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Treatment of advanced ovarian cancer

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Abstract

Chemotherapy for advanced ovarian cancer has evolved over the past 25 years from the initial use of alkylating agents such as melphalan. Combinations containing cisplatin, cyclophosphamide and doxorubicin were studied in the 1980s and showed improved median progression-free survival. The comparison of platinum-based combinations containing alkylating agents (mainly cyclophosphamide) with triple drug combinations containing anthracyclines and alkylating agents did not convincingly show superiority for the more toxic triple drug combinations. Subsequently, cisplatin plus cyclophosphamide was accepted as a new standard treatment. Carboplatin was introduced as an alternative to cisplatin in the early 1990s resulting in a reduced toxicity but similar efficacy. Taxanes were incorporated into the first-line treatment combinations in the mid-1990s, resulting in superior responses and a prolonged survival especially in patients with bulky disease. Despite this, over 50% of all these patients relapse and ultimately die of their disease. Currently, there is no worldwide accepted standard treatment for patients with platinum-refractory ovarian cancer. Topotecan, etoposide, gemcitabine and liposomal doxorubicin have been studied in this patient group and responses of up to 20% can be expected. However, response duration rarely exceeds 12 months and increased efforts are needed in this area of chemotherapy.

Keywords: Ovarian cancer; Chemotherapy; Platinum

1. Introduction

The principal treatment of advanced ovarian cancer over the past 25 years has been radical debulking surgery followed by chemotherapy. The first drugs with proven activity against ovarian cancer were the alkylating agents and until the late 1970s, cyclophosphamide or melphalan monotherapy were considered standard therapy. Combination chemotherapy further improved efficacy, with the combination of doxorubicin and cyclophosphamide demonstrating superiority over single-agent melphalan [1]. Major landmarks in the development of effective chemotherapies were the introduction of cisplatin in the late 1970s and paclitaxel in the 1990s.

2. Cisplatin

Several randomised trials in the US and in Europe demonstrated that cisplatin-based combination therapy produced higher efficacy than alkylating agents or other non-cisplatin combinations. Gynecologic Oncology Group (GOG) trial No. 47 compared doxorubicin cyclophosphamide (AC) with cyclophosphamide-doxorubicin-cisplatin (PAC) in 227 patients [2]. Results showed that the group treated with the cisplatin-containing regimen had significantly superior median progression-free survival (15 versus 9 months) and median survival (20 versus 16 months). A Dutch study group reported similar results with a four-drug combination of cisplatin, doxorubicin, cyclophosphamide and hexamethylmelamine (CHAP-5) [3]. Based on these data, cisplatin-based combination chemotherapy became the standard treatment in the 1980s.

The value of anthracyclines was also debated at this time. Several trials showed no significant benefit of anthracycline-containing regimens (e.g. PAC) over cisplatin-cyclophosphamide (PC), although most studies reported a trend towards better efficacy with the anthracycline-containing arm (Table 1) [4–7]. Consequently, PC was accepted as a new standard treatment. However, there were several shortcomings with these trials; patient populations were too small and observation periods too short to observe superiority of one

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regimen over another. In contrast, meta-analyses involving increased patient numbers showed a significant benefit for anthracycline-based regimens, with 5–10% higher survival after 3–10 years follow-up [8–10].

3. Carboplatin

The cisplatin-based regimens being used produced considerable toxicity and as a result more tolerable platinum drugs were evaluated. Carboplatin was shown to induce less emesis, and less nephro-, oto- and neurotoxicity than cisplatin [11,12]. Importantly, equal efficacy was demonstrated in several randomised clinical trials [13–16] (Table 2). Only one study produced inferior results with carboplatin than cisplatin, but the dose of carboplatin used was extremely low at 150 mg/m^2 [17]. Meta-analysis of all randomised comparative studies did not detect any significant differences with respect to overall survival [18]. This led to carboplatin being accepted as an alternative regimen to cisplatin, with equivalent efficacy and better tolerance.

The development of additional platinum-based regimens, although leading to improved tolerance, failed to increase therapeutic efficacy. Results in the early 1990s were the same as in the late 1980s when cisplatin was introduced.

4. Dose intensification

Dose intensity and increasing the cumulative dose were studied in an effort to optimise platinum-based regimens. A number of trials examined dose intensification with escalation up to 3-fold [19,20] and some studies also escalated the cumulative dose by a factor of 2–3 [19,21]. However, none of these trials showed an increased benefit.

Table 1
Randomised trials comparing platinum-based combination chemotherapy with and without anthracyclines as first-line therapy for advanced ovarian cancer

Regimen	Courses[a]×mg/m^2	Patients		CR (%)		Median survival (months)	Significance
		n	%[b] ⩾2 cm	Clinical	Pathological		
PC	12×60/500	135	73	39	36	21	No
PAC [4]	12×60/40/500	132	74	48	43	26	
P	6×50	174	70	22	20	19	Yes/No[c]
PC	6×50/650	182	71	25	21	20	
PAC [5]	6×50/50/650	175	67	30	26	23	
PC	6×50/600	63	71	20	40	20	No
PAC [6]	6×50/45/600	62	81	41	62	26	
PC	6×75/750	97	50	–	36	24	No
CHAP [7]	6×100/150/35/100	94	51	–	35	26	

P, cisplatin; C, cyclophosphamide; A, doxorubicin; H, hexamethylmelamine; CR, complete remission.
[a] Treatment interval 21–28 days, except for CHAP with 35-day intervals.
[b] Proportion of patients with residual tumours ⩾2 cm (sub optimal disease)
[c] Significant difference between P and PAC only.

Table 2
Randomised studies comparing cisplatin and carboplatin as first-line therapy in advanced ovarian cancer

Regimen	Courses[a]×mg/m^2	Patients		CR (%)	Survival	
		n	%[b] ⩾2 cm		Median (months)	*n*-YSR[c]
PC	6×100/600	143	100	30	17	3 years: 21%
CarC [13]	6×300/600	148	100	33	20	20%
PC	6×75/600	2102	58	36	23	
Carc [14]	6×300/600	207	60	27	25	
PC	6×100/600	29	72	23	19	5 years: 24%
CarC [15]	6×300/600	27	82	46	24	46%
PAC	6×50/40/600	81	69	67	23	
CarAC [16]	6×200/45/600	83	63	63	23	

P, cisplatin; Car, carboplatin; C, cyclophosphamide; A, doxorubicin; CR, complete remission.
[a] Treatment interval 28 days.
[b] Proportion of patients with residual tumours ⩾2 cm (sub-optimal disease).
[c] Survival rate after *n* years.

In conclusion, optimal therapy for advanced ovarian cancer in the early 1990s consisted of platinum combination chemotherapy (PAC, PC-epirubicin [PEC], PC, Carbo-C), with platinum given in conventional doses (i.e. $\geqslant 50$ mg/m^2 cisplatin or $\geqslant 300$ mg/m^2 carboplatin) over 5–6 courses with treatment intervals of 3–4 weeks.

5. Paclitaxel

A new class of cytotoxics, the taxanes, were introduced as chemotherapy for advanced ovarian cancer in the early 1990s. The first compound of this class was paclitaxel and it showed promise as second-line treatment following first-line treatment with platinum [22]. First-line treatment of paclitaxel (135 mg/m^2) combined with cisplatin (75 mg/m^2) as a 24-h infusion was compared with standard PC therapy and shown to be superior with regard to the response rates (complete response [CR]: 51% versus 31%; overall response [OR]: 73% versus 60%), progression-free survival (median 18 months versus 13 months) and median survival (38 months versus 24 months) [23]. The improved efficacy, however, was balanced against a more inconvenient treatment schedule, which made ambulatory treatment difficult. The dosing schedule was made easier using a 3-h infusion of paclitaxel 175 mg/m^2 in combination with the same dose of cisplatin, although, surprisingly, this schedule was associated with a high rate of neurotoxicity; 20% of patients suffered from severe neurotoxicity [24].

One approach to this problem was to substitute carboplatin for cisplatin; improved tolerance with equal efficacy had been recorded with this approach in earlier studies [13–16]. Promising phase I/II data led to three prospectively randomised phase III studies comparing carboplatin–paclitaxel with cisplatin–paclitaxel. The following schedules were compared:

1. Dutch–Danish trial: Cisplatin 75 mg/m^2 versus carboplatin area under the concentration curve (AUC) 5 (both with paclitaxel 175 mg/m^2) given over 3 h [25].
2. German–Austrian trial: Cisplatin 75 mg/m^2 versus carboplatin AUC 6 (both with paclitaxel 185 mg/m^2) given over 3 h [26].
3. US trial: Cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2 given over 24 h versus carboplatin AUC 7.5 plus paclitaxel 175 mg/m^2 given over 3 h.

All three studies have completed accrual and interim analyses are available [27–29]. Analyses of the toxicity data of both European trials showed a significantly more favourable profile for the carboplatin combination, which induced less emesis and nausea, and less neurotoxicity.

Summarising the experiences with the platinum–paclitaxel combination regimens in 2000 reveals at least two combination regimens with similar efficacy and acceptable toxicity, which can be regarded as standard treatment in advanced ovarian cancer:

1. Cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2 as a 24-h infusion.
2. Carboplatin AUC 5-7.5 plus paclitaxel 175 mg/m^2 as a 3-h infusion.

However, two recently presented studies challenged the role of paclitaxel as part of the standard combination chemotherapy in advanced ovarian cancer. A randomised trial comparing single agent cisplatin versus single agent paclitaxel versus cisplatin-paclitaxel combination (protocol GOG # 132) [30] could not demonstrate superior survival for the combination regimen. Furthermore, progression-free survival was significantly inferior in the paclitaxel single agent arm. Nevertheless, subsequent treatment before progression hampered the analysis of the single agent efficacy. Almost half of the patients received some chemotherapy before clinical progression including 52% of patients receiving paclitaxel after single agent cisplatin and 69% of patients receiving platinum after single agent paclitaxel. Early termination of the therapy was observed most frequently in the single agent cisplatin arm and was mostly due to toxicity. Regarding toxicity and efficacy, the authors concluded that "on the basis of patient convenience and cost benefit, combination platinum and paclitaxel should remain the standard of care until further studies indicate otherwise".

Another trial (the 3rd International Collaborative Ovarian Neoplasm Study—ICON 3) compared either carboplatin as a single agent or cisplatin-doxorubicin–cyclophosphamide to carboplatin–paclitaxel [31]. Although not yet available as a full paper, this trial has raised the question of whether carboplatin given as a single agent is still acceptable as a standard treatment. The presented interim analysis reported no significant difference in overall survival between all treatment arms. However, several questions remained open. The results of ICON 3 showed a remarkable heterogenicity when comparing the subgroups recruited from the different countries (Switzerland, Scandinavia, Italy and England). Furthermore, subgroups according to the International Federation of Gynecology and Obstetrics (FIGO) stage or postoperative tumour residuals did not show conclusive results. In addition, results in centres recruiting only few patients significantly differed from those obtained in centres with more patients. In conclusion, final results and detailed publication of this trial should be awaited before drawing any conclusions. Until then, platinum–paclitaxel will remain the accepted standard first-line treatment in the majority of countries.

6. Second-line therapies

With regard to the efficacy of second-line therapy in advanced ovarian cancer, essentially two groups of patients should be differentiated according to their prognosis:

1. Patients with platinum-refractory ovarian cancer: lack of response or progression within 6 months of cessation of primary therapy containing platinum.
2. Patients with a (suspected) platinum-sensitive ovarian cancer responding to primary therapy and a therapy-free interval of at least 6 months after primary therapy.

There is no established standard treatment for patients suffering from platinum-refractory ovarian cancer. Among others, paclitaxel, topotecan, gemcitabine, liposomal doxorubicin and etoposide have shown activity in this population of patients. Responses in approximately 20% of patients can be expected, but the response duration is usually short and rarely exceeds 12 months. Patients who had 'sensitive recurrent disease', i.e. a progression-free interval of over 12 months, may respond to a re-challenge with the initial treatment or should be retreated with a platinum-based therapy.

As well as these two main groups, two further patient subgroups can be identified:

1. Patients not receiving platinum as the primary therapy (an increasingly smaller group)
2. Patients failing therapy with paclitaxel–platinum.

The importance with respect to prognosis of patients failing paclitaxel primary therapy is unclear due to the relatively short time that paclitaxel has been available. Based on phase II data, there is as yet no 'drug of choice' for platinum–paclitaxel-resistant patients, although there are some indications that re-induction is an appropriate strategy for patients fulfilling the criteria of 'sensitivity' as quoted above.

6.1. Topotecan

Topotecan is one of the drugs globally registered for recurrent ovarian cancer. It is a semi-synthetic derivative of camptothecin and has activity in platinum-refractory ovarian cancer. A randomised phase III study compared topotecan (1.5 mg/m^2/day for 5 days every 21 days) with paclitaxel (175 mg/m^2 over 3 h every 21 days) in 226 patients who had failed one previous platinum regimen [32]. The objective response rates were 20.5% in the topotecan arm versus 13.2% in the paclitaxel arm ($P=0.138$). In patients with platinum-refractory disease, the response rates were 13.3 and 6.7% for topotecan and paclitaxel, respectively ($P=0.303$), while in patients with platinum-sensitive disease, the respective response rates were 28.8 and 20% ($P=0.213$). The median duration of response was 32 weeks for topotecan and 14 weeks for paclitaxel ($P=0.002$).

The final analysis of the results showed a similar trend with regard to response rate (20.5% versus 14.0%); median response duration was 25.9 versus 21.6 weeks with topotecan and paclitaxel, respectively, and median time to disease progression was 18.9 versus 14.7 weeks, respectively [33].

Three clinical studies have shown that response to topotecan was higher in patients who were platinum-sensitive (initially responded to platinum-based therapy and relapsed more than 6 months after treatment) (19.2–29%) than in those whose disease was platinum-resistant (early or interim relapse) or refractory (11.3–13.3%) [34–36].

6.2. Gemcitabine

Gemcitabine is an analogous substance of the natural deoxycytidine and causes false nucleotide DNA elongation, which leads to a break in the DNA string and cell death through apoptotic mechanisms. Through an additional action, DNA repair enzymes are inhibited and repair mechanisms disturbed. Furthermore, it leads to competitive inhibition of DNA polymerase [37].

The efficacy of gemcitabine in ovarian carcinoma has been evaluated in various phase II trials. In a multinational, European phase II study, gemcitabine was administered on days 1, 8 and 15 of a 28-day cycle (800–1250 mg/m^2) [38]. In 19% of patients, a partial response occurred with a median duration of 8.1 months (range: 4.4–12.5 months) and the median survival was 6.2 months (range: 0.2–50.6 months). Another trial included 36 evaluable patients and showed a response rate of 22%. The median survival time in this study was 6.7 months and the tumour response averaged 11.1 months [39]. A third study evaluated gemcitabine in 38 patients resistant to platinum and paclitaxel. 4 patients with platinum resistance were partial responders. From the 27 patients who had been pretreated with paclitaxel, 22 were analysed for response. Three achieved a partial response and another three maintained stable disease [40].

6.3. Liposomal doxorubicin

Liposomal doxorubicin is a novel drug formulation with a prolonged circulation time and preferential extravasation at tumour sites. As second-line therapy liposomal doxorubicin has been evaluated in phase II and III studies. Phase II data ($n=35$) on the drug at a dose of 50 mg/m^2 every 3 weeks in patients with platinum- and paclitaxel-resistant disease produced an overall response rate of 26% and a median time to progression of 20 months [41]. No cardiotoxicity or

alopecia was reported and only 3 patients experienced delays in dosing because of myelosuppression. Dose-limiting toxicity appeared to be grade 3 hand–foot syndrome. Subsequent studies have changed the dosing schedule to 50 mg/m^2 every 4 weeks.

A phase III study has recently been completed comparing liposomal doxorubicin with topotecan in platinum-sensitive and platinum-resistant patients. Patients were randomised to receive a 1-hour infusion of liposomal doxorubicin 50 mg/m^2 every 4 weeks or topotecan 1.5 mg/m^2/day as a 30-min infusion for 5 consecutive days every 3 weeks [42]. An interim analysis shows the following results for liposomal doxorubicin and topotecan, respectively:

- Objective Response: 20.3% versus 16.8%
- Complete Response: 4.2% versus 4.2%
- Partial Response: 16.1% versus 12.6%
- Median time to progression: 157 days versus 143 days
- Median survival: 462 days versus 394 days.

The interim analyses show similar efficacy between liposomal doxorubicin and topotecan across all efficacy endpoints.

Toxicity (grade 3/4) results for liposomal doxorubicin versus topotecan were as follows:

Neutropenia:	12% versus 71%
Anaemia:	5% versus 33%
Thrombocytopenia:	1% versus 35%
Palmar-plantar erythrodysesthesia:	25% versus 0
Alopecia	0 versus 8%

Discontinuations due to adverse events occurred in 14 liposomal doxorubicin patients (4 to palmar-plantar erythrodysesthesia) and 16 topotecan patients (5 due to sepsis). There were two treatment-related deaths with topotecan, but none with liposomal doxorubicin treatment.

The authors of this study concluded that the differentiated safety profile combined with the clinically equivalent efficacy supports the role of liposomal doxorubicin in patients who fail first-line platinum-based chemotherapy.

Similar results were produced in subgroup analyses of patients sensitive or resistant to the first-line platinum therapy.

6.4. Oral etoposide

A study by the GOG demonstrated significant activity of etoposide in patients with platinum-resistant or platinum-sensitive ovarian cancer [43]. The objective response rate to a regimen involving a starting dose of 50 mg/m^2 for 21 days was 26.8% (complete response: 7.3%; partial response: 19.5%) in platinum-resistant disease ($n=41$) and 34.4% (complete response: 17.2%; partial response: 17.2%) in platinum-sensitive disease ($n=29$). Grade 3 and 4 neutropenia occurred in 20 and 25% of the patients, respectively; grade 3–4 anaemia was reported in 13% of patients. Furthermore, etoposide as single agent therapy has been shown to be effective even in platinum and paclitaxel pretreated patients in another trial [44].

7. Conclusions

Considerable progress has been gained by optimising first-line chemotherapy for ovarian cancer. Responses are achieved in the majority of patients receiving the standard regimen of platinum and paclitaxel. Furthermore, a substantial increase in median survival and progression-free interval have been achieved. Nevertheless, at least half of all patients will relapse and ultimately die of their disease. Re-challenge with platinum-based regimens is a commonly used treatment in patients with long treatment-free intervals (so-called platinum-sensitive disease). In contrast, no standard treatment for early relapsing ovarian cancer has been established. Even the most active drugs achieve responses in only a minority of patients and the response duration is commonly short. Treatment for these patients is strictly palliative and should take toxicity and quality of life issues very seriously. Among others, etoposide, gemcitabine, topotecan and liposomal doxorubicin are appropriate therapies for refractory ovarian cancer after platinum-paclitaxel first-line therapy. Paclitaxel might also be an option if it has not been included in the first-line therapy in countries where single agent platinum is still regarded as the appropriate standard chemotherapy. However, increased effort is mandatory to improve the second-line treatment of ovarian cancer.

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