Incorporating patient centered benefits as endpoints in randomized trials of maintenance therapies in advanced ovarian cancer: a position paper from the GCIG Symptom Benefit Committee

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Abstract

Background: Quality of life and patient reported outcome measures (PROMs) are important secondary endpoints and incorporated in most contemporary clinical trials. There have been deficiencies in their assessment and reporting in ovarian cancer clinical trials, particularly in trials of maintenance treatment where they are of particular importance. The Gynecologic Cancer InterGroup (GCIG) symptom benefit committee (SBC) recently convened a brainstorming meeting with representation from all collaborative groups to address questions of how to best incorporate PROMs into trials of maintenance therapies to support the primary endpoint which is usually progression free survival (PFS). These recommendations should harmonize the collection, analysis and reporting of PROM's across future GCIG trials.

Methods: Through literature review, trials analysis and input from international experts, the SBC identified four relevant topics to address with respect to promoting the role of PROMs to support the PFS endpoint in clinical trials of maintenance treatment for OC.

Results: The GCIG SBC unanimously accepted the importance of integrating PROM's in future maintenance trials and developed four guiding principles to be considered early in trial design. These include 1) adherence to SPIRIT-PRO guidelines, 2) harmonization of selection, collection and reporting of PROM's; 3) combining Health Related Quality of Life (HRQL) measures with clinical endpoints and 4) common approaches to dealing with incomplete HRQL data.

Conclusions: Close attention to incorporating HRQL and PROM's is critical to interpret the results of ovarian cancer clinical trials of maintenance therapies. There should be a consistent approach to assessing and reporting patient centered benefits across all GCIG trials to enable cross trial comparisons which can be used to inform practice.

Key-words: Quality of life, PROMs, maintenance, ovarian cancer

Introduction

The Gynecologic Cancer InterGroup (GCIG) Fifth Ovarian Cancer Consensus Conference (OCCC) endorsed progression-free survival (PFS) as the primary end point in 1st line and maintenance therapy ovarian cancer clinical trials due to the impact of post progression therapies on overall survival, but also recommended that the magnitude of benefit should be clinically relevant (1). A statistically significant increase in the hazard ratio for PFS in favor of the experimental arm does not necessarily equate to a clinically meaningful benefit to patients and underscores the importance of including and measuring patient centered outcomes in randomized trials to support the primary PFS endpoint. The attendees at the GCIG 5th OCCC endorsed implementing the International Society for Quality of Life research (ISOQOL) (2) and Consolidated Standards of Reporting Trials – Patients Reported Outcomes (CONSORT-PRO) (3) guidelines on incorporating of Patient-Reported Outcomes Measures (PROMs) as endpoints in clinical trials. Although Health Related Quality of Life (HRQL) is assessed in the vast majority of ovarian cancer trials and included as a secondary endpoint, the uptake to include additional patient reported outcomes as secondary endpoints has been slow and inconsistent. Typically, the HRQL endpoints in most ovarian cancer trials are either the mean change scores from baseline in Trial Outcome Index (TOI) score or National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index (NFOSI 18) (4) or global health status in EORTC Quality of Life Questionnaire (QLQ) C 30 (5) in the experimental or placebo arms with a mixed effects model for repeated measures. No clinically significant difference in HRQL using these measures have been reported in any of the trials of maintenance therapy between the experimental arm and control arm. The findings are reported and discussed briefly in the primary manuscript, which commonly also includes a statement that the experimental treatment “had no detriment on HRQL”. This has led to a degree of skepticism amongst clinicians about the value of these measures given the significantly higher frequency of adverse effects observed in the experimental arm compared to placebo in trials of maintenance therapy which are not reflected by the mean change scores in selected HRQL endpoints. More detailed results may be reported at a later date in a secondary publication and include additional post hoc exploratory analyses of PRO’s. However, a minority of contemporary clinical trials include carefully considered, context specific PRO hypotheses and predefined patient centered benefits as endpoints in the

protocol and statistical analysis plan to support the clinical relevance of the PFS primary endpoint. The importance of including PRO's in clinical trials assumes increasing importance and significance in the era of maintenance therapies with antiangiogenics, Poly-ADP ribose polymerase (PARP) inhibitors and immune checkpoint inhibitors either as single agents or in combination in clinical trials. In these trials, patients are usually commenced on maintenance therapy after response to chemotherapy when they are generally well with no cancer related symptoms and the primary aim of the trials is to prolong progression free survival and possibly overall survival. Patient reported outcomes and patient centered benefits including patient reported adverse effects are of particular importance in this setting and can help to support the primary endpoint and provide insight into the impact of adverse effects of treatment as well as impact of recurrence and subsequent treatments on patients .These all need to be offset against the prolongation in PFS with the experimental treatment. It was with these challenges in mind, that a brainstorming session was convened with representation from all GCIG groups to focus on incorporating PROs as endpoints in the next generation of clinical trials of maintenance therapies.

Set-up and goals of the GCIG Symptom Benefit Committee (SBC) HRQL brainstorming meeting

The SBC meets regularly at the bi-annual GCIG assembly and at the 2018 fall meeting, attendees concluded that a formal brainstorming meeting should be held to discuss topics of importance with regard to measuring patient centered benefits in trials and how they would impact on the design and endpoints included in future clinical trials. The ultimate objective was to keep PROMs on the agenda of all GCIG trial groups and improve the design and interpretation of future clinical trials. A scientific committee was set up to identify four topics considered to be critical to the design of next generation of GCIG trials. Accordingly, four working groups with representatives of all GCIG groups carried out a detailed literature review and identified the most relevant questions, which were discussed and debated at the face to face brainstorming session. This meeting led to consensus recommendations regarding future research directions with respect to inclusion of PRO's in clinical trials. This paper summarizes the first (HRQL issues pertaining to immunotherapy and maintenance therapy) and fourth

(Advancing methodology) working groups position on the assessment of HRQL and patient centered benefits in ovarian cancer maintenance trials.

The current landscape of clinical trials for ovarian cancer

The therapeutic landscape and treatment options for women with advanced ovarian cancer have dramatically changed over the last 10 years, largely due to the development of new drugs and treatment strategies, with the greatest change being the positive impact of maintenance therapies with PARP inhibitors and angiogenesis inhibitors on PFS and evolving data on the beneficial effect on overall survival. These results have been rapidly translated into clinical practice and have rekindled interest in the potential importance of maintenance therapies after response to chemotherapy. However, maintenance therapy brings new challenges of how to measure benefit to patients beyond PFS, which is critical to consider given the potential adverse effects and cost of these maintenance therapies. This requires a change in thinking about measuring patient reported outcomes and patient centered benefits in maintenance therapy trials, which are very different to measuring HRQL in patients with advanced ovarian cancer receiving chemotherapy or symptom benefit with palliative chemotherapy. Most patients randomized to maintenance therapy have responded to chemotherapy and either have no evidence of disease on imaging or small volume disease and do not have cancer related symptoms. They are for the most part well and it is not possible to improve HRQL.

The interest in maintenance therapy has evolved in parallel with a better understanding of tumor biology, and the ability to identify patient subsets most likely to gain benefit from PARP inhibitors including those with BRCA mutations or tumors with homologous repair deficiency (HRD). This brings new opportunities to delay the time to progression in women with advanced ovarian cancer who have a high risk of recurrence after 1st or later lines of chemotherapy, but also introduces new challenges which include long term treatments which do have adverse effects. The impact of these adverse effects and the trade-offs that patients are prepared to accept for a prolongation of PFS and possibly overall survival (OS) need to be assessed in clinical trials.

There is now great interest and an expectation that immune checkpoint inhibitors either combined with chemotherapy or as maintenance therapy alone or in combination with other agents such as PARP inhibitors will further improve outcomes of patients with advanced ovarian cancer. Indeed, there is a massive international effort to investigate immune checkpoint inhibitors in trials and 5000 women have so far been enrolled in many large international trials with a particular focus on maintenance treatment for women with advanced ovarian cancer. These trials are characterized by increased complexity and include drugs that are associated with very different adverse effects to cytotoxic chemotherapy and are administered for 1 to 2 years or longer. Yet, it is striking how little attention has been paid to the important question of patient centered benefits of maintenance treatment in these trials. This underscores the importance of investigating the impact of maintenance therapies not only on quality of life but additional patient centered benefits and prospectively including PROM's in clinical trials and including them as pre-defined secondary endpoints.

Limitations of HRQL assessment in previous trials

Although the vast majority of recent trials have included HRQL measures, the focus has been the mean change over time in global scores of HRQL/TOI with most studies reporting no significant differences between the experimental arm and placebo in maintenance trials. However, more recently a number of ovarian cancer maintenance trials of PARP inhibitors (NOVA, SOLO-2 and SOLO-1) have reported and published results of additional patient-centered benefits to support the PFS endpoint although with the exception of SOLO2 these were post hoc analyses (6, 7). There are clearly challenges associated with collecting data on HRQL and PRO's in patients on long-term maintenance therapy and ideally collection of data should continue beyond progression and through the next line of treatment if possible and duration and timing should be informed on the PRO hypotheses and endpoints. Prolonging the collection of HRQL questionnaires beyond progression will provide a greater insight on the impact of progression and subsequent therapies on patients, but the trade-off is the potential burden of extra questionnaires on patients (8). This raises methodological issues including compliance and missing data linked to the duration and frequency of HRQL analysis in these clinical trials. These HRQL assessments in clinical trials are typically not provided to treating

physicians and do not impact on patient management. Hence, they may be viewed by patients only as extra paperwork for trial purposes, and it is essential to explain the value of ongoing assessments to patients. A number of biases induced by long-term assessments have been identified such as the reprioritization and reconceptualization response shifts (9). Furthermore, patient´s preferences and expectations may influence the tolerance of side effects of cancer therapies and should also be assessed in trials focusing on HRQL (10).

The 5th OCCC recommendations include adherence to ISOQOL and CONSORT-PRO guidelines (11) and that the PRO hypotheses and endpoints should be carefully considered and included in the statistical analysis plan and be relevant to the context of the trial and the class of drug under investigation.

There is still a reluctance and hesitancy to include additional PRO hypotheses and PRO endpoints in randomized control trials in ovarian cancer beyond mean change scores in HRQL and this is unlikely to change unless regulatory authorities mandate that these are of fundamental importance to approval and licensing of new drugs.

HRQL and PRO endpoints in trials of maintenance therapy

There are a number of validated HRQL instruments that can be used in clinical trials and the selection of instrument should be based on the PRO hypotheses and specific questions that need to be addressed. There is no shortage of good instruments that are fit for purpose, but most trials have not given due consideration to what are the important questions that need to be addressed to be able to place the improvement in PFS into context and consider the patients perspective.

There have been early attempts to measure patient centered benefits in maintenance therapy trials which include Time Without Symptoms or Toxicity (TWiST) and Quality-adjusted Progression-Free Survival (QAPFS), the impact of progression on HRQL (6, 12) as well as patient preferences and trade-offs. The impact of adverse effects on patients is also of obvious importance. There are many studies that have reported on the discordance between clinician and patient reported frequency and grading of adverse effects. There is evidence to support incorporating patient reported frequency and grading of adverse effects using either the NCI PRO CTC AE or the EORTC library (13, 14). Using these libraries, investigators can select items

to include in clinical trials and capture the unique experience of the patient on treatment. More recently, electronic versions of these questionnaires (the so-called e-PROS) have been evaluated in patients receiving immunotherapy and the results align well with results observed in trials using paper versions (15). Interestingly, patients preferred the electronic version of the EORTC QLQ-C30 at least for physical functioning, and expressed no preference for emotional functioning and feel more involved in capturing their own data to inform trial endpoints (16-18). Taken together, these data support including PRO-CTCAE and ePROs in future trials. Furthermore, consideration should be given to novel approaches to analyzing and reporting adverse effects that incorporate the dimension of time to provide a more meaningful, longitudinal description of toxicities than conventional methods of reporting adverse effects experienced during the entire trial. For example, a recently described longitudinal Toxicity over Time (ToxT) analysis captures toxicity profiles that evolve over time and longer lasting lower grade toxicities, which are particularly relevant to maintenance therapies that patients can be on for years (19).

There should be harmonization and agreement as to which patient centered benefits should be included in trials of maintenance therapies to enable comparison between trials and between treatments. To date these have included Time to First and Second Subsequent Treatment (TTFST, TTSST), QAPFS and TWiST. This is a work in progress and a high priority for the GCIG SBC. Ideally, the same measures should be used in all maintenance therapy trials. There is also a good case to include patient preferences and trade-offs in such trials.

Working groups statements for expanding research into patient centered benefits in ovarian cancer maintenance trials (summarized in Table 1)

1. Adhere to SPIRIT-PRO (Standard Protocol Items: Recommendations for Interventional Trials) guidelines

As its top priority, the working group reiterated the importance of following the SPIRIT-PRO guidelines for the inclusion of PROs in future GCIG maintenance trial protocols. The SPIRIT-PRO Extension recommends that 16 items should be routinely addressed in all clinical trial protocols where PROs are a primary or key secondary outcome (Table 2). Clear guidance exists

to design trials (SPIRIT-PRO), report PRO's (CONSORT-PRO), and analyze HRQL in randomized trials (SISAQOL) (3, 20, 21), but are still not consistently implemented and included in clinical trial protocols

2. Aim to harmonize the selection, collection and reporting of patient centered benefits with maintenance therapies of high quality and clinical relevance. Ideally, these could be considered and included in European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Score (MCBS).

The working group agreed that it was time to move beyond post-hoc analyses of patient centered benefits in trials of maintenance therapies as these are clearly not robust measures of clinical benefit .We now have sufficient data generated by such analyses to inform the design of clinical trials with respect to the inclusion and analysis of PRO endpoints. The group recommended engaging with ESMO and other expert bodies such as the EORTC HRQL committee amongst others to discuss which PRO endpoints should be used in maintenance therapy trials, how these should be analyzed and interpreted. ESMO has developed a very useful and reproducible tool to evaluate the magnitude of clinical benefit in clinical trials (the ESMO MCBS scoring system) that is regularly updated and has utility for benchmarking, assessing health technology and informing practice (22). The highest grade of 3 is awarded to trials that demonstrate a PFS gain of > 6 months and scores are downgraded by 1 level if 30% of patients experience grade 3-4 toxicities which impact on daily wellbeing. The ESMO MCBS score does take HRQL into account, but requires evidence that treatment improves HRQL to upgrade the MCBS by 1 level. They penalize trials with a PFS benefit without a gain in OS or improvement in HRQL. For example, in Study 19, which was a positive trial of maintenance therapy with olaparib vs. placebo in patients with platinum sensitive recurrent ovarian cancer following response to chemotherapy, the score was downgraded from 3 to 2 as there was no HRQL benefit or OS benefit (23). It is not possible to improve HRQL in maintenance trials given that patients have responded to chemotherapy before randomization and do not have cancer related symptoms and ideally consideration should be given to patient centered benefits which support the prolongation of PFS. At present, the ESMO MCBS does not include additional patient centered benefits in the scoring system, largely because the appropriately robust PRO endpoints to demonstrate clinical benefit associated with an increase in PFS have

not been included in the initial statistical plan. The working group recognized the need to open lines of communication with the Chair of the ESMO MCBS committee and ensure that the PRO endpoints selected in clinical trial of maintenance therapy meet their stringent grading requirements. There are a number of patient centered endpoints including QAPFS and TWiST which could be included as endpoints in future GCIG trials of maintenance therapies provided there is agreement that these are valid endpoints to support PFS given that HRQL cannot be improved.

3. Selection of PRO endpoint including frequency and duration of assessment in trials of maintenance therapy.

As maintenance therapy may be prescribed for at least two years or longer following chemotherapy or until disease progression, there are many challenges which need to be addressed including compliance with HRQL assessments as well as frequency and duration of administering questionnaires to patients. Ideally questionnaires should be administered beyond progression and continue through the next line of treatment to determine the impact of recurrence and further treatment on patients. Strategies to increase adherence to questionnaires have been released on the SPIRIT website (https://www.spirit-statement.org/adherence/). It is also of important to monitor dose reductions/interruptions (especially with oral drugs such as PARP inhibitors) and understand how these impact on HRQL.

Finally, investigators should focus on ensuring that the PRO endpoints are considered important and relevant by patients and advocacy groups. PRO items (whatever the library they come from) should be adapted to the maintenance design to capture relevant data (related to specific class of drug, expected toxicities and timeline of side-effects -which are very different with immune-oncology drugs).

Working group statements for improving methodology in HRQL measurement for ovarian cancer trials

1. Combining HRQL measures

Methodological work is also encouraged in the area of combining and interpreting HRQL measures. While there has been some work in this area, there is scope to develop summary measures by combining HRQL scales to characterize patients as having either an improvement, deterioration or stable HRQL profile at key time points (24). This could then lead onto development of individualized measures of the risk of deterioration /improvement at these time points.

2. Combining clinical with HRQL endpoint in trial design

Combined with this approach, clinical benefit (response, PFS, OS) can then be incorporated into risk contours (25). This concept has had success in characterizing benefit of treatment trading off toxicity (23). These approaches can be adapted to examine HRQL trade-offs for increased clinical benefit. Once developed, this approach can then be incorporated into clinical trial designs to determine sample sizes etc., to achieve a minimum determined benefit being at least x% together with a maximum determined HRQL detriment being at most y%. Such studies would look at the joint probability rather than each component separately (which is currently the case). Additionally, the current GCIG database collection of trials can be used to inform new studies about plausible values of x, y and the joint probabilities.

3. Minimizing missing/incomplete HRQL data in clinical trials

HRQL data not collected at key time points is an ongoing problem when trying to interpret trial participants' profiles over time. While imputation methods are available, they are by no means ideal in that (i) they create artificial values which are considered as actual data; (ii) statistical models are assumed which are seldom validated; (iii) the amount of imputation performed is rarely questioned. These problems are further exacerbated when considering subgroup analyses and risk model development. To alleviate some of these problems, issues

of HRQL surrogates have been proposed where clinical factors can be taken into consideration to provide a surrogate HRQL profile (e.g., patient too sick to attend clinic) (27, 28). Consideration should also be given to the ideas of *sampling* HRQL information. Currently the strategy is to collect information on all patients at pre-specified visits. This can be modified such that if data is to be collected at *k* specified time points, each patient will only be required to provide HRQL information at say *k*/5 time points. Hence, for example patient 1 will be asked to provide HRQL information at time 1, 6, 12, 18; patient 2 at times 2, 7, 13, 19, and so on, with HRQL being collected on all patients at baseline. This sampling strategy should still provide sufficient numbers at each time point make sensible decisions, has the benefit of reducing the burden on patients and support staff and hopefully, provide a more complete HRQL dataset in the trial.

Conclusions

The primary endpoint in most ovarian cancer clinical trials including those of maintenance therapies is progression free survival. There is a clear need to include additional measures, including patient centered benefits to help support the PFS endpoint from the perspective of patients as well as regulatory authorities particularly when it could be years before the impact on overall survival is evident. Although HRQL is routinely assessed in clinical trials and included as a secondary endpoint there is a lot more that could be done with relatively little additional effort to improve on reporting and analysis of patient reported outcomes in these trials including patient reported adverse effects. The aim of the consensus statements from the 2019 brainstorming meeting is to stimulate discussion and enhance the design and analysis of future trials. The GCIG SBC is committed to continuously support investigators in assessing patient's quality of life and patient centered benefits in clinical trials as we all want our patients not only to live longer but also (and necessarily) to live better, but we need to demonstrate the latter in our trials.

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569 Table 1: Working group statements at a glance

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	Statement	Goal
1	Adhere to SPIRIT-PRO (Standard Protocol Items: Recommendations for Interventional Trials) guidelines	Trial design quality
2	Harmonize the selection, collection and reporting of patient centered benefits with maintenance therapies of high quality and clinical relevance	Increase the quality of PRO data to better consider patents centered benefits together with PFS in maintenance trials
3	Select PRO endpoint including frequency and duration of assessment in trials of maintenance therapy	Select PRO endpoints adapted to maintenance trials including duration
4	Combine HRQL measures	Better describe HRQL at time points
5	Combine clinical and HRQL endpoints	Improve trial design to investigate trading-off between clinical benefit and PROMs
6	Minimize missing/incomplete HRQL data	Obtain HRQL data of highest quality regardless time points in maintenance trials

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574 Table 2: SPIRIT-PRO items (16)

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SPIRIT section	Item	SPIRIT PRO item description
Roles & responsibilities	1	Specify the individual(s) responsible for the PRO content of the trial protocol
Background & rationale	2	Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies
Objectives	3	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains)
Eligibility criteria	4	Specify any PRO-specific eligibility criteria (eg language/reading requirements or pre-randomization completion of PRO). If PRO will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample
Outcomes	5	Specify the PRO concepts/domains used to evaluate the intervention (eg overall health-related quality of life, specific domain, specific symptom) and for each one, the analysis metric (eg change from baseline, final value, time to event) and the principal time point or value of interest
Participant timeline	6	Include a schedule of PRO assessments, providing a rationale for the time points and justifying if the initial assessment is not pre-randomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires,, whether order of administration will be standardized
Sample size	7	When a PRO is the primary endpoint, state the required sample size (and how it was determined) and recruitment target (accounting for loss to follow-up). If sample size is not established based on the PRO endpoint, then discuss power of the principal PRO analyses

Data collection methods	8	Justify the PRO instrument to be used and describe domains, number of items, recall period, and instrument scaling and scoring (eg, range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.
	9	Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other)
	10	Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.
	11	When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available
	12	Specify PRO data collection and management strategies for minimizing avoidable missing data.
	13	Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.
Statistical methods	14	State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error.
	15	State how missing data will be described and outline the methods for handling missing items or entire assessments (eg, approach to imputation and sensitivity analyses).
Monitoring	16	State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; eg, in the participant information sheet and consent form

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