Patient-reported outcomes in ovarian cancer

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Abstract
Ovarian cancer treatments may negatively impact the physical and functional quality of life domains of patients. Patient-reported outcomes (PROs) and health-related quality of life (HR-QoL) assess the health conditions of patients without interpretation by a clinician of the patient's response. A broad spectrum of validated questionnaires investigating HR-QoL exist. However, none are considered as a gold standard of PRO measures. In clinical trials, PROs are a means of evaluating treatment benefit or risk in a way that complements the typical primary outcome of survival, and are necessary endpoints to support regulatory approval. In clinical practice, PROs are useful in monitoring the ability of patients to tolerate treatment and in identifying patients more at risk for subsequent health problems who would benefit from supportive care during and after treatment.

Key words: clinical benefit, clinical trial endpoints, ovarian cancer, CONSORT PRO extension, patient-reported outcomes

Introduction

Ovarian cancer is the fourth highest cause of cancer death in women in Italy [1]. Advanced disease is present at diagnosis in most cases, and the majority of women develop recurrent disease, which is then managed with palliative chemotherapy. The morbidity associated with the disease course and its treatment is high. Consequently, health-related quality of life (HR-QoL) is often impaired. Knowledge of the symptoms that negatively impact on domains of HR-QoL might guide the identification of patients with ovarian cancer who are at higher risk for subsequent health problems and therefore aid in decision-making during treatment. The assessment of the extent of treatment benefit and of the prevalence and severity of symptoms involves the use of patient-reported outcomes (PROs) and measurement of HR-QoL.

A PRO is defined by the U.S. Food and Drug Administration (FDA) as "any report of the status of patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [2]. As the HR-QoL, it includes symptoms of the disease, side effects of treatments and various aspects of QoL domains. In a clinical trial, PROs are considered to be the gold standard for the capture of symptomatic adverse events and are a means of evaluating treatment benefit or risk. In clinical practice, PROs are useful in monitoring the ability of the patient to tolerate treatment and in identifying patients who would benefit from supportive care during and after treatment. Accordingly, the best approach to patients undergoing cancer therapy should be to include a multidimensional treatment plan consisting of both pharmaceutical and behavioural interventions.

PRO measures

HR-QoL is a broad multidimensional construct with a range of conceptual definitions. Physical and emotional domains were considered to be the most salient domains of QoL. Currently, there is no consensus on what symptoms or QoL domains should be assessed as PROs in ovarian cancer clinical trials. There is wide agreement that HR-QoL assessment should include the core domains of physical, social and emotional functioning or well-being, as well as a number of disease-related or treatment-related symptoms. The most appropriate patient-reported outcome measures (PROMs) to be used may vary [3]. There are well-validated PROMs available for use in ovarian cancer trials that include generic and cancer-specific instruments [4]. As described in a recent systematic review [5], there are

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more than 60 measurement tools, which can be divided into four main groups: general health and physical well-being, disease-specific, symptom-specific and treatment-specific. The effectiveness guidance document on PRO's published online on 2012 by the Centre for Medical Technology Policy recommended five PROMs: the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire, QLQ-C30; the Functional Assessment of Cancer Therapy-General (FACT-G); the M.D. Anderson Cancer Center's Symptom Index (MDASI); the PRO-CTCAE; and the Patient Reported Outcome Measurement Information System (PROMIS) [6]. Each one can be supplemented by ovarian cancer modules or other modules of relevance depending on the trial. These PROMs have been well described elsewhere [4], and are beyond the scope of this paper. However, effort should be made to reach consensus and standardise the choice of the instruments/questionnaires based on the specific objectives of the study and the PRO endpoints. The aim is to provide a higher level of consistency, allowing robust comparisons of the results between different ovarian cancer trials. The "best" questionnaire is the one that best matches the specific aims and objectives of the study. PRO endpoints should be based on the PRO hypotheses, be context specific and reflect the target population and the objectives of treatment.

PROs in clinical trials

The primary endpoint in ovarian cancer clinical trials is usually progression-free survival (PFS), in both first line and recurrent setting, as additional treatments available after progression can impact on overall survival (OS). Co-primary or additional secondary endpoints, including HR-QoL and PROs, are crucial to provide a complete picture of benefits associated with treatments and to support regulatory approval. Despite the great value of PROs and HR-QoL results in the global interpretation of the results of a clinical trial, the results of PRO data analyses are commonly only briefly covered in the primary publication of ovarian cancer trials, more often are published at a later date or not published at all. A recent study [7] reported these deficiencies: less than one third of gynaecological clinical trials provided reliable data on PROs and discussed the clinical significance of HR-QoL findings; 60% had missing data documentation. Important concerns about the standard of reporting of HR-QoL in clinical trials were also raised by Brundage et al. [8]. The systematic review of 794 randomised trials carried out by the authors revealed that only 50% provided a HR-QoL hypothesis, only 56% provided a rationale for the selected outcome measure, only 28% provided information about missing data and 36% did not discuss HR-QoL findings in relation to other trial outcomes.

The purpose of the Effectiveness Guidance Document, published by the Centre for Medical Technology Policy on incorporating PROs into clinical comparativeness research in adult oncology [6], is to better align the design of clinical research with the information needs of patients, clinicians and funding agencies, and the guidelines are intended to set a minimum standard to ensure that studies directly measure the reported experience of patients. Recognising the importance of accurately capturing the patient perspective as complementary information to clinician-based reporting, also the National Cancer Institute (NCI) has subsequently developed a plain language version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [9], that has also been translated and cross-culturally adapted to the Italian language. More recently, the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) have proposed standardised approaches to evaluate the results of clinical trials by either using scores to evaluate the Magnitude of Clinical Benefit [10] or the Net Health Benefit [11], which include survival endpoints in addition to toxicity and HR-QoL.

Evaluation of the patient's acceptance of clinical trial endpoints as well as the acceptable magnitude of effect anticipated in ovarian cancer therapeutic studies is a critical step in ensuring that studies address the needs of our patients, including survival, toxicity, QoL, and cost [12]. The adherence by clinical trialists and journal editors to the Consolidated Standards of Reporting Clinical Trials (CONSORT) PRO statement should also improve the reporting and interpretations of PROs in clinical trials [13].

PROs in clinical practice

Patient self-reporting is the standard approach to assess HR-QoL from the patient perspective. However, the experiences of symptoms as reported by patients in self-assessment questionnaires are often not documented in medical records. Numerous studies have documented discordant reports of symptoms between clinicians and cancer patients. Regardless of the measure used, the majority of studies that have directly compared CTCAE and PRO ratings reveal a systematic underreporting of symptoms by physicians in terms of onset, frequency and severity [14-17]. The explanation of this phenomenon can be sought on the personal values attributed to the impact of symptoms on QoL. Probably, the patients' assessment is compared to their health conditions before treatment. In contrast, the clinicians' judgment is based on an interindividual comparison of their clinical experience [18].

Since PROs have the potential to detect subjective symptoms earlier and better than the CTCAE, the patient's perspective should be considered as the gold standard, and the use of validated PROMs should be encouraged in clinical practice. Future approaches that aim to integrate PROs with clinician reporting of adverse events, especially those of the CTCAE and PRO-CTCAE, would improve our understanding of patient and clinician ratings [19]. Efforts should focus not only on how ovarian cancer treatments affect QoL, but also on developing effective interventions to problems that can potentially be reversed if identified early enough [20].

Discussion

Throughout the sequence of diagnosis, frontline treatment and recurrence, examining and measuring PROs is now considered essential to support therapeutic decision-making and health policy. There is a great commitment to producing good-quality PRO measurements, notwithstanding there are also many challenges in the good conduct of PRO research, including the selection, evaluation, analyses and interpretation of PRO measurements [21].

The patient's subjective information in response to specific questions is quantified validly and reliably using carefully developed and rigorously validated tools: the PRO measures. There are many instruments to choose from; the best PROM is the one that best matches the expected effects of interventions under study on the target patient population. These measurements allow understanding of the prevalence of symptoms and the hypothesizing of better management strategies in clinical practice. The importance of PROs is to ensure that all the benefits of therapy are weighed against adverse effects. PRO data portray the achievement of a trial by supporting the primary outcome results and by providing clinically relevant information, which may be more important from the patient's perspective than a few months increase in PFS. PFS alone might not be sufficient as an endpoint, particularly in settings, such as in the subset of platinum resistance, where prognosis remains dismal [22]. Indeed, other factors, such as side effects, could influence both physicians' and patients' preferences and should also be presented when discussing treatment options, in order to achieve the ideal balance between PFS, QoL and treatment toxicity. In the targeted therapies era, and with the advent of new non-cytotoxic drugs, identifying the symptoms and QoL domains to be incorporated into clinical ovarian cancer studies is a priority objective.

In the design and planning of future clinical trials, it is necessary to encourage the collaboration of statisticians and experts in QoL in order to select the most appropriate PROMs to generate significant data about the target population. Only if the PRO hypotheses are strictly considered and incorporated into protocols, and if the PRO data are collected thoroughly and analysed and reported transparently, the PROs can give a valuable contribution to clinical trials.

Conclusions

From diagnosis to death, HR-QoL must influence clinical management, and the preferences of patients should be considered and discussed when making shared cancer treatment decisions. The challenge is to translate the good-quality PROs findings obtained by clinical trials into clinical practice in order to enhance the QoL of patients with ovarian cancer. Further efforts are needed to fully understand PROs issues and to identify problems that have a significant impact on HR-QoL in order to develop interventions for women at need.

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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