

Integration of new or experimental treatment options and new approaches to clinical trials

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The 3rd International Ovarian Cancer Consensus Conference (OCCC), held September 3–5, 2004, in Baden-Baden, Germany, addressed 12 questions critical to the future directions of clinical research into the treatment of newly diagnosed ovarian cancer. Five of these questions examined issues related to new and experimental treatment options and how to integrate new modalities and translational research into clinical trials. These questions were:

8. C-1. Should maintenance/consolidation treatment be recommended for standard arms in future trials?
9. C-2. Should dose intense therapy or intraperitoneal therapy be a standard arm in clinical trials in first-line treatment?
10. C-3. Are there any subgroups defined by tumor biology who need specific treatment options/trials (and who should not be included in 'mainstream trials'?)
11. C-4. How to integrate new treatment modalities into studies?
12. C-5. How to integrate translational research in clinical trials in ovarian cancer?

8. C-1. Should maintenance/consolidation treatment be recommended for standard arms in future trials?

Despite a high initial response rate to first-line combination therapy, usually a platinum with a taxane [1, 2], most patients with advanced stage epithelial ovarian cancer suffer a recurrence within 2 years. On this basis a number of strategies have been put in place aiming to extend the progression-free interval either by continuing with the initial drug combination ('maintenance') or by instituting a new treatment approach using either different cytotoxic agents or a different modality of treatment ('consolidation').

Extended chemotherapy

Although the optimal number of cycles in first-line treatment is still unknown a recommendation of six cycles as standard is widely adopted for most studies (cf. workshop A).

Several randomized trials have explored the value of extended chemotherapy after standard treatment either at standard dose or using high-dose chemotherapy [3–5] or given intraperitoneally [6]. All but one have failed to show a benefit in progression-free or overall survival.

In the Southwest Oncology Group (SWOG) study [4], paclitaxel was continued following six cycles of cisplatin/paclitaxel for 3 months in one arm and 12 months in another arm. The study closed early because the median progression-free survival in the arm with prolonged treatment was 28 months compared with 21 months in the arm of shorter duration. There was, however, substantially increased toxicity in the 12-month arm. This study has been criticized because the taxane dose was reduced mid-trial due to neurotoxicity in a number of cases and overall survival can never be appropriately analyzed. There were insufficient events in both arms and there would have been substantial cross-over from the 3-month arm to the 12-month arm following the early closure.

The use of overall survival as an end point in such studies is important. Delaying time to disease progression is obviously of value, but may be less attractive if it is at the cost of significant toxicity and when the response to second-line and subsequent therapies is such that overall survival may not be significantly improved. Although it is likely that improved progression-free survival in first-line studies leads to an improved overall survival, the data on maintenance therapy are still lacking. Furthermore, toxicity has to be put into the equation somewhere, since quality of life has to be of increasing importance under these circumstances, particularly since most studies of maintenance therapy have been negative.

There have been a number of studies (Table 1) in which consolidation therapy with different single agents to first-line treatment have been assessed using epirubicin and topotecan following six cycles of combination therapy; initial results have not shown any difference in progression-free survival [7–9].

Some trials on high-dose chemotherapy as consolidation treatment have been initiated, but only one randomized trial has been published in an abstract form [5]. One hundred and ten patients with small volume disease were randomized to high-dose chemotherapy with carboplatin and cyclophosphamide with stem cell support ($n = 57$), or to three cycles of conventional-dose treatment ($n = 53$). There was no significant

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Table 1. Randomized controlled trials on intravenous chemotherapy as consolidation/maintenance treatment in ovarian cancer

Study	Patients	Randomization	Results
Scarfone et al. 2002 [7], <i>n</i> = 162, Italy	III–IV paclitaxel–platinum SLL, pCR	Epirubicin ×4 versus observation	OS NS
Pfisterer et al. 2003 [8], <i>n</i> = 1308, AGO, GINECO	IIB–IV paclitaxel + carbo	Topotecan ×4 versus observation	PFS, OS NS
De Placido et al. 2004 [9], <i>n</i> = 273, Italy	III–IV paclitaxel + carbo cCR, cPR	Topotecan ×4 versus observation	PFS NS
Cure et al. 2001 [5], <i>n</i> = 110, GINECO	III–IV platinum-based CT SLL, pCR, <2 cm	HDCT (carbo + cyclo) versus conventional CT ×3	PFS, OS NS
Markman et al. 2003 [4], <i>n</i> = 277, GOG, SWOG	III–IV paclitaxel + platinum cCR	Paclitaxel 3 or 12 cycles every 28 days	PFS 21 versus 28 months, <i>P</i> <0.005

SLL, second look laparotomy; pCR, pathological complete response; OS, overall survival; PFS, progression-free survival; NS, not significant; carbo, carboplatin; cCR, clinical complete response; cPR, clinical partial response; CT, chemotherapy; HDCT, high-dose chemotherapy; cyclo, cyclophosphamide.

difference in disease-free or overall survival and the data do not support the use of this treatment approach as consolidation in advanced ovarian cancer. Future high-dose studies will not be found attractive owing to toxicity issues, cost, difficulty in patient accrual and the large numbers required to sufficiently power such a study to show a significant benefit.

Radiation therapy, intraperitoneal radioisotopes, biological and immunological agents

Other approaches to improving outcomes in women with advanced epithelial ovarian cancer immediately following first-line treatment include the use of radiation therapy, intraperitoneal radioisotopes (including those linked to an antibody), and the use of biological and immunological agents.

A meta-analysis on the use of whole abdominal radiation as consolidation/salvage treatment in women with advanced epithelial malignancy has suggested that its role is limited [10] and a trial of a monoclonal antibody linked to Yttrium-90 has failed to show a benefit [11]. A randomized Swedish/Norwegian study of whole abdominal radiation did show a benefit in a subgroup of patients with pathological complete response [12], whereas administration of intraperitoneal ³²P after a negative second look laparotomy did not improve median progression-free survival in a recent multicenter trial [13].

A number of approaches using biological and immunological agents as consolidation therapy including γ -interferon [14, 15], MMP1 [16] and a monoclonal antibody against CA 125 [17] have failed to show any benefit in progression-free survival in studies so far. The monoclonal antibody targeting CA 125 did, however, result in a doubling of the median time to treatment relapse in a subset of women who showed an immune response in comparison with those who did not [18] and an improvement in progression-free survival has been reported in an Austrian study of maintenance intraperitoneal cisplatin and cyclophosphamide with subcutaneously administered interferon [19].

A trial of five intraperitoneal administrations of replication-deficient wild-type p53 delivered via an adenovirus vector was also ineffective in improving progression-free survival [20].

The participants adopted the following statement to the eighth question:

Current data do not support a recommendation of maintenance/consolidation treatment as a standard arm in future trials.

All believed that further investigations into the role of maintenance therapy are warranted and, ideally, such maintenance therapy should be compared with an observation arm.

Future approaches using the plethora of biological agents about to be tested offers some hope that maintenance therapy and/or consolidation therapy will become the standard of care for women with advanced epithelial ovarian malignancy in the future. It is likely, however, that gene expression profile technology will direct not only the choice of first-line agents, but also agents to be used either as maintenance or consolidation.

9. C-2. Should dose-intense therapy or intraperitoneal therapy be a standard arm of clinical trials in first-line treatment?

The concept that administration of maximally tolerated doses of cytotoxic chemotherapy over the shortest period of time will provide clinical benefit is attractive. Theoretically, this approach might overcome barriers to drug delivery (physical and molecular) by achieving high peak doses and/or prolonged exposure, bypassing drug resistance by saturation of protective mechanisms including DNA repair, damage tolerance, drug influx, drug conjugation and detoxification, and should provide clinical benefit in terms of prolonged median survival, increased long-term survival or improved quality-adjusted survival, particularly since complications from hematological toxicity can be managed with hemopoietic growth factors, progenitor cell infusions, blood product support and broad spectrum antibiotics. In addition, complications from non-hematological toxicities can be managed by selection of appropriate cytotoxic agents and optimal supportive care.

Methods used to study the potential benefits of dose intensification have been preoccupied with platinum and taxanes, particularly with the incorporation of new agents to create triplet

combinations. Mechanisms used include; increased dose intensity with maintenance of cumulative dose delivery (increased dose per cycle with fewer cycles); increased dose intensity with increased cumulative dose delivery (increased dose per cycle, standard number of cycles); high-dose therapy with hemopoietic support; dose-dense therapy (short cycle intervals using sequential single agents or combinations); and increased regional drug exposure particularly using the intraperitoneal route. It is clear that standard platinum-based therapy has the potential to become more dose intense because of improved disease assessment using imaging and tumor markers, because of increased numbers of women with optimally cyto-reduced disease, the wider availability of supportive care, and an increased preoccupation with drug delivery and cytotoxic therapy cycle scheduling. In this regard, some platinum-based therapies have already achieved high response rates and the majority of patients complete primary treatment in clinical complete remission. As such, the potential use for dose-intense therapy is somewhat limited. On the other hand, it can be argued that most patients are in clinical remission after first-line treatment because of inexact methods to assess disease status. This is reflected in at least a 25% at best pathological remission in patients considered clinically and biochemically free of disease.

Prospective phase III evaluations of cisplatin dose intensity and/or cumulative dose delivery given intravenously have not shown an improvement in either survival or quality-adjusted survival with a variable impact on short-term response rates and progression-free interval at the expense of increased hematological and non-hematological toxicity. This is also true for carboplatin. There have been limited evaluations of paclitaxel at increased dose or with prolonged schedules of treatment with no demonstrated improvement in clinical outcomes, although it must be stated that weekly single-agent dose-dense therapy appears at least as effective as standard dosing, with a reduction in some toxicity.

Prospective phase III trials on intraperitoneal therapy with cisplatin have demonstrated modest improvements in survival at the expense of increased systemic toxicity and regional complications. It has not been established whether the observed clinical outcomes reflect local tumor drug exposure or changes in the peritoneal milieu following treatment, particularly since it has not been demonstrated that small volume or microscopic disease is differentially associated with an improved outcome in this setting. Furthermore, inability to delineate the importance of route of administration from the effect of differing schedules and doses, together with inconvenience, catheter and technical problems, abdominal pain, high systemic toxicity and the necessity for trained teams have all limited the widespread acceptance of intraperitoneal chemotherapy as standard treatment.

It is possible that near maximal achievable benefit has already been realized with conventional doses of platinum-based therapy and there is limited evidence to suggest that an increased dose intensity of platinum, taxanes or other cytotoxic agents will provide meaningful clinical benefit using conventional treatment strategies. Likewise, the use of high-dose chemotherapy with hemopoietic progenitor cell support has not yet demonstrated clinical benefit as either primary therapy or consolidation treatment.

The participants adopted the following statement in response to to the ninth question:

There is no role for dose intense therapy with or without hematopoietic support or for intraperitoneal support or for intraperitoneal therapy as a standard arm in first-line treatment.

Although there are randomized phase III clinical trials addressing the intraperitoneal route of cisplatin therapy in patients with minimal disease, interpretation of the results remains controversial, and therefore its use has not been widely adopted.

The participants believed that further investigations into the role of dose density are warranted. Trials evaluating dose intense therapies or intraperitoneal treatment require design improvement.

10. C-3. Are there any subgroups defined by tumor biology who need specific treatment options/trials (and should not be included in ‘mainstream trials’?)

Both the 1993 and 1998 OCCC examined the question of identifying specific subsets of patients with advanced epithelial cancer whose tumors might respond differently based on a number of prognostic factors, including age, performance status, histology, grade, stage, residual disease, presence of ascites, and molecular markers such as HER-2/neu and p53. The attraction of defining such subpopulations would be to allow delivery of appropriate therapy, avoidance of undertreatment or overtreatment, the individualization of therapy, and the identification of populations who would not benefit from standard treatment. Unfortunately, not much progress has been made in this regard despite a plethora of new prognostic indicators that theoretically could allow the creation of an algorithm for therapy based on likelihood of tumor response. Gene profiling, however, may be the way forward [21].

Tumor burden, histology, performance status and age have all been identified as the key prognostic factors in both previous OCCC. In particular, the importance of tumor burden involving stage of disease, overall tumor bulk at the time of surgery and amount of residual disease, the importance of clear cell and mucinous histologies compared with serous disease, and the value of the Silverberg classification have all been highlighted.

Borderline tumors, both serous and mucinous, have a >95% 5-year survival and should not be included in any future studies of epithelial ovarian malignancy. The presence of micropapillary serous disease as a prognostic factor remains controversial, but it seems clear that just as in its frankly invasive counterpart, these tumors should be optimally debulked where possible since survival is substantially improved with this approach and chemotherapy may not directly influence outcome.

Clear cell cancers in particular have been identified as tumors that carry an adverse prognosis largely due to a diminished response to platinum-based therapy. However, there have been no prospective phase III trials undertaken in these poor prognostic histological subtypes, largely due to their infrequent nature, and it is hoped that the Gynecological Cancer Intergroup (GCIG) will be able to correct this in the next few years.

To date, the presence of either amount of primary disease prior to surgery or disease residuum following the first surgical intervention have not been used in dictating subsequent first-line therapy, but it can be assumed that trials of neo-adjuvant therapy will become more prolific and approaches to treatment based on amount of residual disease and genetic/proteomic profiles will become the norm.

Little progress in the use of biological markers to dictate treatment has been made since the last OCCC. There is insufficient evidence to make any conclusions at this point in time outside the clinical trial area. Likewise, the use of drug-resistance assays has not been validated prospectively.

The incorporation of novel targeted therapies to selective subpopulations of women with epithelial ovarian cancer is undoubtedly possible including potential molecular targets such as EGFR, PTEN, TRAIL and VEGF. Just how these biological agents will be used remains unclear, although combination approaches certainly seem attractive either using biologicals with chemotherapy or radiation, using biologicals in combination, or using biologicals as either sequential or concurrent therapy.

It is hoped that by the time of the next OCCC trial design will have taken into account not only the standard prognostic criteria validated over the last 20 years, but also new molecular information achieved through gene profiling, proteomics and molecular genetics. It is not unreasonable to expect that bioinformatics may lead us to an individual treatment program for any given patient with any given epithelial malignancy.

The participants adopted the following statement to the tenth question:

All subgroups of invasive epithelial ovarian cancer should be included in trials until specific studies are available.

Patients with tumors of low malignant potential should not be included in future trials of invasive epithelial ovarian cancer.

The consensus conference recognized that as more evidence becomes available, certain histological subtypes might show different biological behavior, particularly clear cell and mucinous cancers. Currently, however, there are insufficient data to exclude any subtypes from trials. Different histological subtypes should be documented within phase III trials to allow subgroup analyses/meta-analyses.

11. C-4. How to integrate new treatment modalities into studies?

Cytotoxic agents have to date been generic in their attack on the cancer cell with resultant dose-limiting toxicities and relative lack of long-term efficacy. Newer agents are specifically molecularly designed against tumor-specific targets such as growth factors and their receptors, angiogenic pathways and the extracellular matrix, signal transduction pathways, cell survival pathways and the proteasome. Many of these newer agents have shown activity in other malignant diseases, often in heavily pretreated patients, and it has become obvious that these agents are largely cytostatic rather than cytotoxic, so that classical end points for response need be modified. Many of these agents

can be given orally and due to their relative lack of toxicity, given chronically.

EGFR inhibitors

EGFR overexpression is seen in up to 50% of ovarian cancers and is usually associated with a poorer prognosis. EGFR targeting therapies include monoclonal antibodies such as cetuximab and tyrosine kinase inhibitors such as gefitinib, which has been trialed in patients with advanced recurrent ovarian cancer at a dose of 500 mg daily. Grade 3–4 toxicities were uncommon, with the worst being skin rashes and diarrhea. Four of 27 evaluable patients achieved a progression-free survival of >6 months, but the overall response rate was <5%. All the patients with prolonged progression-free survival had platinum-resistant tumors and there was a significant relationship between skin toxicity and prolonged progression-free survival [22]. Erlotinib has also been evaluated with evidence of partial response and disease stabilization [23].

CI-1033 is a tyrosine kinase inhibitor and although no responses have been seen in patients with advanced ovarian cancer, approximately 30% achieved at least 8 weeks of stable disease [24].

Angiogenesis inhibitors

Elevated levels of VEGF are associated with a poorer prognosis and ascites production. Bevacizumab is currently being evaluated by the GOG both alone and in combination with low-dose oral cyclophosphamide, which is in itself believed to have anti-angiogenic properties.

Metalloprotease inhibitors

BAY12-9566 has been evaluated in a number of diseases, including advanced ovarian cancer, but results have been disappointing and toxicity has been a problem with about 25% of patients having grade 1–2 nausea and a further 25% grade 1–2 fatigue [16].

Monoclonal antibodies

Oregovomab (Ovarex) is a monoclonal antibody against CA 125 administered as a 20 min intravenous infusion. It has been studied as consolidation therapy. The study was negative but a subset analysis suggesting a significant increase in progression-free survival for those patients with optimally debulked disease and normal CA 125 at the completion of therapy. Immune response correlated with clinical response [14]. Immune responses with another anti-CA 125 vaccine, ACA-125, have also been reported [25].

Vaccines

Peptide vaccines designed to mimic HER-2 have shown some encouraging results and preliminary work in melanoma using dendritic cells as antigen presenters is proving interesting [26].

Clinical end points with new agents

Although overall survival is the most important oncological end point for most chemotherapy agents, it is influenced by several

factors including the availability of second- and third-line agents and optimal surgery. Median progression-free survival may be a better reflection of the true activity of an individual chemotherapeutic agent or combination.

Quality of life as an end point is uniformly accepted as being of importance, but to date has been little evaluated in clinical trials. Given the likelihood of stabilization of disease as an important future end point, quality of life may well be the principal measure by which to measure the efficacy of new agents.

The introduction of new agents as first-line single agents, in combination with cytotoxic chemotherapy, in combination with other new agents or as maintenance therapy needs considerable planning. The optimal scheduling of these agents for ovarian malignancy needs ongoing evaluation and it is likely that their place may differ depending on the amount of residual disease following surgery or at the end of first-line treatment. Given their relatively low toxicity, evaluation of their place as maintenance or consolidation therapy seems a priority.

The role of receptor testing as a prelude to administration of biological agents requires elucidation, as does the identification of various subgroups in whom benefit may be achieved. For instance, using Gefitinib in bronchial alveolar lung cancer has revealed a substantial improvement in outcome in women compared with men, in pure non-mucinous tumors and in tumors with high MAP kinase activity and tumors with high MAP kinase and HER-2/neu levels. Furthermore, the presence of an EGFR mutation is highly predictive of a response to gefitinib under these circumstances.

To accurately ensure that these subsets of patients can be identified, tumors, both fresh and formalin fixed, of primary and metastatic disease should be stored throughout all new trials. Finally, these agents are likely to be expensive and pharmacoeconomic analyses and quality of life analyses will be necessary to justify their introduction into routine clinical practice [27].

The participants adopted the following statement to the eleventh question:

It is currently unclear how to best integrate new treatment modalities into studies; however, identification and validation of predictors of response to new biological agents such as targeted therapies, vaccines and monoclonal antibodies should be a priority in such studies.

Standard clinical end points should continue to be used in phase III studies.

The consensus conference was aware of the problems of applying 'old methodology' to 'new approaches', but there was a strong feeling that information on the optimal way to best use these new agents is currently lacking and that it is premature to change study design.

12. C-5. How to integrate translational research in clinical trials in ovarian cancer?

Translational research is the application of basic scientific discovery into the day to day management of patients and

conversely the generation of scientific questions based on day to day clinical observations. The integration of translational research requires an organizational arrangement that promotes inter-disciplinary cooperation and is structured dynamically to involve as many researchers in a given area as possible. Translational research requires bioinformatics to interpret huge amounts of data and to identify pathways in individual tissue samples which may be of physiological or pathological importance. Sharing of analytical approaches and informatic platforms is going to be mandatory to ensure that independent validation of datasets occurs.

To ensure appropriate integration, tissue banks need to be established, databases need to be compiled, uniform consent processes need to be in place to facilitate cross-country requirements as regards regulatory processes, and some agreement as to the use of existing tissue in tissue banks is urgently required.

The implementation of a standardized and formal consent covering current and future unknown purposes is going to be critical, and ideally information sheets and consent forms should be so designed to avoid the need for re-contact for future research and also should include clearance in case of death or drop-out.

There needs to be a hierarchy of need around which basic science should concentrate. Molecular determinants of outcome and of response to novel or existing agents should be a high priority, including the prediction of response to novel small molecules, the understanding and prediction of primary platinum-resistance and the prediction of response to second-line therapy. Measurement of the frequency of germ-line mutations such as BRCA1 should be undertaken and the effect of the mutation status on response analyzed. The comparison of molecular profiles of various histological subtypes as seen on microarrays is urgently required to correlate with subsequent clinical events and to clarify the origin of tumors in the 10% or more who may have metastatic disease. The need to document changes in EGFR phosphorylation and downstream signaling in individual tumors with subsequent response and duration of response is urgently required. Every clinical trial from now on should have a number of molecular questions posed and agreement on the minimal dataset to be captured will be of increasing importance.

The participants adopted the following statement to the twelfth question:

Translational research should be considered in the planning of future clinical trials.

Integration requires harmonization of consent processes and standardization of databases, including minimum datasets, and specimen banks, including central pathology review.

Regulatory aspects of shared samples need facilitation.

GCIG trials should have early consultation with GCIG translational research group.

Conclusion

The GCIG has gathered a large experience within its translational research and harmonization groups, with the latter having

established uniform consent forms and defined regulatory issues associated with sample sharing. Both working groups could offer support if other study groups decide to include translational research in large randomized trials.

Acknowledgements

This document provides the background for the consensus statements related to new or experimental treatment options and approaches to clinical trials developed during the 3rd International Ovarian Cancer Consensus Conference, which was held by the GCIIG from 5–9 September 2004 in Baden-Baden, Germany. This conference was supported by an unrestricted grant from Bristol-Myers-Squibb. Neither selection of the participants nor determination of the agenda nor the results of the conference were influenced by the financial support provided.

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