Controversies in chemotherapy — what is standard treatment?

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Introduction

Ovarian carcinoma is the sixth most common cancer in women worldwide and is the principal cause of death from gynaecological malignancy in Western Europe and North America. IARC (International Agency for Research on Cancer) estimates for the year 2000 indicated a worldwide incidence of 202,520 new cases and 124,381 deaths. In 1976, the SEER (Surveillance, Epidemiology, and End Results) registry reported a 5-year survival rate for all stages of 38%; by 1997, this percentage had improved to 52%, a reflection of the improvements in the treatment and care of women with ovarian cancer.

Primary treatment for all stages of the disease consists of surgery, typically including a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and lymphadenectomy, with cytoreductive intent. The 5-year survival of patients with early stage disease is quite good, but unfortunately the majority of ovarian cancer patients, between 75% and 80%, present with advanced stage disease and experience a 5-year survival rate of only 20% [1]. These women are therefore treated with chemotherapy following surgery.

Chemotherapy can vary from one clinician to another and certainly varies across different countries. However, in any part of the world first-line chemotherapy is based on two premises which are supported by the results of prospective randomised clinical trials and are universally accepted: (1) platinum should represent the core of treatment and should be given at adequate doses, and (2) cisplatin and carboplatin are equally effective.

Major controversies now focus on whether single-agent platinum could represent optimal initial therapy for advanced ovarian cancer and, if not, which are the appropriate patterns and which schedule should be adopted (sequential versus combination, first line followed by consolidation). To answer these questions, the most reliable information results from randomised controlled trials and from systematic meta-analyses which have been conducted and published during the past years.

Primary chemotherapy

Single agent vs. combination

Ovarian cancer was one of the first solid malignant tumours to be treated by chemotherapy, and single alkylating agents were used until the mid-1970s [2]. Since the introduction of cisplatin at the end of the 1970s, this drug has become the mainstay of treatment for women with advanced disease. At the beginning of the 1990s, despite 50 randomised trials conducted in advanced ovarian cancer patients, the results were mostly inconclusive and several questions concerning optimal first-line chemotherapy remained unsolved. The Advanced Ovarian Cancer Trialists Group (AOCTG) conducted and published five meta-analyses, incorporating data on individual patients from 45 randomised trials — including a total of nearly 10,000 patients — and helped clarify the role of cisplatin, its analogue carboplatin and the anthracycline doxorubicin in this disease. Although no firm conclusions were reached, these meta-analyses suggested that in terms of survival (1) immediate platinum-based therapy was better than non-platinum-based therapy, (2) platinum in combination was better than single-agent platinum when used at the same dose, and (3) there was no difference between carboplatin and cisplatin, either as single agents or in combination regimens [3]. Two further meta-analyses focused on the role of doxorubicin. The first [4] included 6 trials comparing the combination of cyclophosphamide and cisplatin (CP) to the same drugs plus doxorubicin (CAP). The meta-analysis of these trials, based on individual patient data, showed that CAP yielded a higher rate of tumour response, as well as a longer survival, than CP, providing an estimated absolute improvement in 2-year and 5-year survival of 6%

(from 50% to 56% and from 20% to 26%, respectively). The second meta-analysis [5] focused on a wider range of doxorubicin-based regimens and confirmed their advantage in first-line treatment over non-anthracycline-containing regimens. Despite these results, which seemed to warrant the use of anthracyclines in the first-line treatment of ovarian cancer, a subsequent prospective randomised trial, ICON2 did not confirm that the three-drug regimen was the most effective treatment for women with advanced ovarian cancer [6]. In ICON2, which compared adequate doses of carboplatin against CAP, carboplatin was chosen for the single-agent group, because of its equivalent efficacy to cisplatin, but improved patient convenience and decreased risk of non-haematological toxicity. Moreover, the optimal dose can be individually determined using the Calvert formula based on estimated renal clearance and targeted area under the curve (AUC) for concentration of carboplatin over time. With 1526 patients randomised, ICON2 showed reliably that there was no difference between these two regimens in terms of progression-free survival and overall survival, and thus, the use of single-agent carboplatin at AUC 6 could represent an acceptable alternative for initial management of patients with advanced ovarian cancer. A paper, very recently published, tried to explain the difference observed between the results of the meta-analysis and those of ICON2 [7]. By using a proportional hazards model, fitted to the meta-analysis data, expected survival curves were constructed for each treatment arm of the ICON2 trial, taking into account patient prognostic features in both the meta-analysis and ICON2. The expected survival curves were then compared with the ones actually observed in ICON2. While there was relatively little difference between the observed and expected curves in the CAP arm, there was a large difference between the expected (using the CP arm of the meta-analysis) and the observed curves in favour of carboplatin arm of the ICON2 trial. These analyses provide highly suggestive evidence that the difference between the survivals in ICON2 and in the meta-analysis is related to the better results achieving with carboplatin alone at an optimally tolerated dose compared with CP at a cisplatin dose of 50 to 60 mg/mq. Despite the evidence from the meta-analyses and from ICON2, the CP combination has been considered "standard treatment" for several years, particularly in the USA.

The role of taxanes

In the early 1990s, paclitaxel was first tested in ovarian cancer. Four randomised trials have been completed comparing the combination of paclitaxel–platinum versus a platinum-based control arm [8–11] (Table 1). In two of these trials, GOG111 (Gynecologic Oncology Group) and OV10 (European–Canadian Intergroup Trial), significant differences in outcome were observed favouring the paclitaxel + cisplatin combination versus an identical cisplatin + cyclophosphamide "standard arm". By contrast, the taxane–platinum combination failed to improve both survival and disease-free survival when compared to single-agent treatments with either cisplatin (GOG132) or carboplatin (ICON3). ICON3 is the first and only trial comparing paclitaxel plus carboplatin against carboplatin alone or a (non-taxane) cisplatin-based control arm. ICON3 included 2074 patients enrolled between 1995 and 1998 who were randomised to receive either single-agent carboplatin (AUC6) or CAP (cyclophosphamide–doxorubicin–cisplatin) against a combination of carboplatin and paclitaxel. The last analysis performed with a median follow-up of 51 months showed no evidence of a difference in overall survival between paclitaxel plus carboplatin and control (hazard ratio 0.98, 95% C.I. 0.87–1.10, $P = 0.74$). The median overall survival was 36.1 months on paclitaxel plus carboplatin and 35.4 months on control. Progression-free survival curves showed no evidence of a difference between the groups, with a median progression-free survival of 17.3 months on paclitaxel plus carboplatin and 16.1 months on control. There was evidence that paclitaxel plus carboplatin was more toxic than carboplatin alone, in particular causing more alopecia, fever and sensory neuropathy. Comparing CAP and paclitaxel plus carboplatin, CAP was associated with increased fever, while paclitaxel plus carboplatin caused greater sensory neuropathy.

Thus, the results of ICON3 suggested that single-agent carboplatin and CAP are safe and effective first-line treatments for women requiring chemotherapy for

Table 1
Trials comparing paclitaxel/platinum combinations with a platinum-based control treatment

Study	No. of patients	No. of events	HR
GOG111	410	313	PFS 0.66S 0.61
GOG132	424	354	PFS 1.06S 0.99
OV10	680	542	PFS 0.74S 0.73
ICON3 – J vs TJ	1421	896	PFS 0.92S 0.98
ICON – CAP vs TJ	653	397	PFS 0.95S 0.99

HR, hazard ratio; PFS, progression-free survival; S, survival; TJ, paclitaxel/carboplatin; J, carboplatin; CAP, cyclophosphamide, doxorubicin, cisplatin.

ovarian cancer, with carboplatin being the preferred treatment because of its better toxicity profile.

The results of ICON3 appear to contradict the earlier positive results seen for paclitaxel and cisplatin in the GOG111 and European–Canadian Intergroup trials. They appear to be more in accordance with those of GOG132, which compared paclitaxel+cisplatin against cisplatin alone.

Several explanations for these unexpected results have been proposed, including: the statistical explanation with false-positive results in GOG111 and the Intergroup trial or false-negative results in GOG132 and ICON3 trials; the extent of crossover to the taxane-based treatment in the control arm; the experimental arm explanation with the use of carboplatin instead of cisplatin; the type of treatment used in the control arm; the different patient population included in the different trials.

The large effect seen in GOG111, which was maintained at the 5-year follow-up, excludes the possibility of a type I error. On the other hand, ICON3 enrolled 2074 patients and the chance of missing an effect of paclitaxel as large as that seen in GOG111 is only 1%.

The high crossover to taxanes before and after progression has been a popular interpretation claimed as the main reason for the results of GOG132. However, since the survival results from OV10 are very similar to those of GOG111, despite a high proportion of crossover to paclitaxel on progression (47%), it is the early crossover (before clinical progression) that is responsible. In this respect, in GOG132, the percentage of crossover to paclitaxel reported in the cisplatin arm is only 24% (47% received other treatment before progression and 52% of these patients received paclitaxel). Moreover, in ICON3 the crossover to paclitaxel in the control arm was only 30% on progression and 6% before clinical progression (Table 2).

The crossover theory cannot therefore completely explain the discordant results of the 4 trials.

The experimental arm in ICON3 differs from that of the other trials, because carboplatin was used instead of cisplatin and because paclitaxel was given at the dose of 175 mg/mq in a 3-hour infusion. However, convincing evidence from randomised studies is now available that carboplatin plus paclitaxel in a 3-hour infusion can substitute for cisplatin plus paclitaxel in a 24-hour infusion without abrogation of activity [12–14].

The control arm is also different in ICON3 and GOG132 compared to GOG111 and the Intergroup trial. The combination cisplatin + cyclophosphamide has never been considered "standard treatment" by the ICON collaborators mainly because of the results of two meta-analyses (previously discussed) showing a possible advantage for CAP, but not for CP in the first-line treatment of patients with ovarian cancer. Two control arms were allowed in ICON3, CAP or carboplatin, but the choice had to be specified before randomisation. The choice of control arms was allowed throughout the course of ICON3 as the mature results of ICON2 reliably showed no clear evidence of a difference between carboplatin and CAP in terms of progression-free survival and overall survival.

GOG132 used single-agent cisplatin at 100 mg/mq as the control regimen.

Both GOG111 and the Intergroup study used cyclophosphamide plus cisplatin as standard treatment.

The control arm theory would suggest that the combination of cisplatin plus cyclophosphamide as given in GOG111 and Intergroup trial may have been inferior to the control arm used in ICON3 and GOG132 of high doses of single-agent platinum. If we exclude the possibility of a detrimental interaction between cyclophosphamide and cisplatin, it can be suggested that the main contribution of the alkylating agents is to the toxicity of the regimen, causing excessive treatment delay and dose reduction. Although there is no evidence of an improvement in survival with higher platinum dose intensity, the addition of cyclophosphamide to cisplatin may have

Table 2
Extent of crossovers in ICON3

	J	TJ	CAP	TJ
None	643 (77%)	341 (81%)	319 (82%)	168 (82%)
Carboplatin-based [a]	40 (5%)	11 (3%)	26 (7%)	9 (4%)
Cisplatin-based [a]	79 (9%)	36 (9%)	17 (4%)	12 (6%)
Taxane-based	31 (4%)	17 (4%)	8 (2%)	10 (5%)
Other chemotherapy (no platinum or taxane)	12 (1%)	7 (2%)	5 (1%)	0 (0%)
Non-chemotherapy (surgery, radiotherapy, hormonal)	24 (3%)	10 (2%)	11 (3%)	7 (3%)
Treatment given, but unspecified	9 (1%)	1 (<1%)	1 (<1%)	0 (0%)

T, paclitaxel; TJ, paclitaxel/carboplatin; J, carboplatin; CAP, cyclophosphamide/doxorubicin/cisplatin.
[a] Not including taxane.

Table 3
Compliance to cisplatin dose and schedule in OV10 trial

	Cyclophosphamide + cisplatin ($n = 336$)	Paclitaxel + cisplatin ($n = 339$)
Dose reduction	72 (21.4)	102 (30.1)
Dose delay	201 (59.8)	123* (36.3)
Median cisplatin dose intensity, mg/m^2 per week		
Theoretical	25	25
Achieved	22.4	24.4*
Median cumulative cisplatin dose, mg/m^2 (25th–75th percentiles)	450 (420–465)	450 (382–488)
No. (%) of patients receiving 90% of theoretical cisplatin dose	165 (49.1)	254 (74.9)

* $P < 0.001$.

induced a dose reduction below the minimum standard. Available data from the OV10 study clearly indicate a statistically significant increase in dose-delay and decrease in median cisplatin dose intensity for the cyclophosphamide–cisplatin group compared with the paclitaxel–cisplatin arm (Table 3).

As previously mentioned, the comparison between the expected and observed survival curves in the meta-analysis and ICON2, showed quite clearly that CP may be inferior to both carboplatin alone and CAP [7]. Thus, the lack of benefit in ICON3 may be because the control group in this trial was superior to the control group used in the two previous trials. The expected survival approach may provide valuable insight in the interpretation of discrepant results between the different randomised trials testing the role of taxanes in ovarian cancer.

Finally, a meta-analysis with individual patient data has been conducted to better clarify the issue of paclitaxel in the frontline therapy of advanced ovarian cancer [15]. By simply pooling the results of four trials, a benefit to paclitaxel/platinum becomes apparent, which is smaller than that originally expected on the basis of GOG111, but still statistically significant. However, the authors point out that there is a clear statistical heterogeneity in these results and there is therefore strong evidence that these trials do not provide answers to the same question. By examining four hypotheses which have been proposed to explain heterogeneous results of the four trials, the authors demonstrate that only one of the proposed explanations appears to be consistent with the data: differences in the efficacy of the control arms is the only plausible explanation for the conflicting results of these trials.

Second-line therapy

Appropriate salvage therapy is based on the timing and nature of the recurrence and the extent of prior chemotherapy. Surgical resection should be considered in patients who relapse following long-term remission, and especially with isolated recurrences and good performance status. In the other cases, the major aim is to deliver active second-line chemotherapy. More critical is the distinction between patients with drug-sensitive or drug-resistant tumours at the time of relapse. In general, patients who progress during treatment or have stable disease in response to initial platinum-based therapy or who relapse within 6 months are considered to have "platinum-refractory" disease. Patients who develop recurrent disease at intervals of greater than 6 months are defined as "platinum-sensitive". This division, used with regard to platinum-based therapy, also applies to chemotherapy in general.

Drug-sensitive tumours

Patients experiencing a durable response to platinum induction chemotherapy have a high probability of responding again to platinum-containing compounds. The choice between cisplatin and carboplatin should be based on an agent used in prior therapy, its tolerability and residual toxicity. Seltzer et al. [16] were the first to demonstrate a favourable response rate (72%) after rechallenge with cisplatin-containing salvage treatments in this subset of patients. Markman et al. [17], in a retrospective study, showed that the frequency with which response was seen increased as the platinum-free interval increased (up to 77% for intervals >24 months). One important question is whether combination chemotherapy could produce better results than single agents in patients with recurrent platinum-sensitive ovarian cancer. Two Italian prospective randomised studies have been published so far and are presented in Table 4. The first study failed to demonstrate an advantage in both response rate and survival for patients treated with carboplatin/epirubicin over the control group receiving carboplatin alone [18]. The second trial compared

Table 4
Randomised trials in patients with recurrent platinum-sensitive ovarian cancer

Author [Ref. no.]	Regimen	No. pts.	RR (%)	Median PFS (months)	Median OS (months)
Bolis et al. [18]	Carboplatin	95	55	14	24
	Carboplatin/epirubicin	95	58	18	28
Cantù et al. [19]	Paclitaxel	50	45	9	25.8
	CAP	47	55	16	34.7

RR, response rate; PFS, progression-free survival; OS, overall survival; CAP, cyclophosphamide/adriamycin/cisplatin; pts, patients.

Table 5
Phase II studies of carboplatin/paclitaxel in patients with recurrent platinum-sensitive ovarian cancer

Author [Ref. no.]	Median TFI (months)	No. of patients	RR (%)	Median PFS (months)	Median OS (months)
Gronlund et al. [27]	16	43	84	10	13
Rose et al. [28]	10	25	90	9+	10+
Dizon et al. [21]	>6	97	70	–	66

TFI, treatment-free interval; PFS, progression-free survival; OS, overall survival; RR, response rate.

paclitaxel with the three-drug regimen CAP [19]. There was a trend towards a higher response rate, a longer time to progression and a longer survival for the combination regimen, but the study lacked the statistical power to reach a firm conclusion. In any case, the question of single-agent versus combination was not answered since the control arm of this study was paclitaxel and non-single-agent platinum.

Among the active combination regimens used in platinum-sensitive patients, carboplatin/paclitaxel has shown interesting activity in several phase II studies with response rates up to 90% [20,21] (Table 5). In order to determine whether the combination carboplatin/paclitaxel should be used at first relapse after platinum-based chemotherapy, two pragmatic trials were designed. ICON4 (coordinated by the Medical Research Council (MRC) and Mario Negri Institute (IRFMN)) and OVAR2.2 (Arbeitsgemeinschaft Gynaekologische Onkologie (AGO)) were two parallel randomised trials comparing a minimum of 6 cycles of platinum chemotherapy (Plat) versus paclitaxel plus Plat (Pac–Plat) in patients relapsing with a treatment-free interval of $\geq$6 months (MRC/AGO), or $\geq$12 months (IRFMN). 802 patients were randomised between 01/96 and 03/02. The last chemotherapies received were carboplatin (34%), cisplatin (30%), and carboplatin plus taxane (36%). By October 2002, with a median follow-up of 34 months, the hazard ratio (HR) for progression is 0.77 and the HR for survival is 0.77 in favour of Pac–Plat ($P = 0.006$). There was no evidence that the effect of Pac–Plat is larger or smaller in any subgroups (randomising group, time to relapse, number of previous lines of chemotherapy, type of prior chemotherapy, age and performance status). These results suggest that Pac–Plat improves survival and PFS in patients with "platinum-sensitive" relapsed ovarian cancer compared with Plat alone.

One question to ask is: why is there an additive effect of platinum and paclitaxel demonstrated in the second line (ICON4), but not in the first line (ICON3). However, the two populations are quite different. Although women in ICON4/AGO-OVAR2.2 should be considered "platinum-sensitive", their disease did relapse after first-line platinum-based chemotherapy and therefore is still likely to be less sensitive to platinum than chemo-naive patients. Paclitaxel may compensate for a relative lack of platinum sensitivity in this group. A possible interpretation may be that initial treatment with platinum is very effective (in about 2/3 of patients), but unless a near eradication of tumour cells is achieved, a *p*53-mutated subset will regrow [22]. Secondary treatment with taxane, which is known to be more active in *p*53-mutated cells, could theoretically make a greater impact in this subset of patients. Such molecular questions need to be explored further.

Drug-refractory tumours

Salvage chemotherapy in platinum-refractory patients typically results in low response rates and short survival. Rechallenge with platinum-based treatments produces a response rate of about 10% [23,24]. Drugs

Table 6
Cumulative response rate of several drugs used in patients with platinum-free interval <12 months

	No. of studies	No. of patients	Cumulative response rate
Topotecan	8	702	18% (13–33)
Paclitaxel	13	1914	23% (0–71)
Docetaxel	4	189	32% (30–46)
Liposomal doxorubicin	6	363	16% (0–25)
Gemcitabine	3	69	20% (15–28)
Doxorubicin	7	258	15% (0–53)
Cisplatin	6	144	31% (5–32)

with demonstrated activity in paclitaxel–platinum refractory disease include topotecan, docetaxel, oral etoposide, liposome encapsulated doxorubicin, gemcitabine, ifosfamide and hexamethylmelamine. Table 6 presents a summary of response rates achievable with some of these agents in a platinum-refractory population. It can be seen that durable response to salvage chemotherapy is rare and cure almost impossible. Since the main goal of salvage therapy in this group of patients is palliation, one should pay particular attention to the side effects of the drug utilised. Patients who have a good PS (performance status) and are motivated to receive further treatment should be considered for experimental trials with new drugs. Perhaps the most interesting role of second-line chemotherapy is in identifying new potentially active drugs, which can then be used upfront.

Ongoing research

As previously discussed, despite modern cytoreductive surgery and platinum-based chemotherapy, long-term survival for patients with advanced ovarian cancer remains disappointing and new strategies are urgently needed. Prof. Kaye discusses the future perspectives elsewhere in this volume. I will report here on ongoing or recently closed clinical trials addressing new questions in front-line chemotherapy.

Main strategies have focused on improving outcome (addition of newer agents, intraperitoneal therapy) and tolerability (substitution of carboplatin, substitution of docetaxel).

The integration of newer agents such as topotecan, gemcitabine and liposomal doxorubicin (Doxil) has a solid basis in preclinical models. However, the addition of a third drug to platinum/paclitaxel may lead to increased and intolerable toxicity.

The German–French AGO–GINECO Intergroup trial OVAR5 (1997–1999) evaluated the role of anthracyclines in addition to platinum/paclitaxel. They randomised 1200 patients to receive either TC: carboplatin (AUC 5)/paclitaxel (175 mg/mq); or the same regimen plus epirubicin 60 mg/mq (TEC). An interim analysis was presented at ASCO 2001 [25]: the triple-drug regimen induced significantly more myelosuppression and emesis/nausea. Responses were slightly higher in the TEC arm and progression-free survival longer in the TEC-treated patients. The advantage seems particularly evident in patients with minimal residual disease. The overall survival analysis is awaited in 2003.

A second trial with a similar design has been conducted by the European–Canadian group, which randomised 888 patients from 3/99 until 8/2001 [26]. Also in this trial the clinical complete response rate was slightly higher with the 3-drug regimen, but final data on progression-free survival and overall survival are still awaited.

Another triple-drug regimen under investigation includes gemcitabine in association with carboplatin/paclitaxel. The AGO–GINECO–NSGO phase III trial OVAR9 started late in 2002 and compares TC with a triple-drug regimen of TC plus gemcitabine as first-line treatment of patients with advanced ovarian cancer. This trial will recruit patients until 2003/2004.

The GOG has conducted a series of phase I pilot studies to define new combinations suitable for phase III trials. Most triplet regimens have exhibited increased bone marrow toxicity and have led to decreased individual drug doses. This raises the question about compromised tumour efficacy. A different strategy consists of the utilisation of sequential single agents, which would allow the administration of full doses, but eliminates the possibility of synergistic effects. The use of sequential doublets allows the administration of adequate doses of individual drugs, but limits the number of cycles with each agent.

The ongoing phase III Gynecologic Cancer Intergroup (GCIG) trial (GOG0182–ICON5) includes 4 experimental arms to evaluate the addition of three new drugs (topotecan, gemcitabine, and pegylated (PEG) liposomal doxorubicin) using two different strategies (sequential doublets and triplet combinations). The control arm is represented by carboplatin/paclitaxel. This 5-arm trial is expected to accrue 4000 patients: an event-triggered interim analysis based on progression-free survival will allow the closure of arms lacking promis as well as the selection of promising arms for full accrual, possibly enhancing the study's power.

Summary

This paper discusses some current controversies regarding optimal first-line treatment for patients with advanced ovarian cancer.

Despite improvements seen in median and overall survival using platinum-based chemotherapy, long-term survival rates for patients with advanced epithelial ovarian carcinoma remain disappointing and several efforts have been made recently to develop more effective primary therapy. In the early 1990s, paclitaxel was first tested in ovarian cancer. In GOG111, the cisplatin+paclitaxel regimen was judged to be superior compared with the platinum–cyclophosphamide control arm, with an improvement of overall response rate, median progression-free interval and overall median survival. These favourable data were confirmed by the OV10 trial. In contrast, in a further GOG trial (GOG132), there was no difference in survival between cisplatin alone and the combination of paclitaxel and cisplatin. ICON3, the first and only trial comparing paclitaxel plus carboplatin against carboplatin alone or a (non-taxane) cisplatin-based control arm, again failed to demonstrate any advantage for the platinum–taxane arm, either in progression-free survival or in overall survival. The results of ICON3, in accordance with the GOG132 study, appear to contradict the earlier positive results seen for paclitaxel and cisplatin in the GOG111 and OV10. Several hypotheses have been raised to explain this discrepancy including differences in the extent and timing of crossover to taxanes in the control group, differences in the type of patients included, differences in the efficacy of research regimens or in the efficacy of the control regimens. A meta-analysis with individual patient data demonstrated a substantial heterogeneity between groups using different control arms, possibly indicating that the cyclophosphamide/cisplatin regimen used in the two "positive" trials may be less effective than the control regimen used in the other trials. It will be almost impossible to achieve an agreement on these proposed explanations. However, this meta-analysis provides evidence that the introduction of taxanes can lead to a survival advantage vastly inferior to that expected after the results of the GOG111 and OV10 trials.

Ongoing research is focusing on the addition of a third drug to platinum/taxane in regimens consisting of triplets or sequential doublets.

Determining the characteristics to define the patient population with relapse is important to evaluate the therapeutic options with the greatest likelihood of success. Appropriate salvage therapy is based on the timing and nature of the recurrence and the extent of prior chemotherapy. The main objectives of salvage chemotherapy include (1) improvement in quality of life and symptoms, (2) tumour load reduction and survival advantage, and (3) evaluation of potentially active new drugs to be included in first-line treatment.

Since the goal is palliation in most cases, monotherapy is generally indicated. Unfortunately, durable responses to salvage chemotherapy are rare and cure almost impossible. The sequential use of the agents currently available for salvage treatment in monotherapy may transform ovarian cancer into a chronic disease and increase the length of survival. Perhaps the most interesting role of second-line chemotherapy is to identify, new potentially active drugs, which can then be used upfront.

For patients with platinum-sensitive disease, it was unclear, until recently, whether the platinum-based combination was superior to single-agent platinum at the time of relapse. The recent results of ICON4 seem to indicate an advantage in both survival and progression-free survival for patients with relapsing platinum-sensitive ovarian cancer treated with the combination platinum/taxane compared with conventional platinum-based chemotherapy.

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