First line therapy: have we made any improvement?

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Introduction

The incidence of epithelial ovarian cancer varies throughout the world (Fig. 1), with higher frequencies in Europe, North America, and Australia, and lower frequencies in much of Asia, Central America, South America, and North Africa [1]. The epidemiologic factors responsible for this variability remain to be defined. However, regardless of where it occurs, ovarian cancer is associated with the highest case-fatality ratio among the gynaecologic cancers, reflecting a propensity for early peritoneal dissemination, and advanced-stage disease at clinical diagnosis.

Approximately 80% of advanced-stage tumours demonstrate high-grade serous histology, and these tumours can arise from the distal (fimbriated) fallopian tube, peritoneal cavity, or surface epithelium of the ovary. While high-grade serous tumours can also arise from the endometrium, these tumours have a somewhat different biology, and are generally managed as endometrial cancer, and are not included in clinical trials of ovarian cancer. As such, most of our current data are derived from extrauterine high-grade serous tumours.

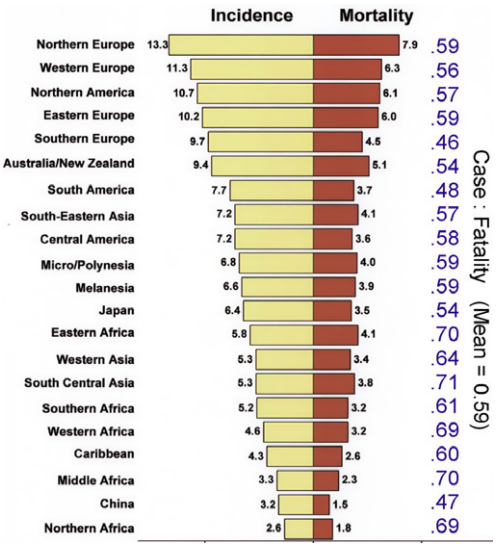

Fig. 1. Global incidence and mortality associated with ovarian cancer. Although the incidence of ovarian cancer varies in different regions of the world, the overall case fatality ratio is similar [1].

Advanced-stage tumours are generally managed with cytoreductive surgery and chemotherapy consisting of carboplatin and paclitaxel, achieving clinical complete remission in the majority of patients. Incremental improvements in median progression-free or overall survival have been achieved with the incorporation of paclitaxel, utilisation of intraperitoneal therapy in selected patients, and dose-dense weekly scheduling of paclitaxel. However, these strategies have not yet been shown to have an impact on overall mortality from advanced-stage disease (Fig. 2), which has changed very little over the last 30 years [2].

Efforts to improve on the long-term results of primary therapy through addition of a third cytotoxic agent have not been successful, including triplet combinations, sequential doublets, alternative taxanes, and extended maintenance (with taxanes or other agents). Over the last 15 years, multiple international collaborative phase III trials, collectively enrolling more than 12,000 women, have been completed without showing clinical benefit from new combinations in primary therapy. Accrual data from many of the published trials are summarised in Table 1. The majority of studies only included two treatment arms, and it is worth noting that over 38 percent of the patients (n = 4353) were assigned to a reference arm [3–10].

Advances in molecular profiling have contributed to a better understanding of the diversity of ovarian cancer, including prognostic information, and potential molecular targets. At this point, we can categorise tumours according to stage, extent of residual disease following cytoreductive surgery, primary histology (serous, endometrioid, clear cell, mucinous), grade (low-grade and borderline *vs* high-grade), and presence of epithelial–mesenchymal transition (carcinosarcoma). As new trials are developed, there is an opportunity to target specific subsets, including mucinous, clear cell, carcinosarcoma, and low-grade invasive serous cancer.

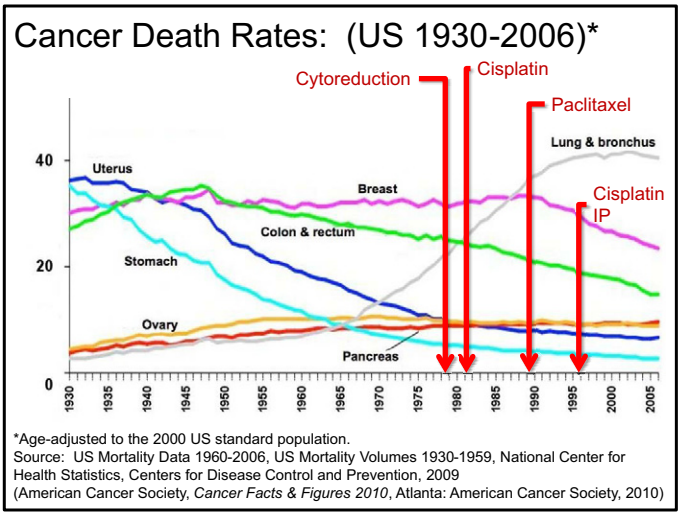

Fig. 2. Overall cancer-related mortality for women in the United States over a period of 75 years. In spite of significant advances in the management of ovarian cancer, we have not yet observed an impact on disease-related mortality [2].

Table 1
Summary of overall accrual on international phase III trials through the Gynecologic Cancer InterGroup (GCIG) to evaluate new cytotoxic agents in the primary therapy of ovarian cancer

Trial	International phase III accrual							
	CP	CPG	CD±P	CT±P	CG	CDoc	CE	Total
GOG0182-ICON5 [3]	864	864	862	861	861			4312
SCOTROC [4]	538					539		1077
AGO-GINECO [5]	635						647	1282
NSGO-EORTC-NCIC-GEICO [6]	444						443	887
MITO [7]	170			156				326
AGO-GINECO-GERCOR-NSGO [8]	882	860						1742
NCIC-EORTC-GEICO OV 16 [9]	410			409				819
MITO-2 [10]	410		410					820
Regimen totals:	4353	1724	1272	1426	861	539	1090	11,265

C, carboplatin or cisplatin; P, paclitaxel; G, gemcitabine; D, PEG-lipo-doxorubicin; T, topotecan; Doc, docetaxel; E, epirubicin.

Resistance to chemotherapy can emerge rapidly, through multiple molecular pathways, and it has not yet been possible to successfully translate single-point laboratory models to achieve clinical benefit in either primary therapy or recurrent disease. Emerging data with inhibitors of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP), particularly in tumours with pre-existing defects in homologous recombination DNA repair, are encouraging, and await phase III randomised trials.

Considerable interest has been focused on molecular targeted and biologic agents that interfere with growth factors, membrane-bound receptors, and intracellular signal transduction cascades. Efforts to target the epidermal growth factor receptor family, including HER2 and EGFR, with antibodies and small-molecule inhibitors of the receptor-associated tyrosine kinase (rTKI) have not been particularly encouraging in recurrent ovarian cancer, and these strategies have not been evaluated in primary phase III trials.

Tumour-associated angiogenesis has emerged as a prominent area of investigation over the last 5 years, based on the role of vascular endothelial growth factor (VEGF) in normal ovarian physiology, as well as VEGF-mediated production of ascites, and over-expression of VEGF by the majority of high-grade tumours. Two phase III randomised trials have been completed with bevacizumab administered during and following primary chemotherapy, achieving a modest, and transient, benefit in progression-free survival, but

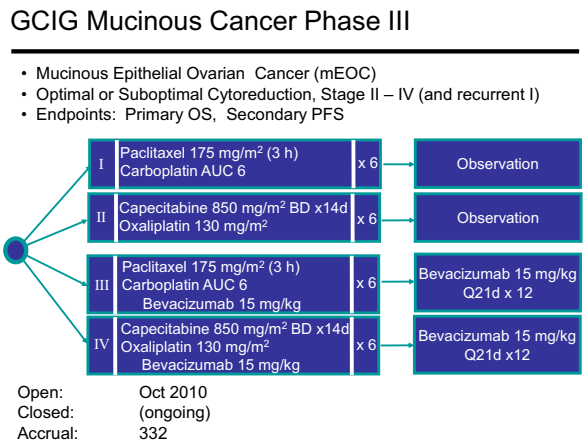

Fig. 3. Design of the ongoing Gynecologic Cancer InterGroup (GCIG) phase III trial for women with mucinous ovarian cancer (mEOC), jointly coordinated by the National Cancer Research Institute (NCRI) in the UK and the Gynecologic Oncology Group (GOG) in the US.

without early evidence of an advantage in overall survival [11,12]. These interesting results raise questions about balancing potential clinical benefit with treatment-related toxicities and the overall financial cost associated with long-term drug administration. Additional randomised trials are in progress with other anti-angiogenic agents, including multi-targeted rTKIs, but data are pending, and there are no ongoing trials directly comparing rTKIs with bevacizumab.

Optimised primary treatment

Current optimal management of advanced-stage ovarian cancer includes maximal cytoreductive surgery and a programme of chemotherapy with a platinum agent (carboplatin or cisplatin) and paclitaxel [13,14]. This is a validated, well-tolerated, and effective approach. However, there are widely adopted variations in clinical practice as applied to individual patients, including intraperitoneal drug administration, neoadjuvant chemotherapy, and weekly scheduling of paclitaxel. In addition, we now recognise that ovarian cancer includes many different biologic and molecular subtypes, with the potential for tailored treatment interventions. However, there are few comparative trials, and as of today, no regimens have demonstrated superiority to platinum–taxane combinations in any tumour subset.

Platinum compounds remain dominant as the most active category of cytotoxic agents. Historical improvements in the therapeutic ratio of platinum-based primary chemotherapy have been achieved through the development of better tolerated analogues (carboplatin), together with evolving data on dosing, sequence, and duration of treatment. In general, the administration of higher doses of chemotherapy with haematopoietic support, or extended administration of multiple cycles of chemotherapy (beyond 6 cycles), has not improved long-term outcomes, and these strategies carry an increased risk of serious cumulative toxicity [15]. Intravenous carboplatin (or intraperitoneal cisplatin), remains the agent of choice in primary therapy, although oxaliplatin is undergoing evaluation as primary therapy for mucinous carcinomas in the context of an international phase III trial (Fig. 3).

Intraperitoneal delivery of cisplatin has been shown to improve overall survival in phase III randomised trials, and is an appropriate option for selected patients [16]. However, the dose of cisplatin in phase III trials has been high (100 mg/m^2), with an impact on host toxicity, including nausea, vomiting, abdominal pain, and neuropathy. It has become common practice to utilise a better-tolerated dose of 75 mg/m^2 in clinical practice, and this is now being prospectively evaluated in a phase III GOG trial (Fig. 4). There has also been interest in the substitution of intraperitoneal carboplatin. Both cisplatin and carboplatin are rapidly absorbed from the peritoneal cavity; however, carboplatin requires a much longer time for activation via aquation, due to the larger size of the molecular leaving groups. As such, it remains unproven if intraperitoneal carboplatin will be equivalent to cisplatin, and this is also being prospectively evaluated in phase III trials

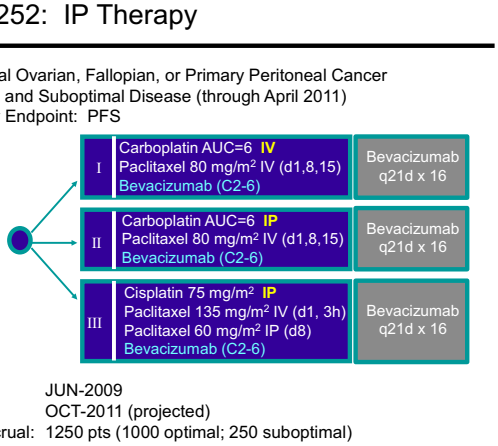

Fig. 4. Design of the ongoing phase III trial within the Gynecologic Oncology Group (GOG) to evaluate regimens with intraperitoneal carboplatin and a modified dose of intraperitoneal cisplatin (GOG0252). Note that the reference arm utilises dose-dense weekly paclitaxel, and that all patients receive bevacizumab. In addition, the protocol also enrolled patients with suboptimal residual disease to evaluate the role of intraperitoneal therapy in that setting.

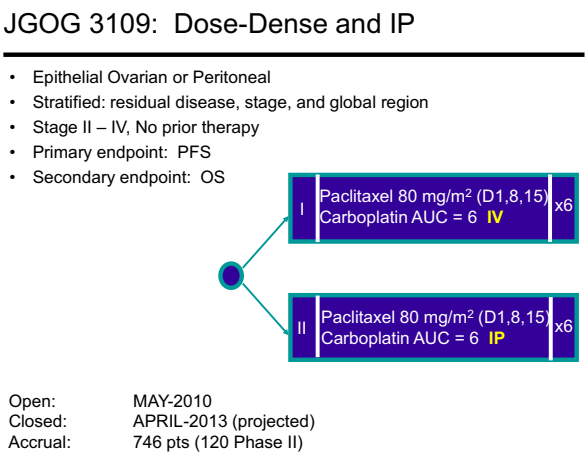

Fig. 5. Design of the ongoing phase III trial within the Japanese Gynecologic Oncology Group (JGOG) to evaluate intraperitoneal carboplatin with dose-dense weekly paclitaxel.

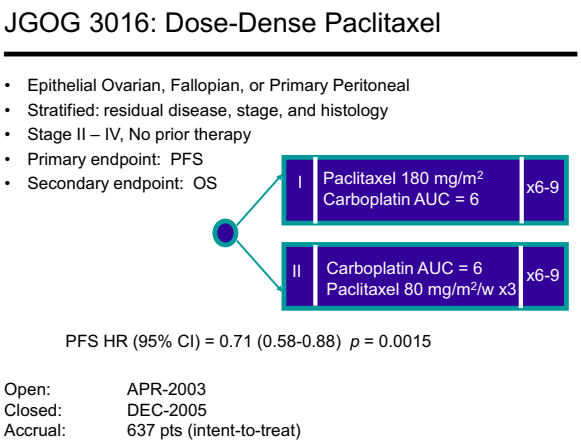

Fig. 6. Design of the completed trial coordinated by the Japanese Gynecologic Oncology Group (JGOG) to evaluate dose-dense weekly paclitaxel in combination with standard three-weekly carboplatin [19].

conducted by GOG, in combination with bevacizumab (Fig. 4), and JGOG, without bevacizumab (Fig. 5). In addition, most studies of intraperitoneal therapy have historically been limited to patients with small-volume residual disease, based on initial assumptions related to drug penetration from the peritoneal cavity. The potential relationship between effectiveness of intraperitoneal chemotherapy and extent of residual disease has never been prospectively evaluated in a randomised trial. However, a provocative retrospective analysis of GOG104 suggested that patients with microscopic residual disease did not experience additional benefit from intraperitoneal cisplatin, compared to the benefit observed in patients with macroscopic disease [17]. Recently, several GOG and JGOG pilot studies enrolled patients with larger-volume residual disease, and enrollment of patients with suboptimal residual disease was subsequently permitted on the two ongoing phase III trials, with analysis pending.

In view of the importance of paclitaxel, a number of studies have evaluated the dose, schedule, sequence, and route of administration, as well as alternative formulations, taxane analogues, and non-taxane anti-microtubule agents. In a phase III trial, a prolonged infusion of paclitaxel (96 h) increased mucosal and bone marrow toxicity, but without improved efficacy [18]. Shorter infusions (<3 h) are generally better-tolerated from a haematologic perspective, although higher individual doses can increase the risk of arthralgia–myalgia and neuropathy. Weekly scheduling permits higher cumulative dose delivery, while avoiding haematologic toxicity and alopecia, and has demonstrated consistent activity in patients who have recurred within 6 months of primary therapy with conventional carboplatin and paclitaxel.

The JGOG conducted a phase III trial in women with newly-diagnosed advanced-stage ovarian cancer (Fig. 6), demonstrating superiority of weekly dose-dense paclitaxel in combination with standard doses of carboplatin compared to three-weekly scheduling of the same drugs [19]. This is an important finding, illustrating the need to carefully examine how we use established agents, in addition to strategies to incorporate new agents. Of note, the GOG0172 phase III trial of intraperitoneal chemotherapy incorporated a second dose of paclitaxel (intraperitoneal) on day 8, which may have contributed to the superiority of the experimental arm [16]. Ongoing phase III trials through GOG and other groups aim to extend the JGOG findings, including integration with intraperitoneal chemotherapy and molecular-targeted agents (Figs 4 and 7), as well as weekly dosing of carboplatin (Fig. 8). However, there is some concern that carboplatin is not particularly schedule-sensitive, and fractionating the dose will reduce peak drug levels, with a potential impact on tumour delivery.

Host–tumour interactions are complex, and laboratory models have not been highly predictive of clinical outcomes. For example, it was suggested that docetaxel would be more effective than paclitaxel based on potency, binding kinetics, and molecular targeting. However, there are no data to indicate clinical superiority of docetaxel when compared to paclitaxel in the management of newly diagnosed or recurrent epithelial ovarian cancer. Substitution of docetaxel is an acceptable alternative to paclitaxel in the front-line setting with a reduced risk of neuropathy and hypersensitivity reactions, but with an increased risk of dose-limiting haematologic toxicity, based on a phase III trial [4]. Alternative taxane formulations,

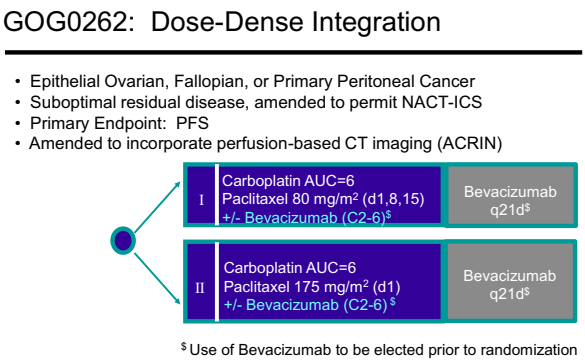

Fig. 7. Design of the ongoing phase III trial within the Gynecologic Oncology Group (GOG) to evaluate dose-dense weekly paclitaxel, with optional election to receive bevacizumab (GOG0262). The study also permits patients to receive neoadjuvant chemotherapy with interval cytoreductive surgery (NACT-ICS).

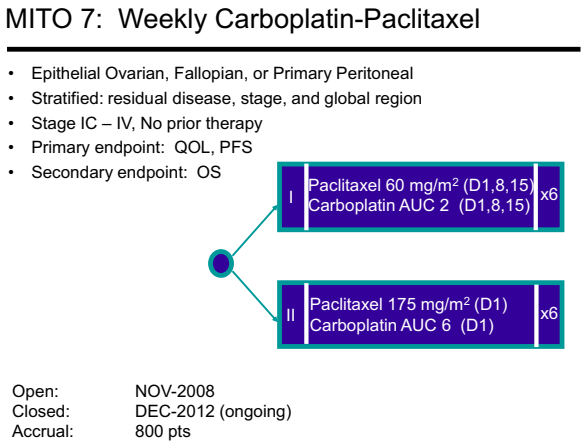

Fig. 8. Design of the ongoing phase III trial for the Multicenter Italian Trial in Ovarian Cancer (MITO) group, coordinated by the National Cancer Institute in Naples, to evaluate a combination of weekly paclitaxel and weekly carboplatin compared to a standard three-weekly regimen.

including nanoparticle albumin-bound paclitaxel, as well as non-taxane anti-microtubule agents, such as the epothilone derivatives, have not been directly compared to paclitaxel using an optimised weekly schedule.

Challenges incorporating a third cytotoxic agent

There has been considerable interest in the incorporation of a third cytotoxic agent, balanced by expectations of increased host toxicity. However, based on multiple international phase III trials to evaluate topotecan, gemcitabine, PEG-liposomal doxorubicin, and epirubicin, the addition of a third cytotoxic agent has not been shown to improve long-term clinical outcomes [3–10]. Some agents, such as topotecan and gemcitabine, exhibit schedule- and sequence-dependent haematologic toxicity, particularly when combined with carboplatin. These agents can interfere with repair of platinum-DNA adducts, but often at the expense of increased haematologic toxicity. In contrast, combinations of paclitaxel with carboplatin are well-tolerated, with capability of administering full doses of both drugs. This has been attributed to a "platelet-sparing" effect of paclitaxel on carboplatin-mediated thrombocytopenia, raising questions about possible drug–drug antagonism [20]. Indeed, one potential advantage of weekly paclitaxel could be the temporal separation from carboplatin, optimising the tumour-related cytotoxicity of both agents.

In reviewing the cumulative results of these phase III trials, one is struck by the consistent lack of benefit, including subpopulations with more favourable prognostic features, such as microscopic optimal cytoreductive surgery. At some level, this is perplexing, in view of previously documented single-agent activity for these agents, and a demonstrated benefit in combination with carboplatin in the setting of platinum-sensitive recurrent disease for gemcitabine and PEG liposomal doxorubicin.

There are several potential explanations for these observations:

- First, perhaps the dose or schedule of chemotherapy was not optimal. This would appear unlikely, as there are several trials with similar agents using different doses, sequences, or schedules. In view of the large number of patients, one might hypothesise a trend for improvement, even if the dosing was suboptimal.
- Second, perhaps only a subset of patients is sensitive to each new agent, but this effect is lost in the setting of a trial with randomised allocation of drugs among the entire population. In theory, this could be evaluated by tumour profiling prior to randomisation. While potentially important, this explanation also seems unlikely, as there should still be a smaller trend for improvement associated with incorporation of new agents, which was not observed.
- Third, it is possible that the short-term effectiveness of primary therapy may limit the opportunity to observe incremental benefit from a new agent. Ovarian tumours are initially platinum-sensitive, and the majority of patients begin chemotherapy following optimal cytoreductive surgery, rapidly achieving clinical complete remission. It is possible

that the addition of a third non-curative agent, even though active, might contribute little to clinical outcomes during primary therapy.
- Fourth, emerging data regarding stem-like behaviour have been observed in subpopulations of ovarian cancer cells, including dormant cells with a low mitotic index that exclude cytotoxic drugs from their cytoplasm and demonstrate increased resistance to chemotherapy [21,22]. These stem-like populations are generally enriched following primary chemotherapy, and could limit the effectiveness of any third cytotoxic agent.

The last two arguments are supported by clinical observations. These points could explain the somewhat paradoxical benefit of platinum-based combinations in the setting of recurrent disease, when these same combinations have not always demonstrated increased benefit in the front-line setting. Evaluating combinations in patients with platinum-sensitive recurrence is a useful clinical paradigm, but recurrent tumours are not the same as newly diagnosed (untreated) disease. While remissions do occur in the setting of recurrent disease, it is less common to observe a complete remission, the time to further disease progression is generally shortened, and a higher proportion of tumours will demonstrate rapid evolution of platinum resistance during treatment. In this setting, a second (or third) drug with additive benefit, particularly against tumours that are already becoming platinum resistant, may show an advantage in clinical trials.

As an alternative strategy, a number of groups have evaluated a third agent as maintenance therapy for patients in remission after completion of primary therapy [23–27]. In general, maintenance chemotherapy has not been associated with improved clinical outcomes in solid tumours, and is clearly associated with an increased risk of cumulative toxicity. In women with ovarian cancer, all studies using chemotherapy have been negative, with the exception of one study evaluating extended paclitaxel administered on a three-week schedule [28]. In that study, there was an early difference in progression-free survival favouring extended therapy, and the trial was closed by recommendation of the data-monitoring committee following a scheduled interim analysis. This observation remains controversial, due to the uncertain clinical benefit associated with a modest improvement of PFS (that was substantially less than the difference in total treatment times) without any benefit in overall survival. GOG is currently completing a phase III maintenance trial that will attempt to resolve the question, but other studies of maintenance paclitaxel have been negative, and there is not currently any established role for maintenance chemotherapy in women with ovarian cancer.

Several cytotoxic agents have recently been developed with encouraging activity in recurrent disease, including epothilone analogues (ixabepilone, patupilone), alternative taxane formulations (nanoparticle albumin-bound paclitaxel), multitargeted anti-folates (pemetrexed), a DNA minor groove binding agent (trabectedin), folate-vinca alkaloid drug conjugates (EC145), irinotecan–polymer conjugates (NKTR-102), and inhibitors of aurora kinases (MLN-8237). However, in view of this substantial body of negative phase III trials, the threshold for moving a new cytotoxic agent to primary therapy appears quite high. Thus far, none of the newer agents seem to have sufficient activity, or other compelling justification, for incorporation in primary therapy.

Biologic advances with an impact on primary therapy

In advanced-stage serous tumours, distinct molecular profiles have been associated with low-grade (Type I) compared to high-grade (Type II) neoplasia. Low-grade invasive adenocarcinoma generally arises in conjunction with borderline tumours of low malignant potential. These tumours are not generally sensitive to platinum-based chemotherapy, retain functional p53, and harbour activating mutations of either B-ras or K-raf [29,30].

In contrast, high-grade serous tumours tend to have inactivation of p53 through chromosomal deletion and/or mutation, and are initially sensitive to platinum-based chemotherapy. Some high-grade ovarian cancers are associated with sarcomatous differentiation, recognised as carcinosarcomas or mixed Müllerian tumours. This is thought to occur through a process of epithelial–mesenchymal transition (EMT) associated with down-regulation of epithelial markers (such as epithelial membrane antigen), and up-regulation of mesenchymal markers (such as vimentin) [31]. These changes contribute to cellular motility, production of proteolytic enzymes, and invasive behaviour. Aggressive mesenchymal features have also been identified through analysis of gene expression profiles, even without visible evidence of sarcoma [32].

Although primary ovarian mucinous tumours are rare, collaborative retrospective review of international data has verified that mucinous tumours are not generally responsive to platinum-based chemotherapy [33–35], and patients with advanced mucinous tumours

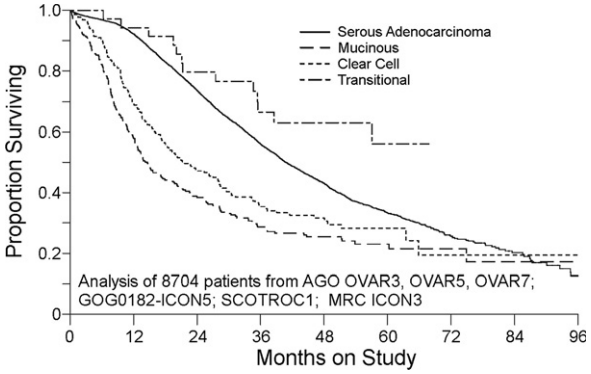

Fig. 9. Combined analysis of overall survival according to histology from 8,704 patients enrolled on 6 phase III trials through the Gynecologic Cancer InterGroup (GCIG).

have inferior long-term survival, compared with serous or endometrioid subtypes (Fig. 9). An international collaborative phase III trial has been initiated to evaluate alternative regimens modeled after colorectal adenocarcinoma (Fig. 3).

Advanced-stage clear cell tumours exhibit more aggressive patterns of metastatic spread and are frequently resistant to platinum-based chemotherapy. Analysis of gene expression profiles has identified characteristic patterns associated with clear cell tumours from other primary sites, but optimal treatment strategies for clear cell tumours of ovarian origin remain to be defined. Accrual has been completed on a phase III international collaborative trial coordinated through JGOG, evaluating a combination of irinotecan and cisplatin, and mature results are awaited (Fig. 10).

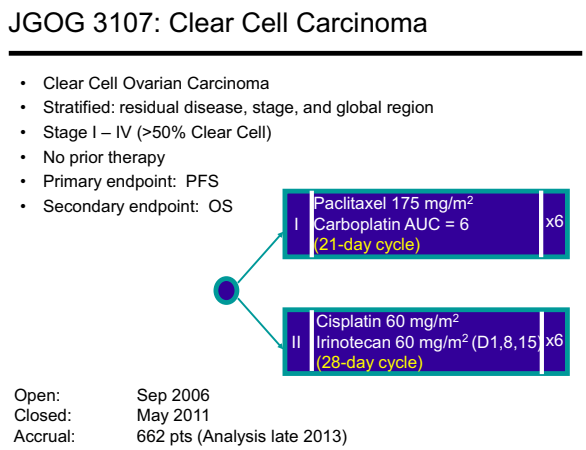

Fig. 10. Design of the international trial for patients with clear cell carcinoma coordinated by the Japanese Gynecologic Oncology Group (JGOG).

Targeting angiogenesis

High-grade serous ovarian cancer is characterised by over-expression of VEGF, which drives dysfunctional tumour-associated angiogenesis, contributing to high interstitial pressure and production of ascites. Direct targeting of this pathway can be achieved by sequestration of VEGF protein using monoclonal antibodies (bevacizumab) or engineered binding site molecules (aflibercept). Blockade of the VEGF receptor-2 (VEGFR2) can be achieved with monoclonal antibodies (IMC-1C11), or inhibition of receptor-associated tyrosine kinases using low molecular weight agents (axitinib, cediranib, pazopanib, sorafenib, and vargatef). Indirect strategies include targeting genes involved in the regulation of VEGF expression, such as hypoxia inducible factor 1-alpha (HIF1a), or angiopoietin-2, inhibition of cytoplasmic tyrosine kinases that are activated following VEGF receptor-mediated phosphorylation, or interference with other convergence pathways, such as the serine-threonine specific protein kinase (AKT) or the mammalian target of rapamycin (mTOR).

Thus far, the most widely studied agent has been bevacizumab, initially as a single agent, and subsequently in phase III trials with concurrent chemotherapy and maintenance. Single-agent activity with bevacizumab in recurrent ovarian cancer is more substantial than previously observed in most other tumour types. As such, it was anticipated that combinations of bevacizumab with carboplatin and paclitaxel would improve long-term outcomes for women with ovarian cancer, as observed in other histologies, including tumours with low response rates to single-agent bevacizumab. Thus far, two phase III trials for newly-diagnosed ovarian cancer have reported a non-sustained and modest improvement in progression-free survival, without any preliminary improvement in overall survival [11,12]. Both of these trials incorporated maintenance administration of single-agent bevacizumab after completion of chemotherapy, based on experience in other clinical settings.

These positive results have attracted considerable attention. Although both trials met their primary endpoints for improvement in PFS, the magnitude of benefit was not as great as what had been anticipated on the basis of phase II data in patients with recurrent disease. Due to the design of the trials, it is not possible to determine how much of the improvement in PFS is related to the total duration of therapy, the integration with concurrent chemotherapy, or maintenance following chemotherapy. However, maximal benefit was achieved in the population that received

bevacizumab during and following chemotherapy. In addition, both trials demonstrated a trend for greater benefit in patients with more extensive disease, based on the cytoreductive surgery (ICON7), or through exclusion of patients with small-volume disease and CA-125 progression (GOG0218). Expected toxicities from bevacizumab were observed (including thromboembolic events and hypertension). However, most of the serious events tended to occur during primary chemotherapy and within the peri-operative period, with fewer dose-limiting events noted during maintenance therapy. Initially, there was concern regarding the potential risk of bowel perforation, but this did not emerge as a significant bevacizumab-related toxicity in either randomised trial.

In other tumour settings, improvements in survival have been attributed to enhanced drug delivery as a result of pseudo-normalisation of tumour vasculature and a reduction in interstitial pressure. However, this hypothesis has not actually been validated in clinical studies, and there are other actions associated with VEGF that could have an impact on tumour behaviour. In addition, most patients with ovarian cancer undergo optimal cytoreductive surgery and then receive platinum-based chemotherapy prior to receiving any bevacizumab. The combined impact of surgery and chemotherapy would tend to minimise tumour-associated VEGF production, as well as the size of any residual disease, which is quite different from the management of large-volume metastatic disease in other settings. Taken together, these effects could theoretically reduce the impact of bevacizumab during primary chemotherapy, and might favour using bevacizumab in the setting of recurrent disease, pending mature results from a positive phase III trial in patients with platinum-sensitive recurrence.

Neither study has yet demonstrated true clinical benefit, and questions remain regarding the optimal dose, schedule, timing, and integration of anti-VEGF therapy. Thus far, it appears that VEGF blockade may have greater impact in preventing tumour regrowth, or in the management of recurrent disease, rather than augmentation of primary chemotherapy, and mature data are awaited from these completed trials, as well as ongoing studies evaluating multitargeted inhibitors of receptor-associated tyrosine kinases (pazopanib and BIBF-1120) in the setting of primary therapy and maintenance (Figs 11 and 12).

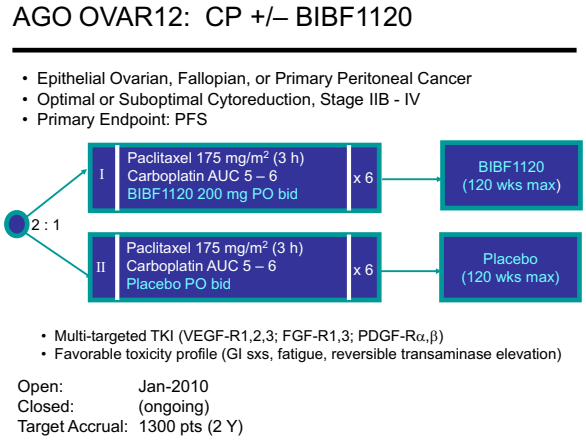

Fig. 11. Accrual has been completed on this phase III GCIG trial (with leadership from AGO) to evaluate extended maintenance therapy (up to two years) with an oral tyrosine kinase inhibitor (Pazopanib).

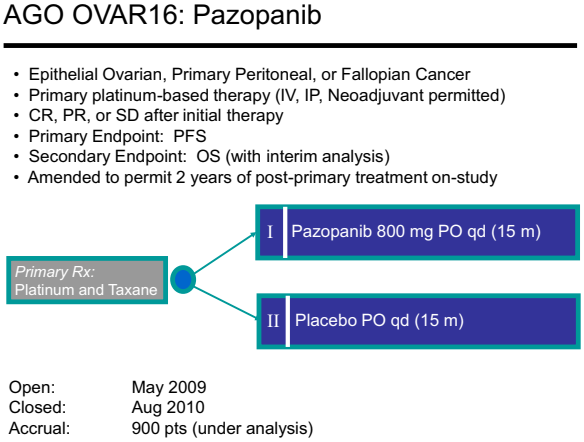

Fig. 12. Accrual is ongoing for this phase III GCIG trial (with leadership from AGO) evaluating concurrent and extended maintenance therapy with a multitargeted oral tyrosine kinase inhibitor (BIBF-1120, Vargetef).

Overcoming chemotherapy resistance

The most important pattern of resistance observed in ovarian cancer is related to the platinum compounds (cisplatin and carboplatin). Resistance is multifactorial, involving decreased active transport, increased efflux, rapid detoxification of platinum through glutathione conjugation, increased DNA damage tolerance, reduced detection of DNA damage, accelerated removal of platinum–DNA adducts, enhanced DNA repair, and defective apoptotic signaling, often associated with loss of tumour suppressor protein p53, but also independent of p53. Resistance can be intrinsic, or evolve in response to selective pressures from chemotherapy exposure. As such, some components of resistance might be reversible, over a period of time. Preclinical models have suggested a variety of strategies to prevent or overcome resistance, but these ideas have not been successfully translated to clinical practice.

Nucleotide excision repair (NER) is the primary mechanism to remove platinum–DNA adducts, and excision repair cross-complementing-1 (ERCC1) is a critical NER component. Resistance to platinum has been linked to ERCC1 mRNA expression in ovarian cancer and other tumours, and ERCC1 levels are predictive of clinical outcomes in lung cancer patients treated with platinum-based chemotherapy [36]. Whether ERCC1, or other markers, could be used to guide chemotherapy selection in woman with ovarian cancer is unknown.

Clearly, our understanding of the biology surrounding drug resistance has improved. However, drug resistance still remains a central problem in the treatment of advanced-stage ovarian cancer, and these findings have not yet led to interventions with improved clinical outcomes. Emerging data with inhibitors of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP), particularly in tumours with pre-existing defects in homologous recombination DNA repair, are encouraging, and phase III randomised trials are being initiated. There are at least two distinct strategies for incorporation of PARP inhibitors, and each approach merits evaluation. First, concurrent combination with platinum-based chemotherapy can increase platinum-mediated cytotoxicity, regardless of genetic defects in homologous recombination. However, this has generally been associated with increased haematologic toxicity, requiring adjustments in dose and schedule to safely administer multiple cycles. Second, PARP inhibitors can be administered as a single agent following completion of primary therapy, creating a synthetic lethal paradigm for tumours with defects in homologous recombination DNA repair. In this regard, it is important to note that these defects are not simply limited to inherited mutations of *BRCA1* or *BRCA2*, but include somatic mutations, methylation status of gene regulatory elements, and mutations in a large number of candidate genes associated with DNA repair, approaching 50% overall incidence in patients with high-grade serous or endometrioid histology. It is likely that two separate phase III trials with similar agents will be initiated during 2012, and that these trials will evaluate concurrent and extended maintenance therapy, but designs are still under development (Fig. 13).

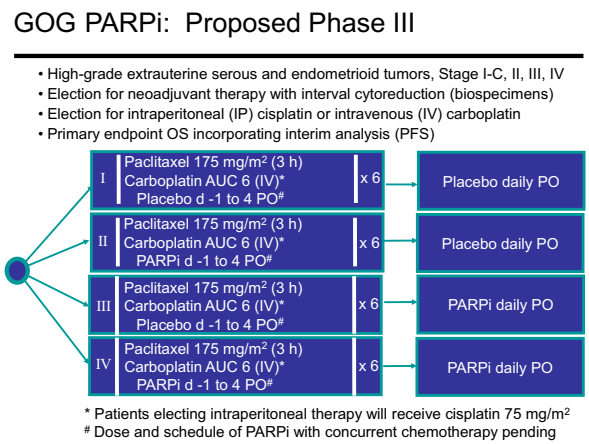

Fig. 13. Proposed design for the GOG phase III trial to evaluate concurrent and maintenance therapy with oral PARP inhibitor.

Discussion

Optimal primary therapy of advanced ovarian cancer has not substantially changed over the last few years, in spite of new cytotoxic agents, and evaluation of diverse treatment strategies. Almost all patients undergo at least one attempt at maximal cytoreductive surgery, and the combination of carboplatin and paclitaxel remains a well-tolerated and widely utilised standard treatment regimen. Recent data favour the selected utilisation of neoadjuvant chemotherapy in patients with bulky disease, and dose-dense weekly paclitaxel in combination with carboplatin, which appears superior to standard dosing of paclitaxel. Intraperitoneal cisplatin and paclitaxel can be administered to patients with small-volume residual disease, and new trials are evaluating intraperitoneal delivery of carboplatin to further improve patient safety and tolerability.

The integration of emerging biologic principles with the development of molecular-targeted reagents is starting to achieve meaningful results, especially with regard to inhibition of VEGF-mediated angiogenesis and interference with PARP-mediated DNA repair. Biologic observations have also contributed to our understanding of tumour classifications, and prompted the evaluation of individualised treatments for patients with clear cell, mucinous, and low-grade histologies. However, the rapid development of drug resistance remains a major clinical challenge for the majority of patients with advanced-stage disease, prompting studies designed to target regenerative subpopulations that are resistant to conventional cytotoxic agents.

The next few years will see mature data from phase III trials targeting VEGF, and related components of angiogenesis. Comparative data among these agents are limited, and selection of high-priority combinations will remain challenging. Ideally, phase I trials should define more relevant endpoints, such as desired serum levels, duration of exposure, sequencing, feasibility of chronic administration at the selected dose, drug–drug interactions, and saturation of biologic targets. With few exceptions, single-agent

phase II trials with targeted agents have been not very informative, and it would be preferable to broadly utilise randomised phase II designs with multiple arms to select promising agents (or combinations) that meet appropriate thresholds. Finally, phase III trials should include multiple arms with selective and adaptive designs based on interim analysis, allowing the investigators to drop arms that appear non-promising or overly-toxic. This type of adaptive research programme would address key scientific questions, while efficiently selecting optimal regimens for fully-powered phase III evaluation.

Conflict of interest statement

The author has an interest in relation with one or more organisations that could be perceived as a possible conflict of interest in the context of the subject of this paper. **Advisory board:** Ad-hoc advisory board participant for Abbott Laboratories, Abraxis Oncology, Astra Zeneca, BiPar Sciences, Bristol Myers-Squibb Oncology, F Hoffman La Roche, Glaxo SmithKline, Johnson & Johnson, Sanofi-Aventis Pharmaceuticals, VentiRx Pharmaceuticals. **Other substantive relationships:** Member, Phase III Data Monitoring Committee, Genentech-Roche and Boehringer-Ingelheim.

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