Update of randomized trials in recurrent disease

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In the absence of significant advance in first-line therapy until recently, the increased knowledge of how to manage relapse accounts for most of the advances observed in ovarian cancer during the last 10 years. In addition, a large number of new drugs, mostly in the category of ‘targeted therapy’, are currently being tested in the setting of recurrent ovarian and are expected to change the course of the disease in the near future. The acknowledgement of the platinum-free interval (PFI) as the major criterion predicting therapy success in ovarian cancer relapse has allowed the development of distinct therapeutic strategies according to the PFI length. This update will indicate the pivotal trials that have led to the largest steps in the management of recurrent ovarian cancer during the last 10 years. Future advances in ovarian cancer treatment need randomized phase II or phase III trials in the recurrent disease setting before being tested in first line. The main ongoing randomized trials in relapsed disease will be reviewed, focusing on phase II or phase III trials.

Key words: cancer, ovarian, randomized, relapse, review

face-to-face comparison of drugs

Pegylated liposomal doxorubicin (PLD), topotecan, paclitaxel or gemcitabine have shown similar activity in ovarian cancer in relapse. In two trials, overall survival (OS) was found significantly prolonged in patients (mainly in the platinum-sensitive subset) treated with PLD compared with topotecan or gemcitabine, but progression-free survival (PFS) was not increased. In platinum-resistant disease, the choice between these active drugs depends on their toxicity profile and convenience of administration, with PLD being the currently preferred control arm in resistant patient trials. Importantly, alkylating agents such as treosulfan or canfosfamide have been found significantly less active than standard topotecan or PLD. The large trial with canfosfamide is the first to show that in third-line treatment standard active drugs such as PLD or topotecan still bring a significant benefit in OS compared with less active agents [1–8] (Table 1).

Currently, the activity of nonpegylated liposomal doxorubicin (Myocet™) is being explored and compared with gemcitabine in platinum-resistant/refractory patients (NCT01100372). Another face-to-face comparison in relapsed disease include paclitaxel versus a new nanoparticle formulation of paclitaxel (Paclical) (NCT00989131).

platinum-resistant disease: comparison of combination versus single agent

Six randomized trials in resistant disease (or with a majority of patients with resistant disease) have failed to show superiority in outcome for a combination versus single agent. However, toxicity was increased in the combination arm [9–14] (Table 2).

platinum-sensitive disease: comparison of combination versus single agent

In platinum-sensitive disease, a single trial has compared a nonplatinum drug, paclitaxel, with a platinum combination (cyclophosphamide/doxorubicin/cisplatin) and has found a significant benefit in PFS and OS for the platinum combination [15]. Another trial has compared a nonplatinum drug, PLD, with a nonplatinum combination, PLD + trabectedin, and found in the platinum-sensitive subset a PFS and OS advantage for the nonplatinum combination [13].

The benefit for patients with platinum-sensitive disease to be treated with a combination has been confirmed by the results of five trials comparing single agent carboplatin with a carboplatin combination. Four of these trials demonstrated an advantage in outcome for the combination either in PFS (three trials) or in OS (three trials) [16–20] (Table 3).

The question of which is the best carboplatin-based chemotherapy has been addressed by two randomized trials. The large CALYPSO trial has shown that carboplatin–PLD has a more favourable benefit/risk ratio than carboplatin–paclitaxel [21] (Figure 1). The results of the randomized trial (HECTOR) between carboplatin–topotecan and other carboplatin-based combinations are awaited (NCT00657878).

In order to better define the respective role of nonplatinum drugs versus platinum combinations in patients with partially platinum-sensitive disease (6–12 months), the MITO 8 trial compares the sequence of PLD followed by carboplatin–paclitaxel versus the reverse sequence (NCT00657878).

A comparison between the best carboplatin combination...
(carboplatin–PLD) and a nonplatinum combination (trabectedin–PLD) is also planned in these patients.

**surgery**

DESKSTOP III is an AGO-led trial assessing the impact on OS of surgery at relapse in patients with platinum-sensitive disease and a positive AGO score. Accrual has started in a trial with >400 patients planned.

Several randomized trials in the United States, Korea and France are ongoing or planned to question the role of chemotherapy plus hyperthermia in relapsing patients treated with surgery plus hyperthermic intraperitoneal chemotherapy (NCT00045461 and NCT01091636).

**antiangiogenic agents**

Three trials with bevacizumab (15 mg/kg/3 weeks until progression) have been launched in nearly 2500 patients with ovarian cancer in relapse: one in resistant relapse (AURELIA) and two in sensitive relapse (GOG 213 and OCEANS). OCEANS reached its primary end point (PFS) in 2011 [22]. Bevacizumab plus carboplatin–gemcitabine followed by single agent bevacizumab until progression significantly increased PFS compared with chemotherapy alone [hazard ratio (HR): 0.484; \( P<0.0001 \)], with a median PFS of 8.4 and 12.4 months, respectively. The results of AURELIA will be delivered in 2012 (Table 4).

**Table 1.** Face-to-face comparison of chemotherapy drugs in ovarian cancer in relapse

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Author</th>
<th>Benefit</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel versus oxaliplatin</td>
<td>Piccart et al., 2000</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel versus topotecan</td>
<td>Ten Bokkel et al., 2004</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>PLD versus topotecan</td>
<td>Gordon et al., 2001</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>PLD versus paclitaxel</td>
<td>O’Byrne et al., 2002</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>PLD versus gemcitabine</td>
<td>Mutch et al., 2007</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>PLD versus gemcitabine</td>
<td>Ferrandina et al., 2008</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Topotecan versus treosulfan</td>
<td>Meier et al., 2005</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>PLD or topotecan versus canfosfamide</td>
<td>Vergote et al., 2009</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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</tbody>
</table>

PFS, progression-free survival; OS, overall survival; PLD, pegylated liposomal doxorubicin.

**Table 2.** Resistant disease: comparison of combination versus single agent

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Author</th>
<th>Benefit</th>
<th>PFS/OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel versus epirubicin + paclitaxel</td>
<td>Bolis et al., 1999</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel versus doxorubicin + paclitaxel</td>
<td>Torri et al., 2000</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Paclitaxel versus epirubicin + paclitaxel</td>
<td>Buda et al., 2004</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Topotecan versus topotecan + etoposide or gemcitabine</td>
<td>Sehouli et al., 2008</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>PLD versus PLD + trabectedin</td>
<td>Monk et al., 2010</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Weekly paclitaxel (wP) versus wP + carboplatin or weekly topotecan</td>
<td>Gladieff et al., 2009</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

PFS, progression-free survival; OS, overall survival; PLD, pegylated liposomal doxorubicin.

**Table 3.** Platinum-sensitive disease: comparison of combination versus single agent

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Author</th>
<th>Benefit</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin versus epirubicin + carboplatin</td>
<td>Bolis et al., 2001</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Carboplatin versus paclitaxel + carboplatin</td>
<td>Parmar et al., 2003</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Carboplatin versus paclitaxel + gemcitabine</td>
<td>Gonzales-Martin et al., 2005</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Carboplatin versus gemcitabine + carboplatin</td>
<td>Pfisterer et al., 2005</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Carboplatin versus PLD + carboplatin</td>
<td>Markman et al., 2010</td>
<td>No</td>
<td>Yes</td>
<td></td>
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</tbody>
</table>

PFS, progression-free survival; OS, overall survival; PLD, pegylated liposomal doxorubicin.

**Table 4.** Randomized trials with bevacizumab in ovarian cancer in relapse

<table>
<thead>
<tr>
<th>Name</th>
<th>Chemotherapy</th>
<th>Patient subset</th>
<th>Patients (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AURELIA</td>
<td>PLD or paclitaxel or topotecan</td>
<td>Resistant</td>
<td>330</td>
</tr>
<tr>
<td>GOG 213</td>
<td>Paclitaxel/carboplatin</td>
<td>Sensitive</td>
<td>1600</td>
</tr>
<tr>
<td>OCEANS</td>
<td>Gemcitabine/carboplatin</td>
<td>Sensitive</td>
<td>450</td>
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platinum-sensitive disease (NCT00096200). It is also being compared in combination with topotecan alone in resistant patients (NCT01047891). This ICON6 trial has currently accrued 250 patients.

Sorafenib (Nexavar) in combination with topotecan is currently being compared with topotecan alone in resistant patients (NCT01047891). It is also being compared in combination with chemotherapy (taxol-carboplatin) versus chemotherapy alone in platinum-sensitive disease. This ICON6 trial has currently accrued 250 patients.

Cediranib (Recentin™) is being explored in combination with carboplatin-based chemotherapy and in maintenance in a three-step trial expecting >2600 patients with platinum-sensitive disease. This ICON6 trial has currently accrued >250 patients.

Sorafenib (Nexavar) in combination with topotecan is currently being compared with topotecan alone in resistant patients (NCT01047891). It is also being compared in combination with chemotherapy (taxol-carboplatin) versus chemotherapy alone in platinum-sensitive disease (NCT00896200).

antifolate-receptor agents

Olaparib is the most advanced anti-PARP compound in development and the dose-relationship has been explored in 2 randomized phase II trials in BRCA-mutated ovarian cancer patients in relapse. Olaparib has been found more active in relapse at a dose of 400 mg per os twice a day (p.o. b.i.d.) than at 100 mg p.o. b.i.d., with a median PFS of 5.8 and 1.9 months, respectively [26]. In platinum-resistant patients, the dose of olaparib 400 mg p.o. b.i.d. induces a higher response rate (GCIG including CA125 criteria) of 59% than that of olaparib 200 mg p.o. b.i.d. (38%) which was similar to PLD (39%). PFS curves, however, were similar between the three arms [27].

EC145 is a conjugate of folate and the vinca alkaloid desacetylvinblastine hydrazide (DAVLBH), which binds to the folate receptor and delivers DAVLBH into the cell via endocytosis. The results of a randomized phase II comparing the combination of EC145 and PLD with PLD alone are encouraging [25]. A large phase III is planned.

anti-PARP agents

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Ledermann et al. [28] have recently presented the results of a randomized comparison in 265 patients of olaparib versus placebo in maintenance of a platinum-based chemotherapy-induced partial or complete response platinum-sensitive relapse. PFS by RECIST was significantly longer in the olaparib group than in the placebo group (HR: 0.35; 95% CI: 0.25–0.49; P<0.0001; median 8.4 versus 4.8 months). We are also awaiting the results of a randomized phase II trial in platinum-sensitive high-grade serous cancer of olaparib in combination with chemotherapy versus combination alone (NCT01081951). Moreover, large phase III trials are planned.

ABT-888 (veliparib) is another anti-PARP compound. The accrual of a randomized phase II trial comparing ABT-888 + temozolomide versus PLD in patients with high-grade serous ovarian cancer in relapse has recently been completed (NCT01113957).

results from others drugs

chemotherapy

Patupilone, an epothilone B, was investigated within the largest trial ever performed in 829 resistant/refractory patients. No benefit in OS was found for patupilone over PLD [29].

NKTR-102 (PEG-irinotecan) has shown interesting activity in a randomized trial of resistant/refractory patients, but at the expense of significant toxicity [30].

Decitabine (Dacogen) was not superior in combination with carboplatin versus carboplatin alone [31].

targeted therapies or immunotherapy

AZD0530 (Saracatinib), an anti-Src agent, has not met its primary end point in combination with chemotherapy (taxol-carboplatin) versus chemotherapy alone in a randomized trial in platinum-sensitive disease (NCT00610714).

GDC-0449, a hedgehog pathway inhibitor, failed to improve PFS in maintenance of a second or third complete remission over placebo [32].

Thalidomide was not superior to tamoxifen in patients with an asymptomatic rise of CA125 [33].

other new drugs currently investigated

BIBF 6727 (Volasertib), a polo-like kinase 1 inhibitor; MLN8237, an Aurora A kinase inhibitor; ZD4054 (Zibotentan), an oral antifolate quinazoline derivative thymidine synthetase inhibitor; E7080, an orally active inhibitor of multiple receptor tyrosine kinases; IMC-3G3, an anti-PDGFR receptor-monoclonal antibody; SGN-15, a monoclonal antibody directed against Lewis-y antigen–doxorubicin conjugate; MUC1 dendritic cell vaccine (CVac) (NCT01068509); tucotuzumab celmoleukin (EMD 273066), a novel immunocytokine (NCT00408967); a polyvalent antigen-KLH conjugate vaccine with or without adjuvant OPT-821 (NCT00857545).

In conclusion, randomized trials in recurrent ovarian cancer have brought new chemotherapy standards according to the platinum-free interval: a single nonplatinum agent in refractory/resistant disease; drug combination for partially platinum-sensitive disease (relapse between 6 and 12 months); and platinum combinations for fully platinum-sensitive disease (>12 months).

The combination of monoclonal antibodies or tyrosine kinase inhibitors with chemotherapy and/or in maintenance has shown promising results. Antiangiogenic agents (bevacizumab) and anti-PARP agents (olaparib) are leading the way for the future advances in the management of ovarian cancer.
disclosures

The author declares no conflict of interest.

references


29. Colomba N, Schwartz PE, Bamas A. Results of a randomized, open-label, phase III trial of patupilone (P) versus pegylated liposomal doxorubicin (PLD) in taxane/ platinum refractory/resistant patients with recurrent ovarian, fallopian, or peritoneal cancer. Thirty-fifth European Society for Medical Oncology Congress (Abstr 4843). Milan 2010.


