Therapeutics and Clinical Risk Management

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REVIEW

Treatment of recurrent epithelial ovarian cancer

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
12 June 2009
Number of times this article has been viewed

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Abstract: Epidemiologic analysis reveals that the mortality rate from ovarian cancer is continuously decreasing due to the improvement of surgery and chemotherapy. However, the prognosis of ovarian cancer patients is still unsatisfactory overall considering that only 30% of patients are alive after five years. In fact, although surgery and first-line systemic chemotherapy induces complete and partial response in up to 80% of patients with about a 25% pathological complete remission rate, recurrences occur in the majority of patients. The role of surgery in recurrent disease has been recently studied and many patients can receive an optimal secondary cytoreduction. Most of the recurrent patients are subject to a number of treatment regimens that, although palliative in nature, are also able to prolong survival. Important results have been obtained in particular in platinum-sensitive recurrent disease where a platinum-based chemotherapy is able to prolong progression-free survival and overall survival. Overall, our armamentarium for the treatment of progressive or recurrent ovarian cancer is significantly richer than in the past, and in many patients it is possible to achieve our goal of controlling the chronic behavior of the disease.

Keywords: ovarian cancer, chemotherapy

Introduction

The standard initial treatment of patients with advanced ovarian cancer is cytoreductive surgery, followed by combination chemotherapy with paclitaxel and a platinum compound.[1,2] Despite the activity of this combination chemotherapy, which gives response rates up to 80%, the majority of patients die of recurrent disease.[3] Therefore, a large proportion of patients are candidates for second-line therapy.

Patients who progress on first-line therapy or relapse within three months are considered to be refractory to a platinum re-treatment.[4] Patients who respond to primary treatment and relapse within six months are considered platinum-resistant.[4] Patients who relapse more than six months after completion of initial therapy are characterized as platinum-sensitive.[4] However, the sensitivity to platinum does not follow an exact time pattern, and independently from the cut-off time chosen, a longer platinum-free interval (PFI) increases the chances for a benefit by platinum re-challenge. This has been reported especially for PFI longer than 12 months.[5,6] Therefore, patients who relapse 6–12 months following the end of their initial regimen may benefit less and are classified as so-called partially sensitive. The latter

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represents a challenging grey zone with respect to further use of platinum agents and platinum combination partners.

Treatment of platinum-refractory/resistant ovarian cancer

Refractory/resistant ovarian cancers are not considered suitable for secondary surgical cytoreduction and their treatment is medical (Table 1). However, the value of a second-line therapy and its impact on survival is modest.[4,7] Agents such as epirubicin[8,9] and etoposide[10] and the more recent active drugs topotecan,[11] stealth liposomal doxorubicin,[12,13] and gemcitabine[14] show response rates ranging from 10% to 25%, but lengthy remissions are infrequent.[7] Thus, the treatment of these patients remains a challenge for the near future and there is a need for studies with new drugs. Some new biological agents have been also investigated in this setting; bevacizumab,[15] erlotinib,[16] and pazopanib[17] have shown promising activity and are under investigation in phase III trials.

Pegylated liposomal doxorubicin (PLD) is considered the first choice single agent in these patients. The drug is a preparation of doxorubicin hydrocloridic acid in pegylated liposomes that confers a much longer half-life in blood and a different profile of toxicity than doxorubicin.[18] The surface of the pegylated liposome is coated with methoxipolyethylene glycol polymers, which prevent liposomal detection and destruction by the reticuloendothelial system.[19] In a phase III study, Gordon and colleagues[12] compared PLD with topotecan in 481 patients with either platinum-sensitive (PFI $>$ 6 months) or platinum-refractory (PFI $\leq$ 6 months) recurrent ovarian cancer. Mature survival data demonstrated a significant benefit for PLD in the intent-to-treat population (hazard ratio [HR] = 1.23, 95% confidence interval [CI]: 1.01–1.50; p = 0.038) which was particularly pronounced in patients with platinum-sensitive disease (HR = 1.432, 95% CI: 1.066–1.923; p = 0.017), while no significant difference was found in patients with platinum-refractory/resistant disease. The toxicity profile of liposomal doxorubicin was significantly better compared to topotecan, particularly in the hematological toxicity profile.

A phase III randomized trial (Multicenter Italian Trials in Ovarian cancer [MITO]-3) have recently compared PLD with gemcitabine in patients with PFI $<$ 12 months. The results demonstrated comparable efficacy and improved quality of life with PLD monotherapy compared with gemcitabine monotherapy in patients with recurrent ovarian cancer and a PFI of less than 12 months.[20] No difference in survival between the two groups was shown in the subset of patients with a PFI of $\leq$6 months. However, a statistically significant improvement in survival was observed with PLD in those with PFI of 7–12 months (p = 0.013). Furthermore, patients in the PLD arm experienced statistically significantly higher global quality of life (QOL) scores at the first and second post-baseline QOL assessments.

In this subgroup of patients it has not been demonstrated that combination chemotherapy is better than single agents. The few studies performed showed increased toxicity without any impact on survival. Recently a phase III study was performed comparing topotecan versus topotecan–etoposide versus topotecan–gemcitabine.[21] None of the combinations improved progression-free survival (PFS) or overall survival compared to topotecan alone. Patients in the combination arms were at higher risk of hematological toxicity. Interesting experiences have been published with the combination of stealth liposome doxorubicin with vinorelbine[22] or gemcitabine.[23] Phase III data are needed, although activity and toxicity results seems very promising.

In this setting it is worthwhile to mention also the preliminary results of the study by Monk and colleagues[24] comparing PLD alone versus PLD plus trabectedin showing an advantage for the combination in terms of PFS. A subgroup analysis showed that the median PFS with PLD alone was 7.5 months versus 9.2 months with PLD plus trabectedin (HR = 0.73, 95% CI: 0.56–0.95; p = 0.01) in patients with a PFI of 6–12 months. On the contrary, no difference was observed between single agent and combination therapy in patients with PFI lower than six months, also in this study. Thus, based on the available data, single agent chemotherapy remains the standard treatment in patients with resistant and refractory ovarian cancer.

Interesting data have been also published with single-agent weekly paclitaxel at the dose of 80 mg/m^2 in platinum/refractory ovarian cancer. In this study, an objective response rate of 20.9% was found and serious adverse events were very uncommon.[25] Biological agents targeting specific cell factors have gained an important position in the treatment of many solid cancers. However, in ovarian cancer no new drug has reached the market up to now. Anti-endothelial growth factor (EGF) receptor antagonists have been studied in resistant ovarian cancer. Data with erlotinib[16] and gefitinib[26] showing very low response rate, being in the range of 0%–6%. However, a certain number of disease stabilization in patients have been found, which justifies more studies in this setting of patients. The data on the use of the anti-vascular endothelial growth factor (anti-VEGF) antibody, bevacizumab, is noteworthy. The Gynecologic

Oncology Group have shown in a phase II study that the drug is able to induce a 18% response rate with 42% of patients progression-free at six months.[15] Some caution in the treatment of heavily pre-treated patients has been claimed due to some cases of bowel perforation. However, the results obtained in second line prompted the International Cooperation in Gynecologic Oncology to promote two trials in first-line chemotherapy evaluating the addition of bevacizumab to standard carboplatin and paclitaxel.

An other interesting group of new molecular inhibitors is the family of poly (ADP-ribose) polymerase (PARP). In particular, the PARP-inhibitors AZB2281 has shown significant anticancer activity on patients with BRCA-deficient ovarian cancer.[27]

Treatment of platinum-sensitive ovarian cancer with platinum-free interval >12 months

Many important studies have shown improvement in the outcome of fully platinum-sensitive recurrent ovarian cancer. Other studies will be completed very soon. One important question is when to initiate chemotherapy. In fact, the increase in CA 125 levels is often the first sign of recurrence without confirmatory imaging preceding symptoms and radiological signs of some months. There is no data indicating that early treatment during CA 125 increase improved survival compared to delayed treatment during clinical or radiological relapse, although a trial by the European Organisation for Research and Treatment of Cancer (EORTC) is ongoing. Early treatment may negatively impact on QOL while the burden of disease may be too big if treatment start too late. A discussion with the patient is important in our view in order to tailor the start of treatment according to the patient's expectations.

According to current dogma, sensitivity to a new treatment with platinum increases proportionally to PFI being at maximum after 18 months.[4] As optimal cytoreduction is considered a major goal of treatment in the first-line setting, it has been proposed that a secondary cytoreduction may improve survival also in patients with sensitive recurrences. No prospective randomized data is available, but retrospective series suggest[28] that when a cytoreduction with no residual disease is achieved, this can significantly impact on survival. The problem of patient selection for surgery is crucial and predictive scores have been recently proposed. The DESKTOP OVAR (Descriptive Evaluation of preoperative

Table 1 Phase III studies in platinum-resistant/refractory ovarian cancer

Study	Treatment	Objective response	Progression-free survival (median)	Overall survival (median)
Gordon et al[12]	PLD 50 mg/m^2 (n = 239) Topotecan (1.5 mg/m^2 daily for five consecutive days) (n = 235)	19.7% 17.0% (P = 0.390)	16.1 wk 17.0 wk (P = 0.095)	60 wk 56.7 wk
O'Byrne et al[13]	PLD 50 mg/m^2 (n = 107) Paclitaxel 175 mg/m^2 (n = 107)	17.8% 22.4% (P = 0.34)	21.7 wk 22.4 wk (P = 0.15)	45.7 wk 56.1 wk (P = 0.44)
Ten Bokkel Huinink et al[11]	Topotecan 1.5 mg/m^2 daily for five consecutive days (n = 112) Paclitaxel 175 mg/m^2 (n = 114)	20.5% 13.2% (P = 0.138)	18.9 wk 14.7 wk (P = 0.08)	63.0 wk 53.0 wk (P = 0.44)
	Topotecan 1.25 mg/m^2 daily for five consecutive days (n = 178)	27.8%	7.0 month	17.2 month
	Topotecan 1.0 mg/m^2 daily for five consecutive days and oral etoposide 50 mg on days 6 to 12 (n = 177)	36.1%	7.8 month	17.8 month
	Topotecan 0.5 mg/m^2 daily for five consecutive days plus gemcitabine 800 mg/m^2 on day 1 and 600 mg/m^2 on day 8 (n = 47)	31.6% (P = 0.368)	6.3 month (P = 0.3798)	15.2 month (P = 0.2344)
Ferrandina et al[20]	PLD 40 mg/m^2 (n = 76)	16%	16 wk	56 wk
	Gemcitabin 1,000 mg/m^2 on days 1, 8, and 15 (n = 77)	29% (P = 0.056)	20 wk (P = 0.411)	51 wk (P = 0.048)

Abbreviation: PLD, pegylated liposomal doxorubicin.

Selection KriTeria for OPerability in recurrent OVARian cancer) score considers three prognostic factors (platinum sensitivity, absence of residual disease at primary surgery, presence of ascites) was able to select patients in which there was a 67% probability of obtaining an optimal cytoreduction (no residual disease after surgery) for recurrent patients.[29] A prospective study (DESKTOP3) is ongoing in order to prospectively compare surgery vs no surgery in patients with recurrence of disease and a positive DESKTOP score.

Two large randomized studies in platinum-sensitive disease have demonstrated that the addition of a second drug to carboplatin improve the outcome of the patients.

The ICON4/AGO2.2 trial[5] compared a platinum-based chemotherapy (70% carboplatin alone) with a carboplatin–paclitaxel combination. In this study with 802 enrolled patients, there was an absolute difference in one-year PFS of 10% and in two-year survival of 7%. The combination induced an acceptable toxicity profile with neurotoxicity (20% G2–4) as the major complaint. This high rate of significant neurotoxicity can represent a limit since it has been shown that a significant proportion of recurrent patients have residual neurotoxicity from first-line treatment.[30]

Similar results has been obtained with the combination of carboplatin and gemcitabine versus carboplatin in patients with PFI $>$ 6 months.[6] In this AGO study, the combination significantly improved PFS along with a better QOL. In particular, median PFS was 8.6 months (95% CI: 7.9–9.7 months) for gemcitabine plus carboplatin compared to 5.8 months (95% CI: 5.2–7.1 months) for carboplatin alone ($p = 0.0038$). Toxicity was prevalently hematological, while neurotoxicity was of lower degree, and, as expected alopecia was not present. This study was not powered to show differences in overall survival, however PFS data were clearly in favor of the combination.

Due to these results the combinations of carboplatin–paclitaxel and carboplatin–gemcitabine are in the market with the indication for treatment of platinum-sensitive recurrent ovarian cancer.

A phase II study from the French group, GINECO, has evaluated the combination of carboplatin and liposomal doxorubicin in platinum-sensitive recurrence. In this study, GINECO evaluated 30 mg/m^2 of PLD every four weeks with carboplatin AUC5 in 104 patients who had received both a platinum and taxane as first-line (60%) or second-line (40%) therapy.[30] The majority of patients (96%) had a PFI of $\geq$6 months; however, nearly half had a PFI of $<$12 months. Even with a significant proportion of patients having partially-platinum-sensitive disease, the overall response rate was 62%. Median PFS was 9.4 months, and median overall survival was 32 months.

Based on these data a randomized phase III trial CALYPSO (EORTC 55051), is underway and has fully accrued. CALYPSO compares PLD–carboplatin with paclitaxel–carboplatin using a 30 mg/m^2 dose of PLD every four weeks. The primary endpoint of this trial is PFS. A total of 976 patients with recurrent ovarian cancer relapsing $>$6 months after first- or second-line platinum-based therapy were enrolled. An interim safety analysis of the first 500 patients has been presented in abstract form.[32] Premature discontinuation of therapy due to toxicity appeared to be more frequent in the paclitaxel–carboplatin arm (36 patients [14%] vs. 15 patients [6%]). Treatment-related serious adverse events were also more frequent in the paclitaxel–carboplatin arm (76 patients [30%] vs. 44 patients [18%]). These data reveal variations in the toxicity profile between the two combinations. The PLD–carboplatin treatment was associated with more grade 3/4 thrombocytopenia and more grade $\geq$2 mucositis and palmar-plantar erythrodysesthesia. In contrast, paclitaxel–carboplatin was associated with more grade $\geq$2 allergic reactions, alopecia, neuropathy, and arthralgia/myalgia. Final efficacy data are awaited to demonstrate whether carboplatin–PLD can be a tolerable alternative to paclitaxel–carboplatin in the setting of platinum-sensitive recurrent ovarian cancer.

Treatment of platinum-sensitive ovarian cancer with a platinum-free interval between 6 and 12 months

In partially platinum-sensitive disease (progression-free for 6–12 months), the choice of treatment may or may not include a platinum agent. There is no randomized trial answering this question and thus there are only indirect evidences to discuss. When a platinum combination is chosen while waiting for the results of the CALYPSO, the treatments of choice are carboplatin–paclitaxel or carboplatin–gemcitabine. Phase III data reported for gemcitabine–carboplatin in this population demonstrated the utility of this combination.[6] The median PFS with gemcitabine–carboplatin was 7.9 months versus 5.2 months with carboplatin alone (HR = 0.69, 95% CI: 0.49–0.97; $p = 0.03$) in patients with a PFI of 6–12 months.

When a nonplatinum treatment is planned, PLD seems the treatment of choice based on the data of the Gordon study showing superiority for PLD over topotecan.[12] Also, the MITO-3 data showed a survival advantage for PLD single agent over gemcitabine in patients between six and 12 months.[20]

In this setting, the preliminary results of the study comparing PLD alone versus PLD–trabectedin indicate that this scenario may quickly change. In this study, an advantage for the combination in terms of PFS was found in patients with recurrence between six and 12 months.[24] These data may indicate that at least in partially platinum-sensitive patients a nonplatinum combination including trabectedin and PLD may have advantages compared to PLD alone. However, the question of platinum versus nonplatinum remains and should be answered by clinical trials.

In fact, utilizing nonplatinum agents in this setting to prolong the PFI is another issue of interest. *In vitro* and clinical data suggest that by using this strategy, platinum sensitivity may be restored.[33–36] In fact, some preclinical studies suggest that some of the resistance mechanism of cisplatinium-resistance, such as the ability to repair DNA or the drug efflux systems, may be unstable over time.[33,35,36] The topic is controversial since other studies suggest data adverse to this hypothesis.[37] A multicenter randomized phase III trial (MITO-8) is ongoing to evaluate whether utilizing PLD monotherapy to prolong the PFI in turn prolongs survival. Patients who progress for 6–12 months following initial platinum-based therapy will be randomized to receive either PLD monotherapy followed by paclitaxel–carboplatin at the next progression or the reverse: paclitaxel–carboplatin and then PLD monotherapy at the second progression. The primary endpoint will be overall survival.

Conclusion

In the last fifteen years, several steps forward have been done in the field of medical treatment of ovarian cancer. In the setting of recurrence treatment, many drugs have shown significant activity and some trials showed that is possible to prolong survival, particularly in patients with platinum-sensitive recurrences. The correct sequence of the treatment and the best chemotherapy combinations are under investigation and the results of several phase III studies will be soon available. In the next few years we will know whether the new molecular inhibitors will be effective in ovarian cancer as it was proven in other malignancies. Phase III studies are ongoing worldwide to clarify whether the new biological agents will be able to change the medical treatment paradigm in recurrent ovarian cancer.

Disclosure

The authors report no conflicts of interest in this work.

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