of carboplatin/cyclophosphamide. The progression-free interval is the period between the start of carboplatin/cyclophosphamide and the first date of progression. Survival is the interval between the start of drug treatment and the last follow-up or death.

RESULTS

30 patients were evaluable for toxicity and 28 for response, time to progression and survival. Inevaluable for response were 2 patients; 1 patient went off study after the first cycle because of toxicity, the second patient died early due to lung embolism. The median number of carboplatin/cyclophosphamide cycles per patient was 5, range 1–9. The median percentage of protocol dose given in cycles 1 + 2 vs. cycles 3 + 4 was 0.83 (range 0.6–1.0) vs. 0.69 (0.4–1.0) for carboplatin and 0.86 (range 0.5–1.0) vs. 0.73 (0.5–1.0) for cyclophosphamide.

Table 3. Response rate and progression-free and overall survival in relation to therapy-free interval

Ref.	No. of patients	TFI	RR	CR	PFS	Survival
17	11	22 (5–56)	73%	36%	8 (2–15)	12 (2–24$^+$)
22	32	19 (12–72)	63%	22%	–	11 (3–26)
23	24	–	48%	25%	9 (2–15)	–
23	18	–	33%	11%	8	–
21	55	21 (3–71)	56%	18%	11	67%*
This study	28	12 (3–61)	32%	18%	8 (2–23)	12 (2–35$^+$)

TFI = therapy-free interval, RR = response rate, CR = complete response, PFS = progression-free survival.
*Alive at 11 months.

Response

The median follow-up at the time of analysis was 12 months (range 2–35). Among the 28 evaluable patients there were 5 (18%) complete responders, 4 (14%) partial responders, 15 (53%) with stable disease and 4 (14%) with progressive disease. At the time of analysis 26 patients had progression and 20 patients had died of progressive disease.

The progression-free survival was 2–23 months (median 8 months). Overall survival was 2 to more than 35 months (median 12). 2 patients with a complete response who relapsed did respond completely to cyclophosphamide/carboplatin again for a second and a third time, respectively. Correlation between response and therapy-free interval of less or more than one year is shown in Table 2.

Toxicity

Subjectively, the treatment was well tolerated. The major side-effect was thrombocytopenia: 7 patients had thrombocytopenia grade 4, and 6 patients required platelet transfusions; 2 of them had had prior abdominal radiotherapy. One of these 2 patients was taken off study after the first cycle because thrombocytopenia was complicated by haemorrhagic ascites. The median platelets nadir was 91 × 10^9/l (range 8–286). Median WBC nadir was 3.0 × 10^9/l (0.6–9.4) No toxic death has occurred. Non-haematological toxicity consisted of nausea and vomiting, grade 2 (5 patients) and grade 3 (17 patients). No increase of neurotoxicity or nephrotoxicity and no alopecia was observed.

DISCUSSION

Although the treatment was subjectively well tolerated, 20% of the patients needed supportive care with platelet transfusions. This cost has to be viewed in the perspective of 32% responses and a median progression free-survival of 8 months. Reported response rates to salvage cisplatin or JM8 containing chemotherapy vary from 33–73% [17, 21–23], but the median progression-free and overall survival results are identical to what we have observed (Table 3). Of note, the median therapy-free interval in the 5 reported studies is almost twice as long as in this study. The data from our study combined with the reported results from others lead to the conclusion that second-line therapy after cisplatin containing regimens should only be instituted to palliate symptoms, because the median time to progression and survival are short and the toxicity cannot be ignored.

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In vitro Antiproliferative and Metabolic Activity of Eight Novel 5-fluorinated Uracil Nucleosides

Boudewijn J.M. Braakhuis, Gerard W.M. Visser, Ingelise Stringer and Godefridus J. Peters

The *in vitro* growth inhibitory activity of eight novel 5-fluorinated uracil nucleosides was assessed in four human tumour cell lines, one of colon and three of head and neck squamous cell origin. These compounds are ribose or deoxyribose sugars with an acetoxy or an hydroxyl-group at the 6-position in the uracil part of the molecule, and their respective diastereoisomers. Antiproliferative effects were tested in an automated microculture assay based on the reduction of a tetrazolium dye, the MTT assay. Using a continuous drug exposure for four days, all novel nucleosides were more potent inhibitors of cell growth than 5-fluorouracil (5-FU). Most drugs were very active, having an IC_{50} value at least 10 fold lower than that of 5-FU, and this was consistently found for all cell lines. The 6-acetoxy compounds were generally more active than the compounds with a hydroxyl-group at the 6-position, while diastereoisomerism did not seem to influence the antiproliferative effect. Their capacity to inhibit the incorporation of tritiated deoxyuridine into DNA, which reflects the inhibition of thymidylate synthase, was measured in a short term assay. When tested at a concentration of 10^{-6} mol/l, most of the compounds were found to block this incorporation more efficiently than 5-FU.
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INTRODUCTION

5-FLUOROURACIL (5-FU) has been used for several decades for the chemotherapeutic treatment of several types of cancer [1, 2]. In an attempt to improve the antitumour effect of 5-FU, several prodrugs have been synthesised. As such, we have evaluated doxifluridine (5′-deoxy-5-fluorouridine) in murine colon tumours and xenografts of head and neck squamous cell carcinomas and demonstrated that this drug has a better antitumour activity than 5-FU [3]. Other well known drugs of this class of agents are tegafur (N_1-tetrahydrofuran-2-yl-5-fluororacil) and floxuridine (5-fluoro-2′-deoxyuridine, 5-FUdR). Response rates with these drugs have been variable,