Evidence-based chemotherapeutic management of potentially platinum-sensitive recurrent ovarian cancer

The results of several excellent Phase III randomized trials have helped establish appropriate management of patients with recurrent (potentially platinum sensitive) epithelial ovarian cancer. Data suggest that combination platinum-based chemotherapy is superior to single-agent platinum treatment, but the overall utility of a combination regimen versus the planned sequential administration of a platinum agent plus a second (or third) drug known to be biologically active in ovarian cancer remains to be determined. Future studies will hopefully define optimal treatment in this clinical setting more critically, including the role of therapy based on unique molecular profiles demonstrated in individual patients' tumors.

KEYWORDS: carboplatin ▪ chemotherapy ▪ gemcitabine ▪ liposomal doxorubicin ▪ ovarian cancer ▪ paclitaxel

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Despite the high objective response rate (70–80%) of advanced epithelial ovarian cancer to platinum-/taxane-based chemotherapy the majority of patients treated for this condition ultimately experience recurrence of the disease process [1–3]. At the time of documented progression of the malignancy, these individuals are candidates to receive a second-line management strategy.

It is well recognized that ovarian cancer patients who experience evidence of a favorable biological and clinical effect from their initial chemotherapy regimen may respond again to the same or a similar platinum-based treatment program [4–8]. Retrospective data have also revealed that the likelihood that an individual patient's cancer will exhibit tumor shrinkage in the second-line setting is influenced substantially by the duration of time between the completion of the primary chemotherapy and evidence of disease progression (so-called 'platinum-free' or 'treatment-free' interval) [6–9]. For example, in one reported series, the objective response rate to second-line platinum was 33 and 59% for patients with platinum-free intervals of 7–12 and over 24 months, respectively [6].

However, while the importance associated with the administration of platinum in the recurrent setting has been established, including quite limited Phase III trial data suggesting the superiority of a platinum-containing strategy compared with nonplatinum-based treatment in this patient population (Table 1) [10], the issue of the optimal platinum regimen to be employed in recurrent ovarian cancer remains an open and evolving question.

In this chapter, currently available peer-reviewed published or publicly discussed (abstracts presented at a major oncology meeting) evidence-based (Phase III trial) data that address the chemotherapeutic management of recurrent (treatment-free or platinum-free interval of ≥6 months) epithelial ovarian cancer will be highlighted.

Platinum without paclitaxel versus platinum plus paclitaxel

The ICON4 study, published in 2003, demonstrated the superiority (improved progression-free and overall survival) of a platinum plus taxane combination chemotherapy strategy compared with the administration of a platinum regimen without a taxane in the management of recurrent ovarian cancer (Table 2) [11].

Unfortunately, the trial had a rather complex design that precludes a simple description of either its treatment arms or conclusions. Patients with a treatment-free interval of over 6 months following the completion of a platinum-based primary cytotoxic regimen were randomized to receive either platinum-based chemotherapy without paclitaxel ('control arm') or platinum-based chemotherapy with paclitaxel ('experimental arm').

Thus, the specific platinum regimen to be utilized and the individual drug concentrations to be delivered in either of the treatment arms were not specified. In fact, approximately 70% of patients in the control arm received single-agent carboplatin, and 80% of women randomized to the experimental arm were treated with the combination of carboplatin plus

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Table 1. Platinum versus nonplatinum chemotherapy in recurrent ovarian cancer.

Type of chemotherapy	Clinical complete response rate (%)	Median progression-free survival (months)*	Median overall survival (months)**
Cyclophosphamide/ doxorubicin/platinum (n = 47)	30	15.7	34.7
Paclitaxel (n = 50)	17	9	25.8

**p = 0.038; hazard ratio: 0.60.*
***p = 0.043; hazard ratio: 0.58.*
Data taken from [10].

paclitaxel [11]. However, a minority of patients in the control arm received either single-agent cisplatin or a platinum-based nonpaclitaxel-containing combination program, and in the experimental arm a small group of individuals were treated with cisplatin plus paclitaxel. It should also be noted that 57% of patients entered into this second-line trial had not been treated with paclitaxel as a component of their primary treatment program.

A total of 802 patients entered this study, which revealed at its conclusion that the platinum plus paclitaxel regimen was associated with both superior progression-free (hazard ratio [HR]: 0.76) and overall survival (HR: 0.82), compared with the nonpaclitaxel-containing approach [11]. Another, perhaps even more relevant manner in which to express the benefits of the platinum-based paclitaxel-containing combination strategy is that the 2-year overall survival for patients treated with this approach was 57 versus only 50% for patients randomized to treatment without the taxane.

While examination of the outcomes of study subgroups (e.g., platinum-free interval of 6–12 months or over 12 months; previous treatment with paclitaxel or no prior exposure to paclitaxel) is always fraught with hazard, owing to limited patient numbers in the individual categories, there was no valid evidence that a particular group failed to achieve an element of benefit from delivery of paclitaxel with platinum in the second-line setting [11].

However, this study also provided quite poignant data regarding the potential negative impact of clinically relevant toxicity that may accompany second-line ovarian cancer treatment, and the cost to the patient associated with the demonstrated gain in survival. Peripheral neuropathy, grade 2 or above, was reported in 20% of patients treated with the 'experimental' paclitaxel-containing approach versus only 1% in the control treatment arm [11].

This study, particularly the side-effect profile noted, raises an additional relevant issue for each of the trials to be discussed in this manuscript; that of the true superiority of a

Table 2. Phase III trials including platinum agents in recurrent ovarian cancer.

Treatment	Overall response rate (%)	Median progression-free survival	Median overall survival (months)	Ref.
Study 1 ICON4 (n = 802)				
Platinum-based (without paclitaxel)	54 (p = 0.06)	9 months (p = 0.0004; HR: 0.76)	24 months (p = 0.02; HR: 0.82)	[11]
Platinum-based (with paclitaxel)	66 (p = 0.06)	12 months (p = 0.0004; HR: 0.76)	29 months (p = 0.02; HR: 0.82)	[11]
Study 2 (n = 356)				
Carboplatin	30.9 (p = 0.0016)	5.8 months (p = 0.003; HR: 0.72)	17.3 months (p = 0.74; HR: 0.96)	[13]
Carboplatin plus gemcitabine	47.2 (p = 0.0016)	8.6 months (p = 0.003; HR: 0.72)	18 months	[13]
Study 3 (n = 61)				
Carboplatin	32 (p = 0.02)	8 months (p = 0.02)	18 months (p = 0.2)	[17,18]
Carboplatin plus pegylated liposomal doxorubicin	67 (p = 0.02)	12 months (p = 0.02)	31 months (p = 0.2)	[17,18]
Study 4 CALYPSO (n = 976)				
Carboplatin plus paclitaxel	Not reported	9.4 months (p = 0.005; HR: 0.821)	Not reported	[23]
Carboplatin plus pegylated liposomal doxorubicin	Not reported	11.3 months (p = 0.005; HR: 0.821)	Not reported	[23]

HR: Hazard ratio.

combination chemotherapy strategy in recurrent ovarian cancer versus the potential utility of the planned sequential administration of two (or more) biologically active agents in this clinical setting.

Thus, it may be asked, if the favorable impact on survival observed in the ICON4 study resulted from the delivery of a platinum agent and paclitaxel together, or simply the relatively early use (before disease progression) of both classes of biologically active drugs in the natural history of the cancer in individual patients. The hypothesis to be tested (hopefully in a future Phase III trial) is that the sequential administration of known active cytotoxic agents with overlapping clinically relevant toxicities (e.g., neuropathy, bone marrow suppression) will result in equivalent survival and a more favorable toxicity profile compared with combination chemotherapy.

While it must be acknowledged that this highly relevant question remains unanswered the results of a previously published Phase III trial that examined the administration of single-agent cisplatin, versus single-agent paclitaxel, versus the combination of cisplatin plus paclitaxel as primary chemotherapy of advanced epithelial ovarian cancer supports the potential utility of sequential drug administration in the setting of recurrent disease (Table 3) [12]. In this particular trial it is known that a large percentage of patients initially managed on the single-agent study arms 'crossed over' to the alternative study drug (i.e., single-agent cisplatin- and single-agent paclitaxel-treated patients subsequently received single-agent paclitaxel or cisplatin, respectively) even before documented disease progression, perhaps explaining the provocative observation of equivalent overall survival associated with all three study arms despite documented (and rather striking) differences in both the objective response rates and progression-free survivals between the two single cytotoxic agents [12].

Single-agent carboplatin versus carboplatin plus gemcitabine

A multicooperative group effort, headed by the Arbeitsgemeinschaft Gynakologische Onkologie (AGO) study group, compared the combination of carboplatin plus gemcitabine to single-agent carboplatin in recurrent ovarian cancer (platinum-free interval >6 months) (Table 2) [13]. This study, in contrast to the previously described ICON4 trial, precisely defined the treatment drugs, doses and schedules to be utilized in the two study arms.

A total of 356 women were randomized to treatment on this trial. The study revealed superior progression-free survival in favor of the combination regimen. Furthermore, the two-drug program was found to produce higher overall and clinically defined complete response rates. However, there was no difference in overall survival between the regimens.

It is not possible to provide a definitive explanation for the somewhat surprising difference in the observed outcome of this trial compared with the previously described ICON4 study, where a similar relative degree of improvement in progression-free survival (ICON4 study HR: 0.76; AGO study HR: 0.72) was able to be translated into a statistically significant impact on overall survival (ICON4 study HR: 0.82; AGO study HR: 0.96).

One possible rational explanation for the results is the observation that the large majority of patients (approximately 70%) in the AGO trial received 'third-line' chemotherapy following their completion of, or removal from, the study. Such treatment may have included a 'cross-over' to gemcitabine or the delivery of other anticancer agents with known activity in this clinical setting (e.g., pegylated liposomal doxorubicin or topotecan) [14]. The administration of biologically active 'third-line' therapy may have resulted in a favorable impact on overall survival for those women treated on the 'inferior' (single-agent carboplatin) study arm.

Table 3. Evidence for the relevant impact of subsequent treatment after completion of 'primary chemotherapy' of epithelial ovarian cancer (n = 648).

Treatment	Overall response rate (%)*	Median progression-free survival (months)**	Median overall survival (months)***
Paclitaxel (single agent)	42	11.2	26
Cisplatin (single agent)	67	16.4	30.2
Cisplatin plus paclitaxel	66	14.0	26.6

**p < 0.001, paclitaxel compared with cisplatin-containing regimens.*
***p < 0.001, paclitaxel compared with cisplatin-containing regimens.*
****p = 0.31, between treatment groups.*
Data taken from [12].

While only a hypothesis, existing evidence-based data support the potential effectiveness of third-line chemotherapy in this clinical setting (TABLE 4) [15].

As noted with the experimental arm of the ICON4 study, treatment with carboplatin plus gemcitabine was associated with greater risk of clinically relevant toxicity compared with the control arm, in this case bone marrow suppression (neutropenia, anemia and thrombocytopenia). While there was no difference in the treatment programs in the incidence of febrile neutropenia, patients managed with the combination program experienced a greater need for transfusions (red blood cells and platelets) and the use of bone marrow colony-stimulating agents.

As might have been anticipated based on the known toxicity profiles of the individual agents in the combination program, there was no difference in the incidence of clinically relevant nonhematologic side effects between the study regimens, most notably peripheral neuropathy.

As previously stated in the discussion of the results of the ICON4 trial, it remains unknown if the planned sequential delivery of carboplatin followed by gemcitabine might be equally effective in prolonging survival (both progression-free and overall), but also less toxic than that observed with the combined use of the agents.

One might also question if it is necessary to administer gemcitabine at a dose of 1000 mg/m^2 (day 1 and 8 of a 21-day cycle) since there is no convincing evidence that this concentration is required to maximize the drug's therapeutic effect (at least in the management of ovarian cancer), and a lower dose (in combination with carboplatin) will almost certainly be better tolerated (as regards the degree of anticipated bone marrow suppression). This point may be particularly relevant in individuals known to have experienced excessive bone marrow suppression during their first-line carboplatin-based ovarian cancer chemotherapy program. Clinicians encountering such patients may wish to consider modification in the gemcitabine dose when utilizing this combination regimen [16].

Carboplatin versus carboplatin plus pegylated liposomal doxorubicin

Similar to the design of the single-agent carboplatin versus carboplatin plus gemcitabine trial, a Southwest Oncology Group (SWOG) Phase III study compared single-agent carboplatin with the combination of carboplatin plus pegylated liposomal doxorubicin in recurrent ovarian cancer (TABLE 2) [17,18]. Unfortunately, this study was discontinued early due to inadequate accrual, but the trial does provide support for the superiority of combination platinum-based treatment in this clinical setting. Patients randomized to the two-drug regimen of carboplatin plus pegylated liposomal doxorubicin experienced superior progression-free survival, and a higher objective response rate, compared with single-agent carboplatin reatment.

One particularly provocative observation in this trial was the fact that patients randomized to the pegylated liposomal doxorubicin arm experienced an unexplained, but impressively reduced risk for the development of carboplatin-associated hypersensitivity reactions [18]. It is recognized that as many as 10–15% of ovarian cancer patients treated with carboplatin in the second-line setting may experience such a reaction, which may vary in its consequences from a relatively minor inconvenience/discomfort (e.g., mild diffuse rash) to a severe toxic event (e.g., dyspnea, hypotension, cardiopulmonary arrest and death) [19–22].

Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin

The first evidence-based trial to directly compare different platinum-based combination chemotherapy regimens in recurrent ovarian cancer has recently been reported. This study, known as CALYPSO, was a multicooperative group

Table 4. Evidence of the relevant impact of 'third-line' treatment of epithelial ovarian cancer (n = 461).

Treatment	Response rate (%)	Median progression-free survival (months)*	Median overall survival (months)*
Pegylated liposomal doxorubicin or topotecan	10.9	4.4	13.6
Canfosamide (TLK 286)	4.3	2.3	8.5

**p = 0.0001.*
Data taken from [15].

effort that randomized patients to carboplatin plus either paclitaxel or pegylated liposomal doxorubicin [23].

The study, designed as a noninferiority trial whose major study question addressed the important issue of the relative toxicity profiles of the two programs (assuming equivalent efficacy) included a total of 976 patients. However, for patients managed on this trial the pegylated liposomal doxorubicin-containing regimen was actually found to be associated with superior progression-free survival (HR: 0.82; p = 0.005) compared with the carboplatin plus paclitaxel program. In this preliminary report, data on overall survival were not available.

The reported toxicity in this study was perhaps as interesting as the data related to progression-free survival. In addition to the anticipated differences in the regimens regarding such side effects as alopecia (more with paclitaxel) and stomatitis (more with pegylated liposomal doxorubicin), the pegylated liposomal doxorubicin-containing regimen was demonstrated to be associated with a statistically significant reduced incidence of clinically relevant carboplatin-associated hypersensitivity, as noted in the previously discussed SWOG trial [17,18].

Furthermore, this lower incidence of allergic reactions was (unsurprisingly) found to be associated with a lower risk for discontinuation of study-based treatment for reasons other than documented disease progression [23].

It is reasonable to advance the hypothesis that the superior progression-free survival observed in this trial may be explained (partially or completely) by the fact that the population of patients treated with carboplatin plus pegylated liposomal doxorubicin was able to receive a larger number of treatment cycles containing a platinum agent, arguably the single most important class of drugs in the management of ovarian cancer [12].

In fact, an oncologist may rationally decide that an individual patient should not continue treatment with this class of agents, despite evidence of a favorable clinical effect, owing to the legitimate concern for the potential future development of a serious hypersensitivity reaction after the woman has experienced an initial allergic event [19–22]. The ultimate impact of this decision in some patients may be an accelerated time to disease progression. Again, while the preceding discussion must be considered only a hypothesis, the available data are not inconsistent with this conclusion.

The relative importance of insuring the opportunity for the 'optimal delivery' of platinum in recurrent ('platinum-sensitive') ovarian cancer is emphasized by previously published data involving a subgroup of participants in a Phase III trial that compared single-agent pegylated liposomal doxorubicin to single-agent topotecan [24,25]. Study participants with platinum-sensitive recurrent disease who were treated with pegylated liposomal doxorubicin experienced a modest (although statistically significant) improvement in progression-free survival (median 5.6 weeks), but a far greater difference in overall survival (median 37 weeks).

One rational explanation for these interesting results is that the recurrent disease patients (whose cancers might remain platinum sensitive) managed with the less marrow toxic pegylated liposomal doxorubicin may have experienced less difficulty in subsequent attempts to deliver third-line carboplatin, compared with women given the far more marrow toxic topotecan following the research subjects' removal from the trial. The effective administration of carboplatin in this setting may have been largely (or even completely) responsible for the observed differences in progression-free and overall survival outcomes noted in this study [24,25]. Again, this is only a hypothesis, but one that is consistent with the available data, and supported by the results of the CALYPSO trial [23].

Nonplatinum regimens employed in the treatment of recurrent ovarian cancer

Several older Phase III trials explored the potential utility of nonplatinum-containing regimens in the management of recurrent ovarian cancer. These included single-agent studies that compared paclitaxel to topotecan (equivalent efficacy, different toxicity profiles) [26] and (as previously noted) pegylated liposomal doxorubicin to topotecan (superior efficacy for pegylated liposomal doxorubicin) [24,25]. However, it is important to state that in the absence of a platinum-containing control arm, it remains unknown if the activity of any such regimen (single-agent or combination chemotherapy strategy) is equivalent, superior or inferior to a platinum-based program.

In this regard, it is relevant to note a recently reported trial that compared single-agent pegylated liposomal doxorubicin to the combination of pegylated liposomal doxorubicin plus trabetedin in the 'second-line management' of ovarian cancer [27]. The study included a

subgroup of individuals with moderately platinum-sensitive (platinum-free interval between 6 and 12 months) disease. The trial revealed superior progression-free survival in favor of the trabectedin-containing program in this specific patient population. Unfortunately, the combination program was also associated with greater toxicity. At the time of the initial study report, data on overall survival were not available. This information may assist in the determination of whether the toxicity of the combination regimen justifies the potential risk of increased side effects.

It is reasonable to suggest that despite the demonstrated utility of platinum in recurrent ovarian cancer, a population of patients will always exist (in the second-line setting) where platinum will be relatively (or absolutely) contraindicated. This will include women who developed serious platinum hypersensitivity during the administration of their primary chemotherapy regimen, individuals with persistent clinically relevant neuropathy from prior therapy, and potentially patients who previously experienced uncontrolled debilitating platinum-induced emesis.

Conclusion

The results of several well-designed and conducted Phase III clinical trials have helped to define rational chemotherapeutic management strategies in the setting of recurrent ovarian cancer. Despite these established advances and unequivocal evidence of improved survival, treatment of patients with recurrent ovarian cancer is principally palliative in intent [16,28]. New strategies are clearly required that will hopefully eventually be documented to (substantially) favorably impact outcome.

Future perspective

Based on the reported activity of bevacizumab in Phase II trials in the setting of platinum-resistant ovarian cancer [29,30], several Phase III studies that add this agent (and other antiangiogenic drugs) to a carboplatin-based program (containing paclitaxel or gemcitabine) in the management of recurrent ovarian cancer have been initiated. The results of these studies are awaited with considerable interest.

In the future it is likely that clinical research efforts in recurrent ovarian cancer will increasingly focus on unique molecular profiles shown both to be present within, and of clinical relevance to the biology of, individual cancers of patients with this most difficult malignancy.

It is also relevant to note the potential role for secondary surgical cytoreduction in ovarian cancer. It will be important for future antineoplastic drug studies to carefully evaluate the integration of the two therapeutic modalities.

Finally, with the recent data questioning the clinical utility of early treatment of ovarian cancer based on a rising cancer antigen 125 level [31], the impact of immediate versus delayed therapy of the malignancy will need to be considered.

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Executive summary

- Combination platinum-based chemotherapy is superior to single-agent platinum-based chemotherapy in the treatment of recurrent (potentially platinum-sensitive) epithelial ovarian cancer.
- However, it is currently unknown if combination drug delivery is superior to the planned sequential administration of a platinum drug immediately followed by one (or more) additional agent(s) with known biological activity in epithelial ovarian cancer.
- Recently reported Phase III trial data demonstrate the superiority of a carboplatin plus pegylated liposomal doxorubicin regimen compared with carboplatin plus paclitaxel in recurrent ovarian cancer, with the pegylated liposomal doxorubicin program being associated with a lower risk of clinically relevant carboplatin-associated hypersensitivity.

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