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Management of recurrent ovarian cancer with systemic therapy

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ABSTRACT

The majority of patients with recurrent ovarian cancer receive palliative chemotherapy. Several factors have been identified as predictors of response, but the main factor related to second-line treatment response is platinum-free interval (PFI). Patients with a PFI of <6 months have a poor prognostic profile and can be described as platinum resistant, while those patients with a PFI of >6 months are described as platinum sensitive. In platinum-sensitive patients the goal is to prolong survival, whereas in platinum-resistant patients treatment can only produce palliative benefits. An alternative classification of ovarian cancer has been proposed relating to platinum-refractory disease. Patients with refractory disease are those who have progressive disease during treatment or those with a treatment-free interval (TFI) of 4 months or less, intermediate group patients have a TFI of 4–12 months, while patients with sensitive-recurrent disease have a TFI of 12 months or more. Trial data have confirmed the superiority of platinum-based combination chemotherapy versus platinum monotherapy in platinum-sensitive patients. In patients pre-treated with paclitaxel plus carboplatin, a gemcitabine plus carboplatin combination is promising, avoiding alopecia, neurotoxicity and other toxicities, and may also benefit platinum-sensitive patients who have suffered early recurrence. Trials are currently under way for various compounds, including bevacizumab, erlotinib, pertuzumab, imatinib, enzastaurin, epothilones, topotecan and trabectedin. Clinical trials are also ongoing for combinations of molecular-targeting agents and conventional chemotherapeutics.

1. Introduction

Ovarian cancer is the second most frequently occurring gynaecological tumour, with approximately 48,000 new cases diagnosed annually in Europe, and 25,500 in the USA. Mortality from ovarian cancer is high, ranking as the fourth most common cause of cancer death in women, after lung, breast and bowel cancer. Annual monitoring of cancer deaths shows that approximately 31,000 women die each year from the disease in Europe, with 16,000 deaths annually in the USA. Ovarian cancer also remains the most frequently reported gynaecological tumour in the literature [1].

More than 80% of patients with recurrent disease will receive chemotherapy as palliative treatment. Several factors have been identified as predictors of response to chemotherapy. The probability of achieving a response to second-line treatment remains mainly related to platinum-free interval (PFI). In relapsed or recurrent

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Table 1 – Current most frequently used single-agent chemotherapeutics[a]. Courtesy of Dr M. Bookman

	Platinum	Paclitaxel	Topotecan	Gemcitabine	PEG-liposomal doxorubicin
Target:	DNA	b-tubulin	Topo-I	RN-reductase, nucleotide pool	Topo-II
Mechanism:	DNA adduct formation	Tubulin aggregation	Stabilise DNA–Topo complex	↓ DNA synthesis	↓ DNA synthesis
Schedule:	Independent	Dependent (toxicity)	Dependent (efficacy)	Dependent phosporylation	Prolonged clearance
Resistance:	↑ GSH, ↑ tolerance, ↓ retention	↑ MDR-MRP, tubulin mutations	↓ Topo-I, ↑ BCRP	↑ RN-reductase, ↓ transport, ↓ cDK	↑ MDR-MRP, ↓ Topo-II
Platinum interaction:	N/A	Platelet sparing	Enhanced toxicity	Enhanced toxicity	Enhanced toxicity

[a] Abbreviations: PEG, polyethylene glycol; DNA, deoxyribonucleic acid; Topo, topoisomerase; GSH, glutathione; MDR-MRP, multidrug resistance-multidrug resistance protein; BCRP, breast cancer resistance protein; cDK, cyclin-dependent kinase; N/A, not applicable.

disease, patients with a PFI of less than 6 months have a poor prognostic profile.

1.1. *Platinum-sensitive versus platinum-resistant disease*

Treatment following cytoreductive surgery and chemotherapy fails for the majority of women with advanced ovarian cancer, leading to a relapse. How rapidly this occurs following chemotherapy determines whether the patient is considered to be sensitive or resistant to taxanes generally or to platinum agents. Platinum sensitivity and resistance can be defined according to different specifications. Most commonly, *platinum-sensitive* patients are defined as those with an initial response to platinum therapy and a PFI greater than 6 months; *platinum-resistant* patients are defined as those with disease progression whilst on platinum therapy, a best stable response to prior platinum therapy or relapse less than 6 months after prior platinum therapy [2,3]. Platinum-resistant patients often have poor performance status, multiple disease sites, large tumour volume and mucinous or clear cell histology [4].

In platinum-sensitive patients the goal is to prolong survival, whereas in platinum-resistant patients, while some patients experience a prolonged progression-free survival (PFS) with treatment, most only achieve palliative benefits. To observe these benefits, however, platinum-resistant patients must be included in clinical trials with special emphasis, assuming that quality of life (QoL) is crucial and that no further 'active treatments' are an option.

1.2. *Consideration of platinum-refractory disease*

An alternative to classifying disease as platinum sensitive or platinum resistant was proposed at the *Second International Ovarian Cancer Consensus Conference* in 1998. This classification proposed that patients with refractory disease are those who have tumour progression during treatment or a treatment-free interval (TFI) of 4 months or less; intermediate group patients have a TFI of 4–12 months, while patients with sensitive-recurrent disease have a TFI of 12 months or more [5]. Patients with refractory disease have the lowest response rate to second-line therapy. This classification has yet to be accepted worldwide, but may perhaps be a more realistic means of assessing response following second-line treatment.

2. Impact of post-recurrence/progression treatment on first-line therapy endpoints

At the *Third International Ovarian Cancer Consensus Conference*, 2004, the impact of post-recurrence/progression treatment on the endpoints of first-line therapy was assessed [6]. It was concluded that although this therapy had an impact on overall survival (OS) it was not currently possible to standardise treatment. Moreover, even though OS is an important endpoint, PFS may be the preferred primary endpoint for trials assessing the impact of first-line therapy. This is because of the confounding effect of post-recurrence/progression therapy on OS [6]. There is a need to protect the validity of analysis of OS when PFS is the primary endpoint. How PFS is determined should also be made clear.

3. Activity of single-agent regimens in recurrent ovarian cancer

Should single-agent or combination regimens be selected for recurrent ovarian cancer? Today there is an expanding armamentarium of single agents at our disposal (Table 1). However, most of these drugs have limited activity in platinum-resistant ovarian cancer.

Results from randomised studies comparing the activity of some single agents have shown differences between preliminary and mature results. For instance, early Kaplan–Meier data for time-to-death of patients with recurrent ovarian cancer receiving topotecan versus paclitaxel demonstrated that the initial benefits in

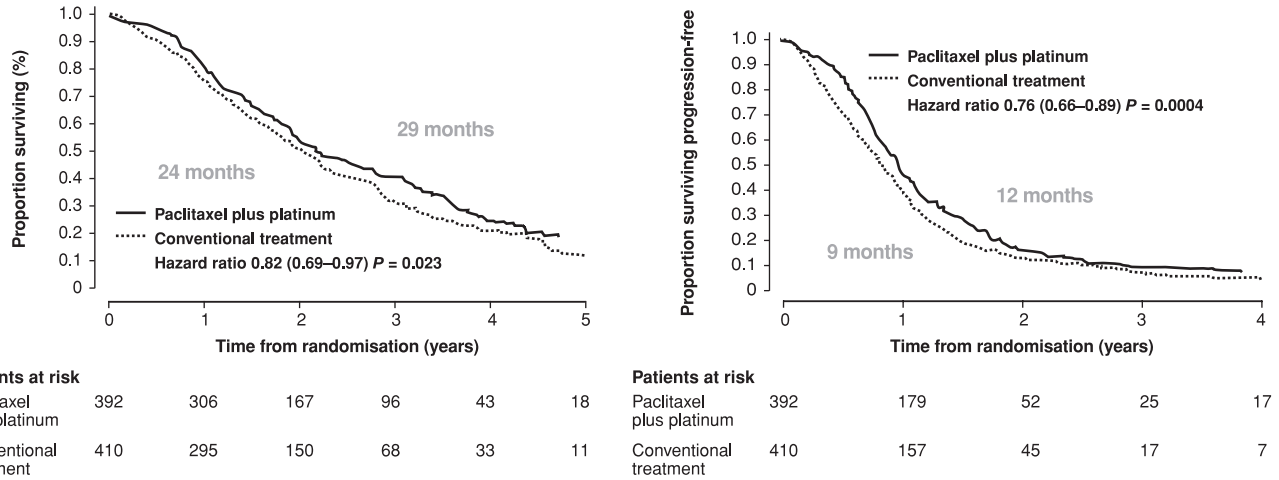

Fig. 1 – ICON-4 trial showing improved OS and PFS for combination therapy over monotherapy [14]. OS, overall survival; PFS, progression-free survival. © 2003 Reprinted with permission from Elsevier.

survival observed with topotecan in an early intention-to-treat (ITT) analysis were annulled by the late-stage analysis [7,8]. In another study, where platinum-sensitive and all-patient groups were treated either with topotecan or L-doxorubicin, preliminary results showed no statistical difference between groups in terms of OS. However, final data did appear to favour L-doxorubicin [9,10].

In a further randomised study, PFS data from a comparison of single-agent gemcitabine versus L-doxorubicin demonstrated no difference between the regimens in long-term PFS in platinum-resistant ovarian cancer patients [11]. Taken together, data from single-agent randomised studies have confirmed the importance of long-term survival analysis in the evaluation of second-line therapy. But how do combination regimens compare with monotherapy?

4. Combination versus monotherapy regimens

Until recently, patients with platinum-sensitive disease were treated primarily with single-agent carboplatin [12]. However, the large trials described below demonstrated that combination chemotherapy is more effective than single-agent carboplatin in platinum-sensitive recurrent ovarian cancer.

4.1. *Combination studies in platinum-sensitive patients*

Long-term survival analysis in the evaluation of second-line therapy appears more relevant in platinum-sensitive patients. In order to assess any benefit of combination regimens over monotherapy in platinum-sensitive patients, three large randomised studies, International Collaboration in Ovarian Neoplasm (ICON)-4, Grupo Espanol de Investigacion en Cancer de Ovario (GEICO)-0199 and Arbeitsgemeinshaft für Gynaekologische Onkologie/Ovarian Cancer (AGO-OVAR)-2.2, were begun. Results of the ICON-4 study were the first published and compared conventional platinum-based monotherapy with a taxane-based combination (paclitaxel plus platinum). It was the largest randomised trial examining second-line treatment for ovarian cancer, having enrolled 802 platinum-sensitive patients who had been treatment-free for 6 months in three countries [13]. It should be noted that patients had been treated with different first-line therapies. The success of the study was attributed both to the OS (the primary endpoint) and PFS emphatically favouring the combination regimen (Figure 1). After a median follow-up of 42 months, data showed that there was a significant improvement in OS. With a hazard ratio (HR) of 0.82, which translated into an increase in median survival of 5 months, and an absolute difference in 2-year survival of 7%, the paclitaxel plus platinum combination provided the better outcome [13].

Furthermore, although a subgroup analysis had insufficient power to detect differences in any particular subgroup of the study, there was a trend favouring the paclitaxel plus platinum combination over monotherapy in most subgroups (Figure 2). This tendency was not evidently clear in patients who had a PFI of 6–12 months, or in those who had paclitaxel as first-line therapy, although it should be noted that patient numbers in subgroups were insufficient to draw an adequate conclusion.

The second study that compared monotherapy with combination regimens in platinum-sensitive patients was published by the Spanish GEICO group [15]. The design of GEICO-0199 was similar to ICON-4 and involved randomising 81 platinum-sensitive patients to carboplatin (AUC 5) or carboplatin (AUC 5) plus paclitaxel (175 mg/m^2) in a phase II study with response rate as the primary endpoint. Again, the results favoured the combination arm. The ITT analysis showed that a higher, statistically significant overall response rate was obtained in the group treated with carboplatin plus paclitaxel (75.6% vs. 50%; P = 0.017). Complete and

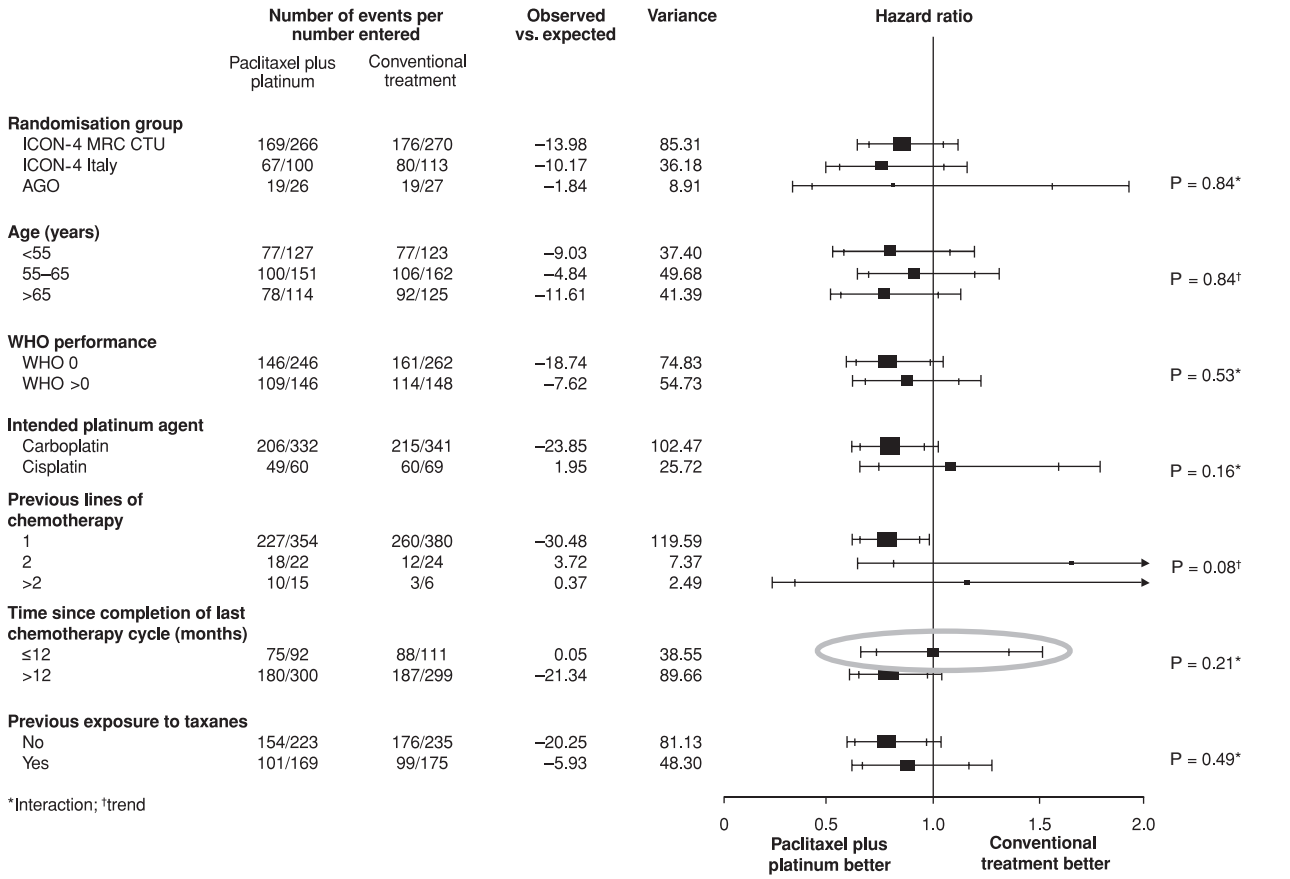

Fig. 2 – Effect of paclitaxel plus platinum chemotherapy on OS in subgroups [14]. ICON-4 MRC CTU, International Collaboration in Ovarian Neoplasm-4 Medical Research Council Clinical Trials Unit; AGO, Arbeitsgemeinschaft für Gynäkologische Onkologie; WHO, World Health Organization. © 2003 Reprinted with permission from Elsevier.

partial responses were also higher for the combination compared with monotherapy (26.8% vs. 20% and 48.8% vs. 30%, respectively). The median PFS for the combination was 12.2 months versus 8.4 months for monotherapy (HR = 0.54 [95% CI: 0.32–0.92]; P = 0.021). As in the ICON-4 study, the global QoL analysis for GEICO-0199, assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30, showed no significant differences between carboplatin plus paclitaxel and single-agent carboplatin regimens [15].

The third study, by Pfisterer et al. in a cooperation between AGO-OVAR, the National Cancer Institute of Canada Clinical Trials Group and the EORTC-Gynaecological Cancer Group as part of the Gynecologic Cancer Intergroup (GCIG), compared the combination of gemcitabine (1000 mg/m^2, days 1 and 8) plus carboplatin (AUC 4, day 1), every 21 days, with carboplatin (AUC 5, day 1), every 21 days [16]. The primary objective of this phase III trial was evaluation of PFS between arms; secondary objectives were response rate and duration, OS, toxicity and QoL. Results were superior for the combination arm. With a median follow-up of 17 months, the median PFS was 8.6 months (95% CI: 8.0–9.7) for the combination, versus 5.8 months (95% CI: 5.2–7.1) for single-agent carboplatin (HR = 0.72 [95% CI: 0.57–0.90]; P = 0.0031). The overall response rate was 47.2% (95% CI: 39.9–54.5%) versus 30.9% (95% CI: 24.1–37.7%), P = 0.0016, for the combination versus carboplatin alone; QoL was significantly higher for the combination. Median PFI at the 6–12-month point was significantly better for the combination (7.9 vs. 5.2 months; HR = 0.69 [95% CI: 0.49–0.97]; P = 0.0311) (Figure 2), which is important to note when comparing data with those from the same point in the ICON-4 study. On the negative side, as expected, grade III/IV haematological toxicities were significantly higher for the combination. Data showed a benefit for the combination group over monotherapy when the median PFI was greater than 12 months (9.7 vs. 6.7 months; HR = 0.72 [95% CI: 0.54–0.96]; P = 0.0254), and also in patients previously treated with platinum plus paclitaxel (9.7 vs. 5.9 months; HR = 0.63 [95% CI: 0.48–0.82]; P = 0.0006) [17].

Overall, data from randomised trials have confirmed the superiority of platinum-based combination chemotherapy versus platinum monotherapy in platinum-sensitive ovarian cancer patients. For patients pre-treated with paclitaxel plus carboplatin,

with residual toxicities, a gemcitabine plus carboplatin combination appears to be promising, avoiding alopecia, neurotoxicity and other toxicities, and may also benefit platinum-sensitive patients pre-treated with paclitaxel plus carboplatin who suffered early recurrence (6–12 months).

4.2. *Combination studies in platinum-resistant patients*

The response rate to a re-challenge with 3-weekly platinum or any non-platinum chemotherapy in platinum-resistant patients is less than 20%. Phase II studies in platinum-resistant patients found that the response to dose-dense once-weekly platinum-based regimens ranged from 48% to 64%, and the majority of patients responded within 8 weeks of treatment initiation [18]. PFS ranged from a median of 5 months with cisplatin plus etoposide to 11 months with paclitaxel plus carboplatin. The median survival was 11–15 months. An outpatient dose-dense weekly paclitaxel (90 mg/m^2) plus carboplatin (AUC 4) regimen seems similarly effective and is better tolerated. However, whether a once-weekly regimen is more effective than 3-weekly paclitaxel plus carboplatin needs further examination, and these regimens are being investigated in the new EORTC trial in resistant disease.

4.3. *Gemcitabine in combination studies*

With a response rate of approximately 16%, gemcitabine has shown promising activity in recurrent ovarian cancer patients previously exposed to platinum plus paclitaxel combination therapy [19]. Gemcitabine has been explored in combination with other drugs including paclitaxel, docetaxel and topotecan. In all of these studies, combination treatments appeared to yield higher response rates than those traditionally observed with gemcitabine monotherapy in platinum-resistant ovarian cancer patients [14,20–22], but no results from randomised studies are currently available. Gemcitabine combined with cisplatin also yielded higher response rates than expected in platinum-resistant patients [23,24], and may even reverse platinum resistance, although this has not yet been confirmed in prospective randomised trials. As such, the role of combination therapy in this patient group remains to be defined; single-agent therapy should still be considered the standard treatment in platinum-resistant recurrent disease.

5. Clinical trials of novel and conventional compounds for second-line ovarian cancer

New molecular-targeting agents and conventional therapies are at various stages of development for treating ovarian cancer. Some of these agents are described.

5.1. *New molecular-targeting agents*

Encouraging data have been obtained from studies of new molecular-targeting agents, including the small molecule epidermal growth factor receptor-1 (HER1/EGFR) inhibitor erlotinib (phase II), the humanised antibody pertuzumab (phase II) that interferes with functional human epidermal growth factor receptor-2 (HER2) heterodimerisation or the monoclonal antibody vascular endothelial growth factor (VEGF) inhibitor bevacizumab (phase II) [25]. Small-molecule VEGF-receptor inhibitors, such as 17AAG and VEGF Trap, are in Phase I/II trials. Other studies with new compounds such as the small-molecule tyrosine kinase inhibitor imatinib (phase I/II) or the protein kinase C inhibitor enzastaurin (phase I) are now ongoing. These data are reviewed elsewhere [26,27].

5.2. *New conventional or cytotoxic agents*

Interesting results have also been obtained with new conventional therapeutics, some of which are described.

Epothilones

Epothilones (phase II/III) are non-taxane microtubule-stabilising agents that differ in their ability to retain activity against multidrug resistant cell-lines and tumours. Agents in this class have shown activity in both platinum-sensitive and platinum-resistant ovarian cancer patients, either as monotherapy or when combined with carboplatin. Examples in development include BMS-247550, EPO-906 and KOS-862, among others.

Topoisomerase I inhibitors

Topotecan, a topoisomerase I inhibitor, is another conventional drug given a new lease of life through alteration of its treatment schedule. The myelotoxicity and suboptimal patient convenience associated with daily ($\times$5) topotecan prompted investigators to explore alternative regimens, including a weekly regimen of topotecan. Thus, in an ongoing phase II study, Gynecologic Oncology Group (GOG)-146Q, the novel schedule of 4.0 mg/m^2/week (days 1, 8 and 15 of a 28-day cycle until progression or toxicity) is being compared with the older schedule of topotecan 1.25 mg/m^2 on days 1–5 of a 21-day cycle. This novel schedule was based on an earlier phase I/II study [28] of second- and third-line treatment in ovarian cancer patients with measurable disease or elevated CA-125, which provided the basis for further investigation of single-agent and combination regimens in previously treated patients, up to a maximum recommended dose of 6.0 mg/m^2/week.

Another topoisomerase I inhibitor being investigated is gimatecan. This novel, orally administered camptothecin analogue has shown a good therapeutic index in preclinical tumour models [29], favourable activity and toxicity in a phase I study [30] and has recently completed a phase II study [31].

Table 2 – Early clinical trials of chemotherapy in combination with molecular-targeting agents for ovarian cancer [31–34] [a]

Investigators	Phase	MTA	Chemotherapy	Setting	Conclusion
Vasey et al. [34]	I	Erlotinib	Carboplatin AUC 5; docetaxel 75 mg/m^2	Front line	MTD of erlotinib, 75 mg (half the conventional dose); DLT, rash, diarrhoea; now in phase III testing
Mavroudis et al. [35]	I/II	Gefitinib	Vinorelbine; oxaliplatin	Second line: one prior treatment or more	MTD of vinorelbine, 20 mg/m^2 d1, 8; MTD of oxaliplatin, 40 mg/m^2 d1, 8; DLT, neutropenia, diarrhoea; 24% RR (5/23) in platinum-resistant patients; 90% RR (9/10) in platinum-sensitive patients
Aghajanian et al. [36]	I	Bortezomib	Carboplatin AUC 5	Second line: one prior treatment or less	MTD not determined; no DLT; 78% RR (7/9) (only one patient was considered platinum-resistant)
Aghajanian et al. [37]	II	Cetuximab	Paclitaxel 175 mg/m^2; carboplatin AUC 6	Front line	Ongoing

[a] Abbreviations: MTA, molecular-targeting agent; AUC, area-under-the-curve; MTD, maximal tolerated dose; DLT, dose-limiting toxicity; RR, response rate.

Pemetrexed

Injectable pemetrexed, a multi-targeted, antifolate, antineoplastic agent, is another new treatment under investigation for platinum-resistant ovarian cancer that includes recurrent ovarian, fallopian tube or primary peritoneal cancer. There are two main ongoing studies: GOG-126 – a phase II study with pemetrexed (900 mg/m^2) given every 21 days, and the randomised JMHF trial – a phase II trial comparing two doses of pemetrexed (500 mg/m^2 and 900 mg/m^2) every 21 days.

TLK286

Another promising agent is TLK286, a pro-drug that activates when it binds with glutathione-S-transferase P1-1, the enzyme over-expressed in ovarian cancer [32]. Two studies in second-line platinum-refractory and -resistant recurrent ovarian cancer, the Assessment of Survival in Solid Tumours (ASSIST)-1 study comparing TLK286 with doxorubicin or topotecan, and the ASSIST-3 study comparing TLK286 plus carboplatin with doxorubicin, are closed and the results are pending.

Trabectedin

Trabectedin (ET-743), a tetrahydroisoquinoline alkaloid derived from a Caribbean sea squirt (*E. turbinata*), has shown interesting preliminary responses. This drug interacts with the minor groove of DNA and alkylates guanine at the N2 position thereby affecting various transcription factors involved in cell proliferation. Sessa et al. published data from patients resistant (n = 30) or sensitive (n = 29) to prior platinum or taxane therapy who were treated with a 3-hour infusion of trabectedin (1300 μg/m^2) every 21 days [33]. The objective response rate was 43% in platinum-sensitive patients (95% CI: 23–65%), which compares favourably with other salvage treatments, and the estimated median time to progression was 7.9 months (95% CI: 7.5–14.1 months); two partial responses were observed in platinum-resistant patients. Responses were durable for up to 12.9 months (median 5 months). The predominant toxicities were neutropenia, asthenia and elevated levels of aminotransferases at the recommended dose [33]. Trabectedin, combined with liposomal doxorubicin, is being compared with liposomal doxorubicin alone in a randomised Phase III study of relapsed ovarian cancer.

Novel combinations

Clinical trials are also ongoing for combinations of molecular-targeting agents and conventional chemotherapeutics. These include erlotinib plus carboplatin plus docetaxel, and gefitinib plus oxaliplatin plus vinorelbine, among others (Table 2) [34–37].

6. How should new treatment modalities be integrated into studies?

According to conclusions from the *Third International Ovarian Cancer Consensus Conference*, 2004 [6], it currently remains unclear how to best integrate new treatment modalities into studies. It was agreed that identification and validation of predictors of response to new biological agents such as targeted therapies, vaccines and monoclonal antibodies should be prioritised in such studies, and that standard clinical endpoints should continue to be used in phase III studies. It should also be remembered that, as with all novel treatments, targeted therapies require a target, and that ovarian cancer is a heterogeneous disease that cannot be treated by homogeneous therapy, as can be the case with other tumours.

Patient accrual into clinical studies must be rapid and include as many patients as possible to swiftly answer major questions. This need was highlighted in the consensus statements of the *Second International Ovarian Cancer Consensus* meeting in 1998. It was suggested that a network of national or international groups might facilitate evaluation of new treatment options [5]. The result was the establishment of the GCIG. Regular meetings with representatives of cooperative groups were organised from 1995 onwards, and the GCIG has

presently evolved to include fifteen cooperative groups. Their aims are to promote international collaboration and clinical research, support educational activities, and improve outcomes through more efficient data gathering and cooperation in relapsed ovarian cancer patients [38].

7. Conclusions

In ovarian cancer, recurrent/relapsed disease is relatively common after first-line chemotherapy: more than 80% of patients will develop recurrent disease after initial treatment. PFI is still the most important predictive variable of response to second-line chemotherapy. In patients who have previously responded to carboplatin or cisplatin, the aim of second-line chemotherapy is to prolong survival. However, in platinum-resistant patients second-line chemotherapy will only have palliative benefits.

The effect of post-recurrence/progression treatment on the endpoints of first-line chemotherapy has recently been investigated, and it has been shown that post-recurrence chemotherapy has an impact on OS. For clinical trials that assess first-line chemotherapy, PFS may be the preferred primary endpoint because of the confounding effects of post-recurrence therapy on OS. Importantly, PFS should be clearly defined. If PFS is selected as the primary endpoint then measures should be taken to protect the validity of OS analysis. However, it is not possible to standardise post-recurrence/progression therapy at present [6].

The efficacy of combination chemotherapy in treating recurrent/relapsed ovarian cancer was considered comparable with that of single agents until the results of the ICON-4/AGO-OVAR-2.5, GEICO-0199 or AGO-OVAR-2.5/NCIG-CTG/EORTC-GCG trials were made available. In all three studies, significant differences in OS and PFS were observed in favour of platinum-based combination therapy in platinum-sensitive patients.

Current questions in the treatment of recurrent/relapsed ovarian cancer relate both to clinical practice and clinical research. For clinical practice these refer not only to the criteria for selecting patients but also to the drugs and endpoints of treatment. For clinical research, the failure of current screening procedures means that the most important points that need to be addressed relate to how and when patients should be screened.

New drugs have thus far shown some advantage in terms of tumour response and, in selected cases, OS only in the patient group defined as potentially platinum-sensitive. From this observation, criteria can be derived for selecting drugs for salvage treatment, and for choosing patients to whom participation in a phase II/III study could be proposed.

Finally, results data of some phase III studies in the second-line setting have also confirmed the importance of long-term survival analysis in the evaluation of second-line therapy, an evaluation that is both relevant and feasible only in platinum-sensitive patients.

Novel agents against new biological targets are being actively investigated in both platinum-sensitive and platinum-resitant relapsed patients. The absence of haematological toxicity enables the combination of these new molecules (erlotinib, gefitinib, bevacizumab, etc.) to be used together with standard chemotherapy. Large-scale randomised trials are ongoing to define the role of these new agents, both as monotherapy and in combination treatments. It is hoped that a combination of treatments, including molecular-targeting agents and conventional therapeutics, will ultimately lead to improved survival.

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