Front-line therapy of Advanced Ovarian Cancer- New Approaches

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Abstract

Background: The five-year survival of ovarian cancer has slowly increased but to date much of this has been due to the use of more lines of treatment rather than better first-line therapy. In this setting, there has been little improvement over the past fifteen years. The introduction of new treatments to extend time to first progression and overall survival remains a key objective of clinical research.

Design: The focus of research in the previous decade has been on the incorporation of anti-angiogenic therapy or dose-dense scheduling of paclitaxel to improve outcome. The new trials being conducted build on the knowledge gained, and are focussing on two new areas of research, the use of PARP (poly-ADP ribose polymerase) inhibitors and immunotherapy.

Results: Ongoing randomised trials using PARP inhibitors or immune checkpoint inhibits are reviewed and the potential benefits and challenges of using these agents are discussed.

Conclusions: Improvements in outcome from some of the many open trials may present challenges; interpretation of the outcome data needs to be taken in the context of clinical benefit and a health-economic assessment. The latter is becoming ever-more important as the cost of trials with combinations of targeted therapy is very great

Key Words:
Ovarian Cancer; first-line chemotherapy; anti-angiogenesis; PARP inhibitors; immunotherapy

Introduction

Surgery and chemotherapy, based on carboplatin and paclitaxel have been long established as the cornerstone for the primary management of ovarian cancer. The completeness of surgery is prognostic and this has led increasingly to the promotion of specialization and centralization. However, except in some cases of early stage ovarian cancer surgery alone is not curative; systemic therapy remains the most important component for the long-term survival of women with ovarian cancer. The three and five-year survival of ovarian cancer have improved over the last two decades and the question is to what extent has this been due to improvements in first-line therapy? Benefits from new first line treatments can be measured in several ways. Firstly, there may be a true increase in cure-rate, as measured by a reduced number of patients relapsing after first-line therapy. The key initial indicator that this might be occurring is an improvement in progression-free survival (PFS), or more specifically recurrence-free survival followed by an increase in overall survival (OS). However, improvements in PFS may not translate into an OS benefit if subsequent treatments have a differential effect, so as to annul differences seen in PFS in the first-line treatment. In contrast, there may be no direct benefit from new first line therapies on PFS but improvements in OS may arise through better use of subsequent lines of treatments.

In this review, the impact on PFS and OS of first line treatments that have been studied over the last decade are discussed in relation to ongoing and new trials. These summarise current strategies to improve the outcome of first-line therapy in ovarian cancer.

A decade of progress in the first line treatment of ovarian cancer?

The publication in 2009 of GOG 182/ICON5, the largest prospective trial of first-line chemotherapy in ovarian cancer comparing four treatment arms of three cytotoxic drugs to three-weekly carboplatin and paclitaxel has served as a benchmark for future trials in ovarian cancer[1]. It showed that a third drug, added to three weekly carboplatin and paclitaxel did not increase the PFS, and that this combination was the standard of care for intravenous chemotherapy, and the control arm for future trials of first-line therapies. Where does the field stand, almost a decade later? There

have been two key strategies explored to improve the outcome of intravenous chemotherapy. The first moved away from adding new cytotoxic drugs and used the anti-VEGFA antibody, bevacizumab, the first molecularly targeted drug to be explored in first-line treatment of ovarian cancer. The second explored dose-scheduling, increasing the dose-intensity of paclitaxel by giving it weekly rather than three-weekly in combination with carboplatin.

Two large phase III trials of three weekly carboplatin and paclitaxel with or without bevacizumab were published in 2012 [2, 3] and it is important to consider the conclusions that can be drawn from these studies. Firstly, the addition of three weekly bevacizumab to chemotherapy and then continued as maintenance after chemotherapy significantly improved the PFS of women with newly diagnosed ovarian cancer who had undergone primary surgery. The benefit, measured as the improvement in median PFS was 3.8 months for GOG218 and the hazard ratio was 0.717 (95% CI, 0.625 to 0.824; P<0.001). For ICON7 the median difference was 2.4 months with a hazard ratio of 0.81 (95% CI, 0.70 to 0.94; P=0.004). The contribution of bevacizumab in both studies was broadly similar. It should be noted that the dose of bevacizumab GOG 218 was twice that in ICON7 (15 mg/kg versus 7.5mg/kg) and the duration of treatment was 15 months in the former study and 12 months in the latter. However, neither trial demonstrated an improvement in OS, so the interpretation of benefit depended on assessing the value extending the median PFS. Agreement about the beneficial value of the difference in PFS was not universal; the drug was approved for first-line therapy (15 mg/kg) by the European Medicines Agency, but not submitted to the Federal Drugs Agency as the overall benefit was believed to be too small to obtain approval. Some countries adopted the lower (unlicensed) ICON7 dose for therapy. This was done as the magnitude of overall benefit was similar to GOG218, but the duration of treatment was shorter, the cost was less. Furthermore, an analysis of patients in a ‘poorer prognosis’ group (sub-optimally debulked disease or stage IVdisease) showed not only a better improvement in PFS but also an improvement in OS. In ICON7 the median OS in this subgroup increased from 34·5 months [95% CI 32·0–37·0] to 39·3 months [37·0–41·7] with bevacizumab; using a restricted mean survival analysis (log-rank p=0·03) [4]. By contrast the better prognosis group showed no PFS or OS benefit.

The added toxicity of bevacizumab (hypertension, proteinuria and fistula formation) was low and 17% patients discontinued bevacizumab due to adverse events. As the use of neoadjuvant chemotherapy is becoming more widely established, it is important to examine how bevacizumab might be integrated and to understand whether there is an increase in the preoperative response rate by adding bevacizumab. Whether this is the case is not entirely clear but a randomised non-comparative phase II trial, ANTHALYA demonstrated a higher complete resection rate at IDS following 4 cycles of chemotherapy with bevacizumab (3 cycles) than in the reference group, without any significant increase in toxicity[5]. However, the different interpretation of data from bevacizumab trials has led to some uncertainty about the true value of the drug in first-line treatment, and there is variation in its use across the world. The 5th Ovarian Cancer Consensus Conference concluded that there was no consensus about the use of first-line bevacizumab but that it was an acceptable control arm for future clinical trials[6]. In many countries within Europe, bevacizumab is accepted as 'the' standard of care, and as the maximum benefit was seen at the time the drug was stopped, a large trial has followed GOG 218 comparing 15 versus 30 months of treatment to see if the benefit – both PFS and OS could be extended further (NCT01462890). The results of this AGO-led 'Boost' trial, which has completed accrual are not yet known.

As the results of bevacizumab trials in ovarian cancer began to emerge, other trials with anti-angiogenic agents were started. These included a trial with the oral VEGFR inhibitor, pazopanib given as 24 months maintenance after surgery and carboplatin and paclitaxel [7] and a trial with the triple angiokinase inhibitor, nintedanib given with chemotherapy and then as maintenance[8]. Both trials demonstrated that there was a statistically significant improvement in median PFS with the anti-angiogenic drugs, 5.6 months and 0.6 months respectively. However, netiher company has decided to take these results forward and submit either drug to the regulatory authorities for licensing, probably because interim analyses showed no benefit in OS. Neither drug has been taken forward for licensing in ovarian cancer. A third trial, TRINOVA-3 with trebananib (AMG386), an angiopoietin inhibitor in Stage III-IV ovarian cancer (NCT01493505) was terminated early due to lack of benefit.

In 2009, Katsumata and colleagues published the results of a Japanese randomised trial comparing the effect of dose-dense weekly or three weekly paclitaxel added to three weekly carboplatin in women with stage II-IV ovarian cancer. In this trial of 631 patients, there was a significant improvement in median PFS in favour of weekly paclitaxel of 28.0 months (95% CI 22.3-35.4) compared with 17.2 months (95% CI 15.7-21.1); (hazard ratio [HR] 0.71; 95% CI 0.58-0.88; p=0.0015 p=0.0015)[9]. An updated survival analysis in 2013 showed that the median OS was 100·5 months (95% CI 65·2-∞) in the dose-dense treatment group and 62·2 months (95% CI 52·1-82·6) in the conventional treatment group (HR 0·79, 95% CI 0·63-0·99; p=0·039)[10]. These results were very provocative, as these differences in both PFS and OS were the largest that had been seen in randomised trials of first line therapy in ovarian cancer. As a result, three further phase III trials were initiated with the purpose of confirming the value of dose-dense paclitaxel. The first, GOG 262 used a similar design to the Japanese study but allowed the addition of three weekly bevacizumab to either arm. This was a patient/physician choice, and bevacizumab was adopted by 84% of the 692 patients in the trial. The results of GOG 262 showed no overall benefit of weekly paclitaxel, although a subset analysis of the patients who did not receive bevacizumab showed a PFS benefit similar to that seen in the Japanese trial[11]. A second international three-arm trial with over 1500 patients, ICON 8 is due to report later this year. In addition to a direct comparison of weekly and three weekly paclitaxel there is a third arm comparing the weekly administration of both carboplatin and paclitaxel with the standard three-weekly regimen. A weekly schedule of both drugs was used in a third study, MITO-7, a trial in more than 800 patients. The dose of paclitaxel, 60 mg/m^2 was lower than in the Japanese study and carboplatin AUC2 was given weekly. There was no difference in PFS between the weekly and three weekly regimens[12]. In conclusion, apart from the Japanese trial, there has not yet been any further evidence to demonstrate a significant benefit of weekly paclitaxel.

Is intraperitoneal therapy still an option to consider?

There is probably no area in the field of therapeutics of ovarian cancer that has generated more controversy than the results of intraperitoneal therapy. The topic is discussed in detail elsewhere and is mentioned here only because it remains an

unresolved issue, and therefore a topic that needs to be considered in designing new trials for the treatment of ovarian cancer. The most recently reported randomised study, GOG 252 compared intravenous carboplatin and paclitaxel to two intraperitoneal regimens; one contained intraperitoneal carboplatin and the other intraperitoneal cisplatin and paclitaxel. The dose of intraperitoneal cisplatin was 75 mg/m^2, lower than the dose used in the previous trial, GOG 172[13]. Bevacizumab was used in all three arms. The trial failed to show any difference in PFS between the three treatment arms [14]. The results of an ongoing Japanese Gynecologic Oncology Group trial, iPocc comparing intravenous and intraperitoneal carboplatin are still awaited (NCT01506856). Even though the long-term follow up of GOG172, intraperitoneal cisplatin and paclitaxel continues to show a survival benefit at 10 years[15] there is currently little global enthusiasm for developing new trials of intraperitoneal therapy. Perhaps the key reason for this lies with the expectation that novel molecular therapies will demonstrate much larger benefits than new trials with intraperitoneal therapy.

Novel targeting approaches to first-line treatment of ovarian cancer

Research into the treatment of recurrent ovarian cancer over the last decade has identified two new approaches that could potentially have a significant impact on first-line treatment. The first involves the use of PARP inhibitors, drugs that inhibit poly-ADP ribose polymerase, an important enzyme involved in the repair of DNA single-strand breaks. PARP inhibitors are oral agents that have been shown to prolong significantly PFS in patients with mutations in a BRCA gene. Cells with a BRCA mutation have impaired repair of DNA double-strand breaks by homologous DNA recombination (HR), and rely on PARP activation to repair DNA damage. In these cells inhibition of PARP leads to cell death by a process called synthetic lethality. It has been estimated that 30-50 % of high grade serous tumours may be susceptible to PARP inhibitors due to mutations in other HR repair genes, or inhibition of BRCA function due, for example to DNA methylation[16, 17]. There is now good evidence that PARP inhibitors, such as olaparib, niraparib or rucaparib have a much wider spectrum of activity in high grade tumours which is broadly correlated with the empirically derived ‘platinum-sensitivity’. It may be possible to enhance the activity of PARP inhibitors further by combining them with anti-

angiogenic drugs. This was demonstrated in a study by Liu and colleagues[18], who compared the activity of olaparib with a combination of olaparib and cediranib, an oral VGFR tyrosine kinase inhibitor in women with platinum-sensitive ovarian cancer. The combination of olaparib and cediranib was more active than olaparib, and this difference was particularly marked in the subset of patients without a BRCA mutation. These findings support the hypothesis that inhibition of angiogenesis may enhance the degree of HR repair deficiency, making cells more susceptible to PARP inhibitors. The question now is whether PARP inhibitors, alone or in combination with other molecular targeted therapies will improve the outcome of first-line therapy.

The second development has been in the field of immunotherapy, using immune checkpoint inhibitors. Studies in ovarian cancer have progressed more slowly than those in other solid tumours, and much of the current information is derived from single-arm phase II studies or 'basket' trials containing cohorts of ovarian cancer patients. Currently, it appears that the response rate to immune checkpoint inhibitors is around 10% but stabilisation of disease is seen in a larger proportion of patients, some of whom have a prolonged period of disease control. These results have appeared sufficiently promising to take forward first-line trials with immune checkpoint inhibitors.

First-line PARP inhibitor trials

Maintenance post-chemotherapy has evolved as a major strategy for using PARP inhibitors, led by the licencing of maintenance olaparib in platinum-sensitive relapsed BRCA-mutated high grade serous cancer in many countries[19]. This approach has been extended to first-line therapy in the SOLO1 trial (NCT01844986) in which olaparib 300mg daily or placebo is given for 2 years post partial or complete response to chemotherapy in patients with BRCA-mutated high grade serous or endometrioid ovarian, fallopian tube or primary peritoneal cancer. The trial has completed recruitment but the analysis, driven by the number of progression events has not yet occurred. A different approach has been adopted in the GOG 3005 trial, an international collaborative trial sponsored by Abbvie, using veliparib in combination with chemotherapy and then as maintenance. In this 3-arm trial patients receive carboplatin/paclitaxel with veliparib or placebo followed by veliparib

maintenance, switch to placebo maintenance or continuations of placebo maintenance (NCT02470585). The trial allows standard three-weekly or dose-dense paclitaxel but it does not include bevacizumab. The trial aims to recruit about 264 patients with a BRCA mutation out of a total of about 1100 patients.

In patients with recurrent ovarian cancer it has been clearly shown that PARP inhibitors have a wider spectrum of activity, beyond patients with a BRCA mutation [19, 20]. Furthermore, the emerging data of the benefit of adding cediranib to olaparib [18] has generated interest in developing further combination studies. Phase I data have shown that olaparib and bevacizumab can be combined [21], although it is not clear if the two drugs are additive. This has led to the PAOLA-1 trial (NCT02477644), a first-line ovarian cancer study in which olaparib maintenance is added to bevacizumab, a standard targeted therapy used in many European countries. This ongoing study, led by the French GINECO group will randomise 612 patients without progression following initial treatment with chemotherapy and bevacizumab to the addition of maintenance olaparib, 300mg daily for 24 months or placebo to standard-dose bevacizumab given for 15 months in total. The trial has almost completed recruitment. Following the recent publication of the NOVA trial with niraparib in recurrent ovarian cancer patients[20] a first-line maintenance trial has been launched in any patient with a stage II-IV high-grade tumour and partial or complete response to surgery and chemotherapy. The PRIMA trial (NCT02655016) will randomise 330 patients 2:1 to niraparib or placebo maintenance until progression or toxicity.

Trials with immune checkpoint inhibitors

In this fast-moving area of clinical cancer research, inhibitors of PD-1 and PDL-1 are now being evaluated in the first-line treatment of ovarian cancer. Following the small but encouraging results of nivolumab in recurrent ovarian cancer[22], publicly presented, but unpublished similar data with avelumab[23], the fully human IgG1 antibody that specifically targets and blocks PD-L1, the ligand for PD-1 receptor, has led to an international first-line ovarian cancer trial. In JAVELIN 100 (NCT02718417) , patients with stage III-IV ovarian cancer are randomised to one of three arms; avelumab maintenance, 10mg/kg two-weekly, placebo, or avelumab with

chemotherapy (avelumab 3-weekly) and then as two-weekly maintenance for 2 years. The trial, which is currently recruiting permits weekly or three weekly paclitaxel, and it also allows neoadjuvant chemotherapy. However, it does not include bevacizumab, and in some countries, this has been felt to be a draw-back in the design, which otherwise accommodates broad-ranging real-world practice. More recently, the ENGOT and GOG partners group in collaboration with Roche have launched IMagyn50, a trial that includes bevacizumab and atezolizumab, an IgG1 antibody targeting PDL-1 (NCT03038100). In this study patients with stage II-IV ovarian cancer are treated with standard three-weekly carboplatin/paclitaxel and bevacizumab with either atezolizumab or placebo added during the chemotherapy phase and as maintenance for up to 22 three-weekly cycles. The trial also allows a cohort of patients treated with neoadjuvant chemotherapy. Notwithstanding the absence of results from these studies discussions are being held about combining checkpoint inhibitors with PARP inhibitors. Early data in ovarian cancer with durvalumab and olaparib in heavily pretreated women are encouraging[24]. Collaborations will be required between companies, as there are several PARP and immune checkpoint inhibitors that could be paired up for such studies. The challenge is to select a design that not only optimises the combination but builds on as yet unknown results from ongoing trials with both agents, with or without the inclusion of bevacizumab.

Evaluation of the results of first line trials in ovarian cancer

Whilst the design of trials becomes more complex with increasing numbers of drugs, there are still fundamental issues relating to the assessment of outcome. These have recently been addressed in the 5th Ovarian Cancer Consensus Meeting. Whilst OS continues to be the ‘gold-standard’ for outcome it is recognised that demonstration of an increase in OS is not often achievable. Multiple post-progression therapies would require an (uneconomically) large sample size to demonstrate a relatively small OS improvement. Furthermore, with a long post-progression survival it would take many years for OS differences to emerge, and this can have a negative effect on financial investment in new drug development. In the consensus meeting it was concluded that PFS remains an acceptable primary endpoint but OS should be a secondary endpoint, and other endpoints such as patient-reported outcomes and other Quality

of Life indicators, time to first- or second-subsequent therapy (PFS2) should be included[6]. It was also acknowledged that several regimens can be used as 'controls'; three weekly carboplatin and paclitaxel remains the standard, but other regimens for which at least one randomised trial has shown superiority could be used, provided that the trial including such alternative regimens was stratified. The strategies being developed are complex and overlap, often employing more than one molecular targeting agent (TABLE). It will not be long before trials emerge that will combine three molecular targeted therapies- anti-angiogenic agents, inhibitors of PARP and immune checkpoints in the same trial.

Concluding remarks

As in many areas of clinical cancer research, many new molecularly targeted drugs are now showing activity in ovarian cancer. Whilst initial studies are performed in patients with recurrent disease, the impetus for developing these new therapeutic agents lies in finding better initial treatments for ovarian cancer. An increase in the rate of cure is the ultimate aim, but novel treatments that fail to do this may nevertheless significantly prolong the time before second line therapies are needed, and with big gains in PFS, differences in OS may emerge. Until the most recent trials with inhibitors of PARP or immune checkpoint pathways began, there had only been a modest improvement in PFS with molecularly targeted drugs, such as bevacizumab. The pace of development of these novel trials is fast, which partly is a reflection on the speed of development of these new agents and also commercial competition for the potential financial gains. The risks are that new trials are being launched ahead of results of some of the ongoing or recently completed trials, and this can pose challenges for the design of new studies. With the exception of trials in $BRCA^{mut}$ tumours, none of the studies use markers known to be predictive of outcome, and cannot currently be claimed to represent personalised therapies. However, the potential benefit of these new agents for patients could be considerable, and recruitment to these studies has not been problematic. But each new drug is expensive and the introduction of combinations of novel targeted agents in the large first-line population could pose major financial burdens on healthcare providers. It is becoming increasingly important to consider the cost-benefit of

therapy and good quality health economic assessments are needed to support a scientific evidence-base.

Table: Ongoing phase III first-line trials in ovarian cancer with targeted agents

	Trial Number	Anti-angiogenic drug	PARP inhibitor	Immune checkpoint inhibitor	Type
Boost (AGO)	NCT01462890	bevacizumab			15 v 30 months bevacizumab maintenance
GOG3005 (Abbvie)	NCT02470585		veliparib		3-arm chemotherapy with veliparib and veliparib maintenance
PAOLA-1 (GINECO)	NCT02477644	bevacizumab	olaparib		olaparib maintenance added to bevacizumab
SOLO-1 (AstraZeneca)	NCT01844986		olaparib		olaparib maintenance in $BRCA^{mut}$ ovarian cancer
PRIMA (Tesaro)	NCT02655016		niraparib		Niraparib maintenance
JAVELIN 100 (Pfizer)	NCT02718417			avelumab	avelumab maintenance and avelumab with chemotherapy and maintenance
IMagyn50 (Roche)	NCT03038100	bevacizumab		atezolizumab	atezolizumab maintenance added to bevacizumab

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