Review article

Harmonizing Clinical Trials within the Gynecologic Cancer InterGroup: Consensus and Unmet Needs from the 5th Ovarian Cancer Consensus Conference

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Abstract

The Gynecologic Cancer InterGroup (GCIG) 5th Ovarian Cancer Consensus Conference (OCCC) was held in Tokyo, Japan from 7-9 November 2015. It provided international consensus on 15 important questions in 4 topic areas, which were generated in accordance with the mission statement to establish "International Consensus for Designing Better Clinical Trials". The methodology for obtaining consensus was previously established, and followed during the 5th OCCC. All twenty-nine clinical trial groups of GCIG participated in program development and deliberations. Draft consensus statements were discussed in topic groups as well as in a plenary forum. The final statements were then presented to all 29 member groups for voting and documentation of the level of consensus. Full consensus was obtained for 11 of the 15 statements with 28/29 groups agreeing to 3 statements, and 27/29 groups agreeing to 1 statement. The high acceptance rate of the statements among trial groups reflects the fact that we share common questions, and recognize important unmet needs that will guide future research in ovarian cancer.

Introduction

Ovarian cancer remains one of the most challenging and lethal cancers affecting women today, despite advances in surgical management, supportive care, and chemotherapy. Current practice guidelines are largely based on evidence generated by clinical trials that have been conducted through international collaboration. Consensus on research methodology can accelerate the design and accrual of pivotal trials while minimizing regional bias.

The Gynecologic Cancer InterGroup (GCIG) has sponsored a series of Ovarian Cancer Consensus Conferences (OCCC) beginning in Elsinore, Denmark (1993) [1], followed by Bergen aan Zee, the Netherlands (1998) [2], Baden-Baden, Germany (2004) [3] and Vancouver, Canada (2010) [4]. The 5th OCCC was convened in Tokyo, Japan (2015), incorporating 29 individual clinical trial groups, with the mission to establish international consensus for designing better clinical trials.

This manuscript provides an overview of the consensus process and outcomes, together with analysis of unmet needs. Individual manuscripts can be consulted for a more detailed discussion of key topics [5-9].

Methodology

The methodology utilized to support the 5th OCCC followed previous guidelines [3, 4]. A Scientific Planning Committee (SPC) was convened in 2013 to develop the agenda and key topics, including critical questions to be addressed in trials over the subsequent five years, with an emphasis on: Individualized Therapy and Patient Factors, First-Line Intervention, Rare Tumours, Recurrent Disease, and Incorporating Patient-Reported Outcomes (PROs) and Quality of Life (QoL). The meeting was hosted by The Jikei University in Tokyo, Japan from 7-9 November 2015 with a total of 95 invited delegates and 92 attendees.

The detailed consensus process has been previously described [4]. In view of the number and diversity of topics, a considerable amount of development was required during the 18 months prior to the actual conference. Consensus statements were drafted in advance for consideration by the SPC and member groups. The conference provided a venue for collaborative discussion and refinement of statements to achieve consensus across the 29 groups.

The 5th OCCC produced a total of 15 final consensus statements, in accordance with the mission to achieve an “International Consensus for Designing Better Clinical Trials”. Full consensus (29/29 groups) was obtained for 11 of the 15 statements, with 28/29 groups agreeing to 3 statements, and 27/29 groups agreeing to 1 statement. Areas of unmet need were categorized and discussed, but without consensus voting.

Summary of Consensus Statements and Unmet Needs

A. Individualized Therapy and Patient Factors

A1: Factors to be evaluated prior to initial therapy

- Clinical: International Federation of Gynecology and Obstetrics (FIGO) Surgical-pathologic stage (applies to ovarian, fallopian tube, and peritoneal cancers); cytoreduction status (primary complete resection *vs*. other); primary treatment modality (surgery *vs*. neoadjuvant chemotherapy); performance status and associated variables; tumour markers (e.g. CA-125) documented prior to therapy; country and/or geographic region of treatment
- Pathology: Histopathology remains the gold standard for classification; In neoadjuvant chemotherapy, tumour grading (and typing) should be based on the pre-chemotherapy biopsy; binary grading of serous carcinoma (low-grade and high-grade), with distinction of micropapillary carcinoma; binary grading is favoured for endometrioid carcinoma, with assignment of FIGO grade 1 to low-grade, and grades 2-3 to high-grade; carcinosarcomas are regarded as carcinomas; carcinosarcoma, clear cell carcinoma and undifferentiated carcinoma should not be graded; mucinous carcinoma should be graded; access to archival tumour specimens should be documented and maintained.
- Biomarkers: Germline mutation testing to include *BRCA1/2* is recommended for all patients enrolled on clinical trials; stratification (if possible) should be performed and knowledge of mutation status should be incorporated into primary endpoint analysis; somatic mutation analysis for *BRCA 1/2* is recommended; predictive biomarkers for targeted agents to be included as companion diagnostics

A2: Factors to be specifically evaluated in recurrent disease

- Treatment Free Interval (TFI) following primary chemotherapy, with reference to last dose of primary platinum agent, and reported as a continuous variable (months). Less robust markers include acquired resistance following platinum-based therapy for recurrent disease. Report last dose of non-platinum therapy and maintenance therapy, particularly anti-angiogenic agents or inhibitors of the enzyme poly ADP ribose polymerase (PARP)
- Outcome following most recent cytoreductive surgery, presence of non-measurable vs. RECIST-measurable disease
- Separate clinical trials, if available, should be utilized for different histological subtypes, although trials can include multiple subtypes
- Collection of tumour specimens at relapse is encouraged.

Three critical categories (clinical, pathology and biomarkers) of initial factors were identified as important for trial design, including potential stratification, depending on trial size and clinical context (A1). Substantial advances in molecular diagnostics were noted, although histopathologic classification remains the gold standard [5]. Details of tumour grading for

Race and ethnicity could be incorporated as important stratification factors in future trials, and the definition and categorization of race/ethnicity would benefit from international harmonization. Clinical trials in specific subpopulations, including the frail and elderly, should be considered, with adoption of appropriate assessment tools for patient categorization. Older and/or vulnerable patients are not adequately represented in clinical trials, and poorly characterized, limiting agreement on standards of care.

B. First-Line Interventions

B1: Clinical subgroups that should be used for comparator studies

- After diagnosis of advanced-stage disease, patients should be assessed (with a gynecologic oncologist) for primary cytoreductive surgery (PCS) or primary NACT with the option to undergo interval cytoreductive surgery (ICS), defining two major clinical subgroups. The goal with primary surgery is macroscopic complete resection. After primary surgery, the extent of residual disease must be clearly documented (no macroscopic residual vs ≤1 cm or >1 cm macroscopic residual).
- After primary chemotherapy, two clinical subgroups emerge: those who are candidates for ICS and those who are not suitable for surgery. If patients undergo ICS, the extent of residual disease must be clearly documented. Patients not suitable for ICS include those with progressive disease and those medically unfit for surgery.
- Patients receiving NACT should be considered for novel combination therapy trials, particularly window of opportunity studies.

B2: Control arms for trials of first-line therapy

- Intravenous 3-weekly carboplatin and paclitaxel remains the standard chemotherapy regimen for first-line therapy in advanced stage ovarian cancer.
- Acceptable additions or variations in dose, schedule, and route of delivery should be supported by at least one clinical trial demonstrating non-inferiority or superiority to a taxane/platinum. So far, the following alternatives have been identified: Weekly intravenous paclitaxel is an acceptable alternative to three weekly intravenous paclitaxel in combination with 3-weekly intravenous carboplatin. The addition of bevacizumab to the control arm after primary surgery is acceptable. Intraperitoneal therapy after primary surgery with less than 1 cm residual disease. If more than one regimen is included in the control arm, patients should be stratified for these regimens.
- Trials are needed to define the control arm for elderly and frail patients, with incorporation of a comprehensive geriatric assessment.
- If chemotherapy is to be used in early-stage disease, platinum-based chemotherapy should be the control arm.

The timing of cytoreductive surgery and the extent of residual disease remain important as integral prognostic factors that define clinical subgroups in advanced-stage disease (B1). However, better methods are needed to triage patients between primary surgery and NACT, such as tissue-based molecular markers, functional imaging, laparoscopic assessment, and comorbidity scores.

Notwithstanding alternatives for the control arm, this statement (B2) has not changed markedly since the last consensus conference. Issues to be considered in first-line therapy include early stage disease, incorporation of maintenance therapy, development of

B. First-Line Interventions (continued)

B3: Endpoints for first-line trials

- Overall survival (OS) is the ideal primary endpoint for first-line trials (+/- maintenance), but superiority is difficult to demonstrate due to long post-progression survival and crossover.
- Progression-free survival (PFS) measured with validated assessment tools is a valid primary endpoint.
- If PFS is utilized as primary endpoint: The projected magnitude of benefit should be considered clinically relevant and clearly exceed risk; methods should be employed to reduce bias and informative censoring; pre-specified assessment schedules must be applied consistently across treatment groups at intervals shorter than projected progression-free intervals; OS must be measured as a secondary endpoint; PFS should be supported by additional endpoints such as time to first or second subsequent treatment, relevant patient reported outcomes (PROs), severity of adverse effects and pharmaco-economic evaluation.
- PRO should include prospective quality of life (QoL) assessment using validated tools; assessment methods should be tailored to the design of the trial, with specific methodologies developed to measure QoL in maintenance trials.
- Specific additional endpoints should be defined for neoadjuvant 'window of opportunity' studies. In addition to PFS, examples include total gross resection rate, treatment response score and molecularly defined endpoints.

With expanded treatment options, patient crossover to new treatments, improvements in primary therapy, and better supportive care, it has become more difficult to demonstrate clinically-significant improvements in OS using conventional phase III trials (B3). This has focused attention on strategies to enhance the value of PFS as a primary endpoint, and to establish a more robust association between PFS and clinical benefit, using patient reported outcomes (PRO) and other QoL measures [9]. It has also encouraged the development of potential surrogates for OS, such as time to second subsequent therapy. Adoption of these hybrid endpoints within clinical trials, and their potential utilization during regulatory review, will require uniform definitions, validated assessment tools, and collection of extended and more detailed post-progression treatment and outcomes data [6].

C. Rare Tumours

C1: Research issues/needs unique to rare ovarian tumour types

- An international harmonized consensus definition of histopathology diagnostic criteria for each rare ovarian tumour type is needed for the purpose of trial and registry eligibility. Expert pathological review is a necessary quality requirement prior to trial or registry participation.
- Priority should be given to translational research studies and the identification of novel therapies.

C2: What should be investigated in rare epithelial ovarian cancer, germ cell tumours, and sex-cord stromal tumours?

- Rare epithelial ovarian cancer (eOC): If indicated, platinum-based chemotherapy is a standard for high-risk early- or advanced-stage rare eOC, and should remain the control arm. Rare eOC is a distinct entity and should be studied separately; dedicated rare eOC trials should be encouraged. Low grade serous cancer (LGSC) and clear cell carcinoma (CCC) can continue to be included in ovarian cancer trials where the question is relevant but stratified on entry and analysed as distinct biological entities. Utilization of well-defined pathology/translational studies will allow analysis across trials.
- Germ cell tumours (GCTs): Definition of a prognostic scoring system in post-pubertal females to guide therapy. Biomarker development, in particular, to investigate any molecular differences between male and female GCTs.
- Sex-cord stromal tumours (SCSTs): There is an urgent need for a prognostic system. The role for systemic treatment after completely resected advanced or relapsed disease should be investigated. Alternatives to the current bleomycin-etoposide-platinum (BEP) regimen are needed.

C3: Are randomised trials possible?

- Randomised trials are feasible in rare epithelial ovarian tumours, but international collaboration is required.
- Randomised trials of adjuvant therapy vs. surveillance in low/intermediate risk GCT are feasible only with international collaboration.
- Randomised trials in poor prognosis or relapsed GCT are best performed as a subset of male and paediatric germ cell studies.
- Phase III trials are unrealistic in SCSTs but randomised phase II studies are possible with strong international cooperation.

Although there is emerging evidence to suggest the presence of distinct molecular profiles in rare eOC subtypes, including LGSC, CCC, and granulosa tumours, there is insufficient validated data to alter current recommendations for primary platinum-based chemotherapy as a control regimen [7]. Trials in these rare subtypes, including exploratory non-randomized cohorts, would clearly benefit from international collaboration. In addition, as promising subtype-specific adjuvant chemotherapy regimens emerge, definitive evaluation would

D. Recurrent Disease

D1: What are the subgroups for clinical trials in recurrent ovarian cancer?

- Trials in recurrent ovarian cancer should incorporate the following to define the trial population: Treatment-free interval (TFI), TFIp (platinum), TFInp (non-platinum), TFIb (biological agent to be specified). Histological type. BRCA status (gBRCA and others including somatic BRCA and HRD to be considered as data emerge). Type of prior therapy (anti-angiogenic agents, PARP inhibitors, chemotherapy, and others). Number of prior lines of chemotherapy (trials should not be limited to second or third line). Presence or absence of symptoms and type (e.g. ascites, abdominal symptoms, pain, performance status). Other factors to be considered include tumour volume and previous surgical outcome.
- Separate trials are needed for populations with unmet needs: Medically compromised and/or elderly patients. Multiple lines of prior chemotherapy

D2: What are the control arms for clinical trials in recurrent ovarian cancer?

- In patients where platinum is not an option, a control arm can include a non-platinum drug as a single agent or in combination.
- The choice of control arms for the subgroup who can receive platinum must be supported by evidence, and it must integrate available predictors as well as prior exposure, which may limit the selection for further lines of therapy. This currently includes 3 potential control arms: Platinum combination, Platinum combination with a licensed anti-angiogenic agent, Platinum combination followed by a licensed PARP inhibitor (maintenance).
- A subgroup exists (e.g. medically compromised and/or elderly patients) where less toxic therapy or best supportive care may be the most appropriate control arm.
- There is no proven effective therapy for patients who have asymptomatic CA-125 relapse.

It is now established that tumour histology and molecular signature influence the outcomes of conventional chemotherapy, as well as emerging targeted agents [8]. The consensus statement ensures that these important variables will be used to categorize individual patients comprising study populations in recurrent ovarian cancer (D1). Depending on the size and nature of randomised trials, some of these factors should be considered for stratification, such as previous treatment, TFI, and utilization of specific maintenance therapy, which may influence the response and outcomes to protocol-directed therapy.

Control arms for clinical trials in recurrent ovarian cancer need to consider prior therapy, TFI, potential contraindications for platinum re-challenge (including allergic reactions), and available clinical-molecular predictive markers (D2). At present, there is insufficient evidence to support assignment of specific control arms according to outcomes from secondary cytoreductive surgery, although this could be a used as a stratification factor in randomised trials. Patient subgroups with special needs related to medical comorbidities, disease-related

symptoms, physiologic age, or multiple prior therapies, were recognized, but there was no consensus in terms of modified control regimens, which will require further investigation.

D. Recurrent Disease (continued)

D3: What are the endpoints for clinical trials in recurrent ovarian cancer?

- PFS is an acceptable primary endpoint in recurrent ovarian cancer trials only if supported by additional endpoints. PFS alone is not an acceptable endpoint.
- In cohorts with expected median OS of more than 12 months, OS is heavily dependent on subsequent therapy. Hence, in this cohort, PFS supported by TSST (defined as Time to Second Subsequent Therapy or Death) and PROs are the preferred endpoints.
- In cohorts with expected median OS of less than or equal to 12 months, the preferable primary endpoint is OS. PFS is an acceptable primary endpoint only if supported by PROs or additional endpoints such as TUDD (Time until Definitive Deterioration).
- Context-specific PROs should be selected to support the study objectives. This would include incorporating appropriate instruments and a predefined statistical analysis plan. PRO collection should have relevant duration of interval between measurements and be continued until TSST. Specific measures to avoid and deal with missing data should be defined.
- Analysis and sample size calculations should account for cross over when OS is a primary endpoint. If estimated OS is long (e.g. more than 3 years), planned cross over may be helpful to avoid informative censoring (in the absence of placebo).

The definition of endpoints for clinical trials in recurrent ovarian cancer has become more complex over the last few years. This is related to several factors, including an increased number of trials with prolonged maintenance therapy in the setting of small-volume asymptomatic disease, as well as the selection of patients according to tumour histology, germline mutation status, or tumour molecular profiles. In addition, as noted in primary therapy, investigators must also consider cross-over and access to additional treatments that can obscure any potential impact on median overall survival. Taken together, these points have emphasized the importance of integrating PRO and QoL to enhance the value of PFS, and the utilization of hybrid endpoints, such as TSST, as a surrogate for overall survival. It is uncertain how regulatory authorities will respond to these newer initiatives, but with international standardization, it should enhance the review and approval process for new agents by providing a more robust measure of clinical benefit.

Clinical trials in patients with an asymptomatic CA-125 progression remain an area of interest. Well-designed trials of targeted therapies or immune checkpoint blockade in patients with a low tumour burden are under consideration.

Conclusions

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