How to approach patients in relapse

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introduction

Although the majority of advanced ovarian cancer patients (70%–80%) respond to platinum-based chemotherapy, the disease will ultimately relapse in most. Recurrent ovarian cancer (ROC) is not curable and while the overall goal is to delay time to symptomatic disease progression and to prolong overall survival (OS), considerable attention is focused on improving cancer-related symptoms and optimizing overall quality of life (QoL). Ovarian cancer is increasingly being viewed as a chronic disease due to the availability of a number of effective options to manage successive relapses.

how to make treatment decision in recurrent ovarian cancer?

platinum-free interval: the major decision factor

The most widely used clinical surrogate for predicting response to chemotherapy and prognosis as well as for stratification in clinical trials has been the progression-free interval or the ‘platinum-free interval’ (PFI). Different definitions have been used in clinical practice and clinical trials with some confusion between PFI and treatment-free interval. The fourth International Ovarian Cancer Consensus Meeting held in Vancouver in June 2010 on behalf of Gynecologic Cancer InterGroup (GCIG) has established definition of PFI as the interval from the last date of platinum dose until progressive disease is documented [1].

This GCIG definition of PFI is simple for practical use but has some limitations. It does not take into account how progression is defined, i.e. CA125 alone, radiological and symptomatic recurrence, despite the fact that each subset might be quite different with respect to prognosis and likelihood of response. It is unclear what the impact of maintenance therapy on the subsequent response to platinum-based therapy will be and whether prolonging the PFI will alter subsequent chemosensitivity or prognosis. This will become increasingly important in the future, because of the increasing numbers of patients who have received or are receiving maintenance angiogenesis inhibitors or other molecularly targeted agents. Another question is how to define patients who have had a non-platinum course of chemotherapy before their latest progression.

Despite these limitations, the recommendation was that PFI should be the arbiter used to categorize patients with ROC into the four subsets as platinum refractory, platinum resistant, potentially platinum sensitive and platinum sensitive (Table 1) [2, 3].

the other decision factors

QoL and symptom relief being a major goal in patients with ROC, tolerability concerns are of particular importance. Consideration should be taken in pre-existing toxicity from previous treatment (such as allergy, neurotoxicity or bone marrow toxicity) which may limit options.

Age, impairment in performance status (PS), in organ and cognitive function, as well as comorbidities or the associated presence of polypharmacy, may influence the ability to tolerate treatment. A comprehensive geriatric assessment may therefore be valuable to be able to adapt treatment according to the individual patient (ESMO Handbook of Cancer in the Senior Patient, 2010).

Other biological factors such as the histological subtype of tumours, grade, as well as molecular markers such as breast cancer (BRCA) mutation status of patients will certainly be of increasing importance in the near future.

Finally, patient wish is of the utmost importance to consider particularly that related to the occurrence of alopecia with chemotherapy and treatment convenience (IV treatment to be administered in hospital), which may have a substantial negative impact on the patients' ability to fulfil work and social commitments and pursue activities and therefore impair QoL.

when to initiate treatment? controversy around CA125

An elevated and rising CA125 twice the upper limit of normal or CA125 level nadir is indicative of progression in patients with a specificity of 95% and this a well-accepted GCIG definition of CA125 progression or relapse [4].

In addition, Rustin et al. showed that remission duration and OS were comparable in patients in whom second-line chemotherapy was initiated early (following a rise in CA125 to
a level twice the upper limit of normal, but who remained asymptomatic) and in those in whom treatment was initiated following clinical or symptomatic recurrence [5].

These last results have generated much discussion and debate about the role of CA125 in surveillance. Although commencing chemotherapy in asymptomatic patients on the basis of a rising CA125 alone does not appear to be beneficial, the advantages and shortcomings of CA125 testing remain controversial. While CA125 plays an important role in monitoring the disease status and in providing appropriate information for patients to plan their daily life, it can generate anxiety. There are also other important questions that still need to be addressed such as determining the significance of CA125 velocity as well as the impact of an early detection of recurrence by CA125 on the efficacy of surgical treatment.

what is the role of cytoreductive surgery for ROC?

There is no level I evidence to demonstrate a survival advantage associated with surgical cytoreduction in women with ROC. Randomized phase III trials such as GOG 213, AGO-OVAR DESK-TOP 3 evaluating the role of surgery in ROC are a priority.

Surgery may be useful in patients in whom the goal of zero residual tumour is feasible. The DESKTOP OVAR I trial of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) demonstrated that only complete resection was associated with prolonged survival in ROC [6], an observation which has been confirmed in a meta-analysis of 40 retrospective studies, including >2000 patients [7]. In addition, in multivariate analysis, the following variables were found to predict successful surgery in the trial: Eastern Cooperative Oncology Group PS = 0, no residuals after primary surgery or initial International Federation of Gynaecology and Obstetrics stage I/II, absence of ascites >500 ml. The feasibility of these variables as a predictive score for resectability in platinum-sensitive ROC has been validated in the prospective AGO DESKTOP OVAR II trial [8]. The AGO score could predict complete resection in at least two out of three patients. These results will aid in the selection of patients who might benefit from secondary cytoreductive surgery.

Useful imaging approaches for women suspected of having ROC include computed tomography combined with positron-emission tomography [9] or contrast-material enhanced, magnetic resonance imaging. There have been no prospective trials comparing these various imaging techniques. Open laparoscopy may be useful in identifying patients who may benefit from surgical exploration.

chemotherapy of platinum-resistant relapse

Pegylated liposomal doxorubicin (PLD), topotecan, paclitaxel or gemcitabine have shown similar activity in ovarian cancer in relapse. In two trials, OS was found prolonged in patients (mainly in the platinum-sensitive subset) treated with PLD compared with topotecan or gemcitabine, but PFS was not increased. The choice of these active drugs in patients with platinum-resistant disease depends on their toxicity profile and convenience of administration, with PLD being the current preferred control arm of 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 the third line of treatment, standard active drugs such as PLD or topotecan still bring a significant benefit in OS compared with less active agents (Table 2).

Six randomized trials in patients with resistant disease (or with a majority of patients with resistant disease) have failed to show superiority in outcomes for a combination versus single agent. However, toxicity is increased in the combination arm. Thus, single agent is standard in platinum-resistant disease. Enrolment in clinical trials of investigational agents is an attractive option that should be considered.

chemotherapy of platinum-sensitive relapse

The probability of a response to a platinum-based regimen following recurrence depends significantly on the length of the interval between the last dose of platinum therapy and current relapse. Therefore, platinum-based combination chemotherapy is recommended in the case of a fully platinum-sensitive relapse (PFI > 12 months) [1] (Figure 1) and often preferred in the intermediate platinum-sensitive subset of patients relapsing between 6 and 12 months.

The question of the best carboplatin-based chemotherapy has been addressed by two randomized trials. The HECTOR trial showed a trend for worse global survival in patients treated with carboplatin-topotecan compared with others.

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**Table 1.** Distinct patient subgroups according to platinum-free interval (PFI)

<table>
<thead>
<tr>
<th>Platinum-free interval</th>
<th>Supposed sensitivity to platinum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression while receiving the last line of platinum-based therapy or within 4 weeks of last platinum dose</td>
<td>Refractory</td>
</tr>
<tr>
<td>1–6 months</td>
<td>Resistant</td>
</tr>
<tr>
<td>6–12 months</td>
<td>Partially platinum sensitive</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>Fully platinum sensitive</td>
</tr>
</tbody>
</table>

**Table 2.** Face-to-face comparison of chemotherapy drugs in ovarian cancer in relapse

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Author</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel versus oxaliplatin</td>
<td>Piccart et al. [17]</td>
<td>No</td>
</tr>
<tr>
<td>Paclitaxel versus topotecan</td>
<td>Ten Bokkel et al. [18]</td>
<td>No</td>
</tr>
<tr>
<td>PLD versus topotecan</td>
<td>Gordon et al. [19]</td>
<td>No</td>
</tr>
<tr>
<td>PLD versus paclitaxel</td>
<td>O’Byrne et al. [20]</td>
<td>No</td>
</tr>
<tr>
<td>PLD versus gemcitabine</td>
<td>Mutch et al. [21]</td>
<td>No</td>
</tr>
<tr>
<td>PLD versus gemcitabine</td>
<td>Ferrandina et al. [22]</td>
<td>No</td>
</tr>
<tr>
<td>Topotecan versus Treosulfan</td>
<td>Meier et al. [23]</td>
<td>Yes</td>
</tr>
<tr>
<td>PLD or topotecan versus canfosfamide</td>
<td>Vergote et al. [24]</td>
<td>Yes</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; OS, overall survival; PLD, pegylated liposomal doxorubicin.
carboplatin-based combinations, mainly carboplatin–gemcitabine [10]. In contrast, the large CALYPSO trial [11] has shown that carboplatin–PLD has a more favourable benefit/risk ratio than carboplatin–paclitaxel in patients with platinum-sensitive relapsing ovarian cancer [12]. The PLD combination was found to be significantly superior to carboplatin–paclitaxel in terms of PFS and to be associated with less alopecia, carboplatin hypersensitivity and neuropathy. In addition to platinum-based combinations, a non-platinum combination was found to be an option in platinum-sensitive disease as PLD–trabectedin has shown a PFS and OS advantage over PLD alone in this setting [13]. Notably, the combination of trabectedin and PLD appeared to be particularly beneficial in patients with partially sensitive relapse, resulting in substantially improved PFS and OS over single agent.

the addition of bevacizumab with chemotherapy in relapse

Ovarian cancer is considered as a vascular endothelial growth factor (VEGF)-driven disease as VEGF expression in the tumour is correlated with recurrence and OS, while ascites formation is dependent on VEGF’s capacity to enhance peritoneal vessels’ permeability. Three randomized, multicenter phase III trials with bevacizumab (15 mg/kg/3 weeks until progression) administered concomitantly with chemotherapy and pursued in maintenance until progression have been launched in nearly 2500 patients with ovarian cancer in relapse: two in sensitive relapse (GOG213 and OCEANS) and one in resistant relapse (AURELIA). The results of the GOG213 trial exploring the addition of bevacizumab to carboplatin/paclitaxel chemotherapy in platinum-sensitive disease are pending. However, OCEANS and AURELIA have reached their primary end-point (PFS) in 2011 and 2012, respectively [14]. In OCEANS, bevacizumab plus carboplatin–gemcitabine followed by single agent bevacizumab to 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 [14]. Preliminary OS results did not show a significant difference between both the arms. In AURELIA, bevacizumab plus single agent chemotherapy (PLD, weekly paclitaxel or topotecan) until progression significantly increased PFS compared with single agent alone (HR = 0.48, P < 0.0001) with a median PFS of 3.4 and 6.7 months, respectively [15]. Thus, there is evidence that bevacizumab prolongs disease control in both platinum-sensitive and platinum-resistant ROC. Future trials will provide important answers regarding the exact place of bevacizumab therapy in the recurrent setting according to previous administration of the anti-VEGF monoclonal antibody in first-line or even in the relapse setting.

new targets

A number of novel targets, both on the tumour cell and in the tumour microenvironment are under investigation. Currently, one of the most promising developments is the inhibition of angiogenesis mediated through inhibition of several growth factor receptors simultaneously, including VEGF receptor (VEGF-R). We are awaiting the results of large phase III trials run in first line (nintedanib or BIBF 1120, pazopanib) or in second line (ceridanib).

Another attractive approach is targeting homologous recombination deficiency, a DNA repair mechanism, with inhibitors of poly ADP ribose polymerase (PARP) such as olaparib. Patients with BRCA1 and BRCA2-associated tumours are remarkably sensitive to PARP inhibition. Patients with high grade serous tumours (about half of the patients with advanced ovarian cancer) frequently appear to be deficient in homologous recombination and olaparib treatment was found to significantly improve PFS in these patients compared with placebo in the platinum-sensitive setting [16, 25].
Another appealing target includes the folate receptor alpha expressed in >90% of the ovarian cancers and which can be targeted either by the monoclonal antibody farletuzumab or by EC-145, a conjugate of folic acid and a potent vinca alkaloid anti-tumour agent.

Others targets include PI3K/mTor/protein kinase B (AKT) intracellular signalling, targets involved in the cycle such as polo kinases or aurora kinases and finally immune cells as advanced ovarian cancer prognosis is highly dependent on the presence of T cells within the tumour.

collection

A significant improvement in ovarian cancer OS has been achieved in the last 15 years due to a better management of patients with relapse (including a better categorization of patients through PFI) and a greater number of drug options, including recent advance with bevacizumab. However, progress is nowadays challenged by limitations in drug availability due to regulatory debatable requirements (bevacizumab), drug shortage (PLD) or cost issues.

disclosure

The author has declared no conflicts of interest.

references