First-line treatment of ovarian cancer: questions and controversies to address

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Introduction

There is little doubt that the survival of women with advanced ovarian cancer has improved over the last two decades.[1] Platinum and paclitaxel are the two key drugs that have now been in standard use for over 20 years. This followed the results of two large-scale trials with more than 6 years of follow up that demonstrated an 11% advantage in survival with cisplatin-paclitaxel compared with cisplatin-cyclophosphamide, and about 40% surviving 5 years.[2] Recently, studies with carboplatin and paclitaxel, with or without bevacizumab have demonstrated a median survival of almost 5 years.[3] A key question is what is the contribution of first-line therapies to such improvements in survival? To what extent is the improvement due to the drugs used in first-line treatment, the benefit of better surgery, multidisciplinary care, or the contribution of drug therapies post-progression? To understand this better, it is important to examine the time to failure of first-line treatment, namely progression-free survival.

For many years the strategy to improve first-line treatment was centred around using better chemotherapy drugs and improving the quality of surgery. Meticulous analysis of surgical effort, either through case series[4] or within the context of randomized clinical trials of chemotherapy[5,6] has shown that tumour cytoreduction to microscopic residual disease confers a better outcome. However, surgical effort alone may not be the only factor. In the large multicentre Gynecologic Oncology Group (GOG) 182 trial, disease burden and the extent of disease distribution also affected outcome, independent of cytoreduction to no macroscopic residual disease.[6] The argument that biology leading to easier debulking rather than surgical effort is responsible for a better survival is weakening. Centralized (specialized) care and data from within randomized trials point to surgical effort as being an independent predictor of survival. Thus, more patients undergoing complete removal of disease at primary laparotomy fall into a better group responding for longer to chemotherapy. Progression-free survival (PFS) differences in groups with no residual disease or any residual disease are large which can make interpretation of the additional value of newer systemic treatments more complex; the amount of tumour residuum has been an important prognostic variable and stratification factor in trials. However, until recently trials were not consistent, stratifying 'good prognosis' patients on the basis of less than 1 cm diameter residuum, or no residual disease, which are now known to have very different prognostic values[5] when comparing different trials. While the eradication of microscopic disease may be easier in this group, the eventual outcome of patients will depend upon the quality of the systemic treatment that follows. Such treatment still needs to improve if it is to significantly increase the long-term survival of patients post-surgery.

A decade of trials in first-line therapy

First-line chemotherapy with carboplatin and paclitaxel became the standard chemotherapy combination more than 20 years ago,[7–9] and is the yardstick against which newer treatments are now evaluated. In the late 1900s there was interest in using very high doses of chemotherapy in solid tumours, or multiple sequential drug therapies. Trials using these approaches, published almost a decade ago showed that these strategies did not significantly extend the PFS following first-line therapy.[10,11] As ovarian cancer is usually confined to the peritoneal cavity there has also been a long-standing interest in intraperitoneal therapy. Over 20 years, this therapeutic approach has divided the oncology community into 'believers' and 'doubters' and intraperitoneal therapy continues to stimulate debate, without gaining widespread acceptance. For all the criticism that has been levied, the historical trials have shown some benefit for intraperitoneal therapy and

none has shown any disadvantage in outcome. However, PFS remains largely similar to systemic chemotherapy trials, although case selection, particularly the degree of surgical debulking continues to confound interpretation of this approach. While the long-term outcome of patients with microscopic residual disease, as seen in GOG 172 continues to show a survival benefit with 10 years of follow up[12] the most recently conducted study, as yet not fully published, failed to show any difference in PFS between the intravenous and intraperitoneal arms.[13] Modification of the technique using hyperthermic infusion of drugs (HIPEC)[14] has reported a benefit in PFS in the experimental arm. However, the median PFS was similar to that seen in multiple other trials over the last decade. Nevertheless, the trial reported significant differences in survival which cannot easily be explained. The result continues to stimulate debate and the hypothesis that there may be something unusual about intraperitoneal therapy, with differences in overall survival (OS) visible several years later. Most of the clinical research in first-line systemic therapy over the last decade has followed two directions. One, a simple approach of dose scheduling paclitaxel, using a weekly rather than a 3-weekly schedule. The results of a randomized trial from a Japanese trial (JGOG 3016) suggested that this approach could significantly improve outcome, both by prolonging the PFS and OS.[15] The magnitude of benefit reported was substantially greater than had been seen in any other first-line trial for more than a decade, and this led to a major international effort to confirm the results. The two large trials from the United States of America (USA) (GOG 262) and Italy (MITO 7), neither exactly replicating the experimental question addressed in the Japanese trial, failed to confirm a benefit of weekly paclitaxel.[16,17] However, criticisms of these two studies, one of which allowed the addition of bevacizumab in 85% of the patients and the other that used a lower dose of weekly paclitaxel and also weekly carboplatin, led many to adopt weekly paclitaxel as a standard of care. The results of a third trial, ICON8, the largest of the confirmatory studies, was presented at the European Society for Medical Oncology (ESMO) 2017 Congress. This was a three-arm study that included the 'Japanese' regimen as well as an arm with weekly carboplatin and weekly paclitaxel. None of the experimental arms showed any difference in PFS compared with standard 3-weekly paclitaxel.[18]

The second systemic approach has been to incorporate the anti-angiogenic drug, bevacizumab into first-line treatment. The results of two key first-line trials, GOG 218 and ICON 7 were published in 2011.[19,20] The key finding in the GOG trial was that bevacizumab, 15 mg/kg 3-weekly, given with chemotherapy and for up to 15 months significantly prolonged the time to disease progression compared with placebo. There was no difference in OS. Without debating the cost-effectiveness of a difference of 3.8 months in median PFS, the attitude to the results in Europe and the USA differed. Submission to the European Medicines Agency (EMA) led to regulatory approval but the results were not considered sufficiently compelling to submit to the US Food and Drug Administration (FDA). As a consequence, there has been a divergence in the 'standard of care' of first-line systemic treatment across the two sides of the Atlantic. Bevacizumab has become a standard option in Europe and this has shaped the development of new trials that incorporate this standard of care. The largest difference in PFS for both ICON 7, using half the dose of bevacizumab and for a shorter duration (12 months rather than 15 months for GOG 218) occurred at the time treatment stopped. Thus, it has been hypothesized that a greater benefit (increase in median PFS difference) might be achieved by giving bevacizumab for longer. This is being tested in the 'Boost' trial [ClinicalTrials.gov identifier: NCT01462890; AGO-OVAR 17] comparing 15 with 30 months treatment with bevacizumab. More than 900 women have been recruited to this study and the results are eagerly awaited. However, one might also consider the possibility that the maximum differences in PFS occurred coincidentally at the time bevacizumab was stopped. In the GOG 262 trial bevacizumab, which was given by choice to 84% of the patients was continued until progression/toxicity and the median PFS was about 15 months, not very different from the bevacizumab-throughout group in GOG 218.[16,19] Currently, cost, and to a lesser extent toxicity, has led to many countries to adopt the lower dose of bevacizumab and shorter duration of therapy, as used in the ICON7 trial. This choice, using the drug 'off-label' has been reinforced by a subgroup *post hoc* analysis showing that patients predicted to have a 'poorer prognosis' (stage III with >1 cm residual disease, or stage IV), had the greatest benefit from bevacizumab; the median PFS difference in this subgroup was 6.5 months,[20] and in this subgroup there was an OS benefit.[21] The demographics of

the patients entered into GOG 218 and ICON 7 were slightly different, but in a retrospective analysis no difference in survival was seen in patients with a similar prediction of a poorer prognosis; it was only in the stage IV subset of GOG 2018 that an OS benefit was seen, but these results are not fully published.[22]

Not surprisingly, efforts to demonstrate the value of anti-angiogenic drugs in first-line therapy have been explored further, using oral inhibitors of vascular endothelial growth factor (VEGF) receptor tyrosine kinase. However, neither of the two large trials with 2 years of pazopanib maintenance therapy or nintedanib with chemotherapy and as maintenance for a total of 24 months have demonstrated sufficient differences in median PFS to lead to applications for a licence to the regulatory authorities.[23,24] Bevacizumab is now the most consistently used additional drug in the first-line treatment of ovarian cancer, and several years after publication of the results, it is now being considered by the US FDA as an option for first-line therapy in the USA (https://www.gene.com/media/press-releases/14685/2017-10-25/fda-accepts-genentechs-supplemental-biol). Table 1 summarizes the results of a number of strategies used to improve the results of first-line treatment over the last 18 years. While inter-trial comparisons should be made with caution due to differences in prognostic variables, particularly the amount of residual disease, the median PFS for 3-weekly carboplatin and paclitaxel within these studies is remarkably consistent and there has been little advance in time to failure of first-line chemotherapy in the various intravenous chemotherapy strategies employed over the last two decades.

Current trials and evaluation of first-line therapies

Before reviewing ongoing clinical trials and future strategies, it is worthwhile reflecting on how improvements in first-line therapy are measured and evaluated. While the aim is to develop treatments that increase OS these are difficult to demonstrate. The ideal scenario is to develop a treatment that would demonstrate a significant benefit in PFS during first-line treatment and the difference between treatments would continue to be upheld during subsequent treatments, leading ultimately to a difference in OS. This is rarely seen, partly because of the long post-progression survival in ovarian cancer, with multiple subsequent treatments and in some situations, cross over to the experimental therapy. This is exemplified by the trial of maintenance olaparib therapy in platinum-sensitive recurrent ovarian cancer (study 19) which led to very large differences in PFS but much smaller differences in OS.[27] An exploratory analysis removing patients (and centres) where crossover occurred showed a significant difference in OS with maintenance olaparib.[28] Additionally, because of a long post-progression survival, OS results often become available several years after recruitment to the trial is completed. As there is both a commercial and, to some extent, academic pressure to analyze results early, PFS has become a primary endpoint for many first-line trials. Important secondary endpoints can be used to support improvements in the PFS result, without waiting for OS data, and the uncertainty about whether a difference will emerge. The relevance of these secondary endpoints becomes even more important if the difference in PFS is relatively small, and unlikely to lead to an OS difference. An exploratory secondary endpoint, such as the time to subsequent progression (after the next line of therapy), also known as PFS2, indirectly determined as the TSST (time to second subsequent treatment) was measured in study 19, due to the absence of an OS difference. This endpoint has some value, given the difficulties in demonstrating OS differences. However, like OS PFS2 may be influenced by the timing of further treatment in the two arms as well as differences in the subsequent treatment. Nevertheless, a sustained differences in PFS2 shows that the benefit of an investigational drug continues after progression, at least to a subsequent progression.[28] This supplementary endpoint, demonstrated prospectively in the SOLO-2 trial of maintenance olaparib, is acceptable to the EMA as a coregulatory endpoint to a PFS difference in situations where in the significant OS differences are not demonstrated, or have not had sufficient time to mature.[29] While these endpoints became established in trials of recurrent ovarian cancer, similar considerations are now being applied to first-line therapy trials, with recommendations following the Fifth Ovarian Cancer Consensus Conference (OCCC) of the Gynecologic Cancer InterGroup that in situations where OS is not the primary endpoint, PFS2 or quality of life should be used to support differences in PFS.[30]

For comparisons of new cytotoxic chemotherapy, one could argue that PFS is the most important endpoint. In the absence of a demonstration of

Table 1. Two decades of first-line chemotherapy trials in ovarian cancer.

Trial question	Details	Median PFS (months) carboplatin/ paclitaxel	Median PFS (months) experimental	Comments
Carboplatin/paclitaxel versus **cisplatin/paclitaxel**				
Neijt and colleagues[8] (2000)	Cisplatin-paclitaxel standard	16.0	16	44% <1 cm residual disease
Ozols and colleagues[9] (2003)	Cisplatin-paclitaxel standard	20.7	19.4	36% no macroscopic residual disease. Large difference in PFS depending on residual disease
Du Bois and colleagues[7] (2003)	Cisplatin-paclitaxel standard	17.2	19.1	60% <1 cm residual disease
Three drugs/ sequential doublets				
Du Bois and colleagues[25] (2006)	Epirubicin	17.9	18.4	58% <1 cm residual disease/ lower stage
Bookman and colleagues[10] (2009)	GOG 182/ICON5 8 cycles, 5-arm study (topotecan, gemcitabine, PLD) sequential doublet/triplet	16.0	16.0	Median PFS 12–130 months depending on residual disease
	Gemcitabine	19.3	17.8	70% <1 cm residual disease
HD chemotherapy with peripheral blood stem cell rescue				
Moebus and colleagues[11] (2010)	3 cycles HD chemotherapy including HD melphalan	20.5	29.6	35% no macroscopic residual disease
Inclusion of anti-angiogenic drugs followed by maintenance				
Burger and colleagues[19] (2011)	GOG 218- bevacizumab 15 months	12.0	18.0	33% <1 cm residual disease
Perren and colleagues[20] (2011)	ICON7- bevacizumab 12 months	17.3	19.0	24% microscopic residual disease
Du Bois and colleagues[23] (2016)	OVAR12- nintedanib 24 months	16.6	17.2	41% No macroscopic residual disease
Dose-dense (weekly) paclitaxel				
Katsumata and colleagues[26] (2009)	JGOG 3016	17.2	28.0	45% <1 cm residual disease
Pignata and colleagues[17] (2014)	MITO7- weekly carboplatin and paclitaxel	17.3	18.3	41% no macroscopic residual disease
Chan and colleagues[16] (2016)	GOG 262- 85% with bevacizumab	14.0	14.7	24% microscopic residual disease

GOG, Gynecologic Oncology Group; HD, high dose; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

superiority, it is unlikely that a new treatment is going to be more effective. The two trials with bevacizumab fit into this group. However, it is reasonable to regard bevacizumab as a disease-modifying agent, rather than a drug that eradicates malignant cells. It acts by delaying growth through interference with the tumour vasculature as long as it is given. This notion is supported by the effect of the drug being greatest at the time it is stopped. One could argue that the

apparent survival benefit in the poorer prognosis subgroup of ICON7 is due to patients being on the drug longer, surviving in a better clinical state to receive subsequent treatment, rather than a direct effect of the drug *per se*. Thus, while the results of AGO-OVAR17 are awaited, it may turn out that prolongation of bevacizumab therapy for 30 months will further extenuate differences in PFS without showing a survival difference. The interpretation, or evaluation of measured differences in PFS is complex, and the extent to which these translate into a 'healthcare benefit' is beyond the scope of this review. Arguments continue about the relative merits of small differences in PFS after first-line therapy and the delay in second-line therapy in the context of little or no benefit in OS. For the future design of trials, the Fifth OCCC concluded that differences in PFS are valuable as a primary endpoint, but trials should be followed to measure OS.[30] Thus, trials should be powered to show differences in PFS and be of sufficient size to allow a robust analysis of secondary endpoints.

The next group of trials to report are examining the inclusion of poly ADP ribose polymerase (PARP) inhibitors. These drugs have shown clear benefit in recurrent ovarian cancer, and maintenance therapy is now being evaluated in first-line therapy. The results of four important trials are awaited. The first trial, SOLO-1 using maintenance olaparib or placebo for 2 years in women with a BRCA mutation who have responded to first-line therapy has been completed. The results are expected within the next year or so. It is expected that PFS will be extended, as only patients responding to chemotherapy are randomized to maintenance therapy, but the importance of this study is whether time-limited olaparib therapy significantly improves OS, or just delays progression without influencing OS. The second study, GOG 3005 which has completed accrual is targeting the concomitant and maintenance use of veliparib in the primary setting [ClinicalTrials.gov identifier: NCT02470585]. The third, PRIMA trial [ClinicalTrials.gov identifier: NCT02655016] is an ongoing study of maintenance niraparib or placebo following therapy of patients with suboptimal stage III or stage IV disease following surgery and chemotherapy. It includes a broader group of women including those without a *BRCA* mutation. The fourth study, PAOLA-1 is a little different as it is evaluating the addition of olaparib or placebo maintenance to bevacizumab following first-line therapy [ClinicalTrials.gov identifier: NCT02477644]. The hypothesis is that bevacizumab increases the activity of the PARP inhibitor, perhaps by increasing the degree of homologous recombination deficiency in the tumour[31] thereby increasing the PFS due to bevacizumab. Clinical data combining the VEGF receptor inhibitor, cediranib and olaparib support this approach.[32] In a subgroup analysis the greatest benefit of combining cediranib and olaparib was seen in the non-germline *BRCA* mutation group/*BRCA* wildtype. In PAOLA-1 which includes patients irrespective of *BRCA* status, bevacizumab continues for 15 months in combination with the trial drug, that is then given for a further 9 months on its own.

Special considerations are needed when interpreting the effect of immunotherapy studies. This is a very different strategy from cytotoxic chemotherapy that that relies on the development of a host immune response. Significant therapeutic benefit has been seen using inhibitors of immune checkpoints that stimulate a host anti-tumour response and prolong survival in many types of solid tumour. Of note, such effects may occur well beyond the time of therapy; having engaged the host immune system, differences in outcome may occur after progression. There are examples from other diseases where differences in OS have emerged without any major difference in PFS.[33]

Future prospects for first-line treatment

While awaiting these important results, clinical trial development in ovarian cancer, led by industry, is moving rapidly and new studies are being designed to evaluate immune checkpoint inhibitors in ovarian cancer. The impetus comes from the results of treatment in other solid tumours such as lung, bladder, and head and neck cancers. To date, the only full publication of the effect of immune checkpoint inhibitors in ovarian cancer is in recurrent disease and reports the activity of the programmed death-ligand 1 (PDL1) inhibitor, nivolumab in a small number of patients;[34] other information is only available as published abstracts. Notwithstanding the paucity of published data, more than 900 patients have been enrolled in the first-line study, JAVELIN 100 [ClinicalTrials.gov identifier: NCT02718417] with the PDL1 inhibitor avelumab. The trial closed to recruitment in January 2018. Patients will receive avelumab for up to 2 years or to progression, so the results will not be available for some while. A second trial, IMaGYN050

[ClinicalTrials.gov identifier: NCT03038100] using bevacizumab and atezolizumab, a PDL1 inhibitor is underway. For JAVELIN 100, PFS is the primary endpoint, but it is vital that follow up is continued to assess OS, the secondary endpoint. For IMaGYN050, PFS and OS are co-primary endpoints. The rapid enrolment seen in these studies is a reflection of the urgent need perceived by doctors and their patients to find a new treatment leading to a step-change in the management of ovarian cancer. The first tranche of results using PARP inhibitors may herald such a change, but we will need to wait several more years before any conclusions can be drawn about the role of immune checkpoint inhibitors. While patients are living longer, it is hard currently to claim that first-line drug therapy has led to any substantial improvement in outcome in the last decade. Until we see better results, 3-weekly carboplatin and paclitaxel will remain the standard of care with continuing discussions about the cost–benefit of adding in bevacizumab to first-line therapy.

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Conflict of interest statement

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