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Papers

The Impact of Received Dose Intensity on the Outcome of Advanced Ovarian Cancer

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It has been demonstrated that the prognosis of ovarian cancer is influenced by the dose intensity of cytotoxic treatment. The impact of received dose intensity of platinum-based combination chemotherapy on disease outcome was analysed in 226 stage III–IV ovarian cancer patients entered into two prospective randomised trials. All patients received either cisplatin or carboplatin and cyclophosphamide with or without doxorubicin for six courses after primary surgery. The impact of the received dose intensity of each drug (RDI), the average received dose intensity of the treatment regimen (ARDI) and the relative total drug dose (RTD) on progression-free survival (PFS) and survival were analysed. In the 198 patients receiving the full six courses of treatment, RDI of cisplatin or carboplatin, ARDI and RTD were > 0.76 in 74.2, 61.1 and 65.1% of cases, respectively. Although the differences were not significant, pathological complete response was more frequently observed in the group of patients with ARDI < 0.75, whereas the partial response rate was higher in the ARDI ≥ 0.76 group. Median survival and PFS were 19 and 13 months; 22 and 10 months; 23 and 13 months for the groups of patients receiving chemotherapy at a ARDI of < 0.75, ≥ 0.76–0.99 and > 1.00, respectively (*P* = not significant). It appears that modest dose modifications and brief treatment delays during first-line platinum-based chemotherapy do not affect response rate, survival and PFS in advanced ovarian cancer patients.
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INTRODUCTION

IN EXPERIMENTAL models, a steep dose–response curve has been demonstrated for several cytotoxic agents [1–3]. Recently, the planned dose intensity (DI) of a cytotoxic regimen, that is, the amount of drug scheduled to be delivered per unit of time, has been correlated to clinical outcome in solid tumours such as breast, lung, colon and ovarian cancer [4–11]. The majority of reports examine the impact on prognosis of the planned DI and do not take into account treatment delays and/or drug dose modifications that may occur in patients receiving multiple cytotoxic courses. The received dose intensity (RDI), i.e. dose of drug actually administered per unit of time, has been shown to predict the outcome of stage II breast cancer more accurately than planned DI [7].

Even if the outcome of ovarian cancer has been correlated to the planned DI of cisplatin-containing cytotoxic regimens [6], no study published to date has addressed the relationship between prognosis and RDI.

In order to analyse the impact of RDI on survival and disease-free survival (DFS) of stage III–IV ovarian cancer patients treated with cisplatin or carboplatin-containing chemotherapy, the clinical charts of 289 patients, entered into two consecutive randomised trials, were reviewed.

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PATIENTS AND METHODS

Patient population

The characteristics of the 289 stage III–IV ovarian cancer patients entered into two consecutive multicentre randomised trials carried out by the Gruppo Oncologico Nord-Ovest (GONO) have been previously reported [12, 13]. The clinical charts of all patients were reviewed, the dose actually administered of each cytotoxic drug and treatment intervals were recorded for every treatment course, and the RDI of each drug calculated. Full data regarding DI and total dose evaluations were not available for 63 patients that were therefore excluded from the present analysis. Thus we considered 226 patients.

Chemotherapy

Chemotherapy regimens in the two trials were as follows:
(1) Cisplatin (CDDP) 50 mg/m^2 and cyclophosphamide (CTX) 600 mg/m^2 (PC) vs. CDDP 50 mg/m^2, doxorubicin (DX) 45 mg/m^2 and CTX 600 mg/m^2 (PAC).
(2) CDDP 50 mg/m^2, DX 45 mg/m^2 and CTX 600 mg/m^2 (PAC) vs. carboplatin (CBDCA) 200 mg/m^2, DX 45 mg/m^2 and CTX 600 mg/m^2 (CAC). All treatment was administered on day 1 every 28 days for six courses. After their sixth course patients with either stable disease (SD) or partially responding disease went on to receive six further courses. Patients with progressive disease (PD) received second-line treatment. Both in cases of clinically non-evaluable disease (residual tumour < 2 cm after primary laparotomy) and in patients achieving a complete response (CR), second-look surgery was carried out. If pathological complete remission (pCR) was documented, no further treatment was administered. After 1985 patients with pCR or minimal residual disease (RD) after second-look were randomly assigned to receive either three further courses of cytotoxic treatment or whole abdominal radiotherapy [14]. In study 2 drug doses were adjusted on the basis of the haematological toxicity observed at nadir as follows: WHO grade 2 or 3, 10 and 50% dose reductions, respectively; no haematological toxicity, 20% increase in drug dose. Since study 2 showed that PAC and CAC administered at equally myelotoxic doses resulted in comparable clinical activity, for DI calculations it was assumed that CDDP 50 mg/m^2 was equivalent to CBDCA 200 mg/m^2 [13, 15].

Calculation of DI

DI was calculated as mg/m^2/week as suggested by Hryniuk and Levin [4] and the planned DI of drugs were as follows: CTX 150; ADM 11.25; CDDP 12.5; CBDCA 50. The RDI was calculated as the ratio of the drug dose actually received to the planned drug dose. To calculate the average relative dose intensity (ARDI) the sum of the RDI of all drugs in the regimen was divided by three, the total number of agents comprised in PAC and CAC. For the PC regimen, which did not comprise DX, a DI of 0 was assigned to the missing drug [6]. RDI and ARDI were calculated after the third and sixth treatment courses. The impact on clinical response and prognosis of the three following arbitrarily chosen RDI and ARDI levels of < 0.75, 0.76–0.99 and > 1.00 was calculated.

To assess the prognostic impact of total dose of drugs received, the ratio of the total drugs actually received (mg/m^2) to the total amount planned (mg/m^2) [relative total dose (RTD)] was calculated and an example follows.

Sample calculation

The RTD was calculated as follows: the total dose (mg/m^2) of each drug received in the first three or six cycles, or fewer if therapy was interrupted earlier, was divided by the scheduled dose and planned duration of three and six courses, i.e. 12 and 24 weeks, respectively, or by the real treatment duration if longer than 12 or 24 weeks.

For example, a woman who received 600 mg/m^2 of CTX for four courses during 18 weeks (1 week of treatment delay at third and fourth course) has:

RDI after three courses = (600 × 3)/14/150 = 0.85
RDI at the end of treatment = (600 × 4)/18/150 = 0.88
RTD after three courses = (600 × 3)/14/150 = 0.85
RTD after six courses = (600 × 4)/24/150 = 0.66

Statistical methods

Survival curves were calculated according to Kaplan–Meier and differences between curves were compared by means of the log-rank test. We performed a first analysis considering all 226 women; relative DI and RTD intensity variables were correlated with survival and progression-free survival (PFS) of the patients. In order to avoid the bias due to the fact that patients with PD (15 patients) or those who died (13 patients) during the first 6 months did not complete the scheduled treatment, a second analysis was performed excluding these patients. All those patients who died were considered progressed for our PFS analyses. Consequently, median time to survival and PFS were computed from the seventh month. Using this approach, DI variables can be considered as prognostic factors.

RESULTS

To test the contribution of chemotherapy to clinical outcome, overall survival and PFS of 226 patients were compared in different strata of DI variables, drugs and levels after three and six courses. No differences were observed.

Then we performed a second analysis excluding 28 patients who did not complete the six-course treatment program; 198 patients were considered. First-line platinum-comprising cytotoxic treatment in 198 stage III–IV cancer patients was PAC in 100 patients (50.5%), CAC in 70 patients (35.4%) and PC in 28 patients (14.1%). The RDI of each drug comprised in the regimen, the ARDI of the regimens and the RTD were calculated both after three and six courses of treatment. Patient characteristics according to RDI of CBDCA or CDDP after three courses of treatment are shown in Table 1. In the majority of cases (89.4%) RDI was ≥ 0.76 and < 0.75 only in 10.6% of patients. Distribution of patient variables in the three RDI groups considered (< 0.75; ≥ 0.76–0.99; ≥ 1.0) was not significantly different. However, the percentage of patients with ECOG performance status of 0, well-differentiated G1 lesions and no RD after primary surgery was higher in patients receiving CBDCA or CDDP at a RDI < 0.75. 28 patients did not receive the full six courses of treatment due to PD or treatment refusal. The pathological and clinical response rates observed in the 198 patients completing six courses of cytotoxic therapy are shown in Table 2. Although the differences were not statistically significant, pathological and clinical CR were more frequently observed in the group with ARDI < 0.75 and the PR rate was higher in the ≥ 0.76–0.99 ARDI group. No significant difference in response according to ARDI level was observed even when CBDCA-treated patients were excluded from the analysis. The response rate, PFS and overall survival of the 198 stage III–IV ovarian cancer patients treated with six courses of first-line platinum-based cytotoxic therapy were analysed according to RDI of each drug and ARDI of treatment at three and six courses (Table 3). No significant correlation between outcome

Table 1. Patients' characteristics according to received dose intensity (RDI) levels after three courses of treatment of cisplatin/carboplatin (CDDP/CBDCA 3)

	Dose intensity levels					
	≤0.75		0.76–0.99		≥1	
	Patients	%	Patients	%	Patients	%
Age (years)						
≤ 55	10	47.6	27	31.4	51	56
> 55	11	52.4	59	68.6	40	44
PS						
0	16	76.2	55	64	60	65.9
1–2	5	23.8	31	36	31	34.1
FIGO stage						
I	—	—	4	4.7	1	1.1
II	2	9.5	4	4.7	5	5.5
III	15	71.4	62	72.1	64	70.3
IV	4	19.1	16	18.5	21	23.1
Grading						
G1	4	19.0	8	9.2	8	8.8
G2	6	28.6	33	38.4	28	30.8
G3	7	33.4	36	41.9	43	47.2
Gx	4	19.0	9	10.5	12	13.2
Residual disease after primary surgery						
No residual	5	23.8	15	17.4	12	13.2
< 2 cm	4	19.0	21	24.4	25	27.4
2–5 cm	6	28.6	20	23.3	20	22.0
> 5 cm	6	28.6	30	34.9	34	37.4

PS = Peformance status.

of disease and DI was observed. Overall survival and PFS curves according to CDDP/CBDCA RDI levels after three and six courses of treatment were plotted and no significant differences were observed when the curves were analysed by Mantel–Cox and Wilcoxon tests. In addition, PFS and survival of patients with ARDI < 0.75 were not found to be significantly different from dose with ARDI ≥ 0.76 ($P = 0.41$ and $P = 0.8$ for PFS and survival, respectively). CDDP DI in patients receiving PC was compared with that of patients receiving PAC and no significant difference was observed; it appears that the addition of DX to the cytotoxic regimen does not reduce CDDP DI. Response, PFS and survival were not influenced by the RTD of chemotherapy administered.

DISCUSSION

Levin and Hryniuk [11] have demonstrated that the relative DI of CDDP was significantly correlated with prognosis of ovarian cancer patients. This study was based on projected DI of 31 multi-agent and 16 single-agent regimens used at various institutions. The CHAP regimen, described by Greco *et al.* [16], in which CDDP DI is 15 mg/m²/week, was the standard used for comparison. RDI of CDDP is expressed as a ratio of the DI of CDDP in each regimen to the DI of CDDP in the standard regimen. A relationship between RDI of CDDP and both clinical response and median survival time was observed only in patients who received CDDP at a RDI of 40 to 80%, whereas no correlation was observed in patients receiving 81 to 110% of the RDI of CDDP [6].

The RDI of platinum-based first-line cytotoxic treatment in stage III–IV ovarian cancer patients entered into two prospective randomised studies was assessed in order to evaluate the impact of dose and schedule modifications routinely carried out in clinical practice on disease outcome. Three DI levels were arbitrarily selected: < 0.75; ≥ 0.76–0.99; ≥ 1.0. As shown in Table 3, the majority of patients (89.4%) received more than 75% of the planned dose of drugs, which may explain why a relationship between clinical outcome and the RDI of each cytotoxic agent; the average RDI of the regimen and the total drug dose could not be demonstrated. In particular, the RDI of CDDP or CBDCA had no significant impact on survival and PFS. The importance of CDDP dose has been emphasised in trials where high doses of this agent (100–200 mg/m²), in some instances using reduced glutathione as a protective agent, were employed as salvage therapy in women failing standard doses. These studies have reported objective response rates varying from 20 to 50% [17–20]. It therefore appears that the DI of CDDP is a major determinant of clinical outcome and should not be compromised in designing chemotherapy regimens for ovarian cancer patients. However, no published trial has demonstrated the independent contribution of the DI of each cytotoxic agent comprised in a treatment regimen on outcome. In addition, the impact of total drug dose on survival in ovarian cancer has yet to be demonstrated. In the present series total drug dose did not appear to be significantly related with PFS or survival.

It is not known whether clinical outcome can be improved by increasing the DI of platinum derivatives, even if this means the exclusion of drugs like adriamycin from the regimen. Our analysis showed that the inclusion of adriamycin in the PAC/CAC regimens does not adversely effect the average RDI of treatment. A recently published meta-analysis carried out in 1194 patients entered into four randomised trials comparing PC with PAC regimens showed that the addition of adriamycin to PC significantly improved the prognosis of ovarian cancer patients. A 7% benefit in survival ($P = 0.02$) and pCR ($P = 0.01$) were observed at 6 years [21].

A second overview by the Advanced Ovarian Cancer Trialists Group suggests a survival advantage of platinum-based combination over non-platinum regimens and single-agent platinum,

Table 2. Clinical and pathological response in 198 ovarian cancer patients according to cisplatin/carboplatin RDI levels after three courses

	Dose intensity levels		
	< 0.75 %	0.76–0.99 %	> 1 %
Clinical response			
CR	45.5	40.0	35.2
PR	9.0	44.0	40.7
SD	45.5	14.0	22.2
PD	—	2.0	1.9
Pathological response			
pCR	50.0	44.3	35.2
pPR	25.0	47.5	38.0
pSD	16.7	4.9	19.7
pPD	8.3	3.3	7.1

CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease; p = pathological.
P value = not significant.

Table 3. Median progression-free survival (PFS) and overall survival (OS) of 198 ovarian cancer patients treated with platinum-based regimens (170 treated with doxorubicin) according to RDI of single drugs, ARDI and RTD after three and six courses of treatment

	Dose intensity levels										
	< 0.75			0.76–0.99			> 1.00			*P*-value	
	Patients	PFS	OS	Patients	PFS	OS	Patients	PFS	OS	PFS	OS
Dose intensity after three courses											
CTX 3	20	14	18	90	14	25	88	10	22	0.4	0.4
ADM 3	20	10	18	77	12	22	73	10	23	0.6	0.6
CDDP/ CBDCA 3	21	15	29	86	13	21	91	10	23	0.7	0.7
ARDI 3	47	14	19	76	12	21	75	10	23	0.7	0.8
RTD 3	45	15	22	84	12	22	69	11	23	0.7	0.7
Dose intensity after six courses											
CTX 6	52	16	29	84	11	22	62	11	19	0.3	0.6
ADM 6	51	10	18	62	12	24	57	13	23	0.7	0.7
CDDP/ CBDCA 6	51	13	22	82	12	22	65	11	23	0.8	0.8
ARDI 6	77	13	19	68	10	22	53	13	23	0.4	0.9
RTD 6	69	14	22	71	10	22	58	12	23	0.3	0.9

CTX = Cyclophosphamide; ADM = doxorubicin; CDDP = cisplatin; CBDCA = carboplatin; 3 and 6 = months of treatment; ARDI = average relative dose intensity; RTD = relative total dose.

with CDDP and CBDCA equally effective. Although no firm conclusion can be drawn from such analyses, CAP combination appears the standard regimen to which it would be appropriate to compare new chemotherapy treatment [22].

Results from the present series suggest that dose reductions and schedule modifications frequently applied in clinical practice have no impact on response rate, PFS and survival in advanced ovarian cancer patients, receiving platinum-based first-line chemotherapy.

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