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Survivorship as an Element of Clinical Trials in Ovarian Cancer

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Survivorship was identified before the fourth Ovarian Cancer Consensus Conference (OCCC) as an area warranting specific discussion to better address the long-term elements of patient outcomes. Optimal conduct of clinical trials that incorporate survivorship parameters requires an improved level of understanding of the tools, methods of collection, and timing of data collection specific to stages along the ovarian cancer survivorship spectrum. Intervention strategies that have been successful in other cancer sites should be considered in ovarian cancer. It was recommended by the Gynecologic Cancer InterGroup (GCIG) that formal guidelines be developed before the next OCCC.

Although it is the most lethal of the gynecologic malignancies, ovarian cancer is a diverse disease with a wide range in prognosis depending on patient factors such as age and performance status,^{1–5} histological subtype,^{6–9} stage at presentation,^{9–11} residual disease left at the time of surgery,^{4,9,12–16} BRCA function,^{17–20} and treatment received.^{10,21,22} Depending on the above parameters, a patient may be quoted to be between a 10% and greater than 95% 5-year survival rate.^{16,23–25} Even in patients with advanced high-grade serous cancer who recur, chemoresponse rates are favorable and multiple treatment regimens can be administered over a patient's lifetime achieving a relatively long-term survival.

The challenges in addressing long-term survivorship needs of ovarian cancer patients are becoming increasingly apparent. Whether a patient is “cured” or managed as having a “chronic disease,” issues pertaining to malignancy and treatment-related toxicities have implications in all facets of their lives, as well as to the health care systems in their respective countries. Prior investigations in health-related quality of life (QoL) in ovarian cancer patients have often focused on only 1 time period (ie, primary treatment) or only 1 parameter (ie, bone health). Tools used to assess QoL parameters in cancer patients and the

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interpretation of these tools are unfortunately unfamiliar to the majority of health care practitioners caring for ovarian cancer patients.

SURVIVORSHIP: DEFINITION AND SCOPE

Survivorship is considered to encompass the physical, psychological, social, and spiritual domains of individuals with a cancer diagnosis through to end of life.²⁶ Some experts consider survivorship to begin at the time of diagnosis and others, after primary treatment. For the purposes of this article, survivorship is considered to encompass ovarian cancer patients from the time of diagnosis until end of life from cancer-related or independent means.

It is estimated that approximately 1 in 3 people will develop cancer in their lifetime, the majority of diagnoses arising in older men and women. Longer life expectancy results in a greater proportion of the population living with cancer, which in the United States alone translates to more than 3 million people older than 60 years with at least 1 invasive cancer.^{7,28} The majority of these patients have 1 or more comorbidities, and the interplay of other chronic disease and cancer can be complex,^{27–31} which can impact both the treatment administered (eg, drug choices, dose according to renal function, toleration of symptoms, etc) and the cancer itself. Furthermore, the QoL data obtained may also be impacted: what is secondary to the cancer, versus secondary to treatment, versus carried over by the patient's health status, and the manner in which these all may interact.

The young patient can present a very different set of challenges in the consideration of ovarian cancer survivorship. Several issues hold a greater level of importance or relevance to the younger patient, such as fertility, treatment-induced menopause, and treatment-induced secondary cancers. Given the longer cancer-independent life expectancy of this cohort, survivorship issues are perhaps even more important to address.

SURVIVORSHIP PARAMETERS AND CLINICAL TRIALS

Only 10% of all cancer clinical trials include health-related QoL end points.^{32,33} The role and importance of collecting health-related QoL data in both phases 2 and 3 trials have been well voiced.^{34–38} Figure 1 describes some of the QoL concerns encountered at different time points along the ovarian cancer continuum. There have been almost no investigations of the QoL concerns in many of these stages in ovarian cancer patients ie, long-term survivors, surveillance, and palliation.

In first-line therapy, the Gynecologic Oncology Group (GOG) 172 trial incorporated multiple QoL parameters in their methodology and adapted a specific tool to capture patient complaints specific to abdominal discomfort, the FACT/GOG-AD subscale.^{21,39} This subscale was found to be valid and reliable in assessing ovarian cancer-specific symptoms. An ongoing QoL assessment of GOG 252 and a recently published QoL assessment of patients on GOG 152 and 172 protocols are furthering knowledge of treatment associated toxicities.^{40,41} EORTC 55971/NCIC-CTG OV13 collected 2 QoL questionnaires (QLQ-C30 and QLQ-Ov28) at 5 different time points to allow comparison between neoadjuvant chemotherapy and primary surgical debulking groups.¹⁶ Quality-of-life parameters have also

been assessed in patients receiving dose-dense (weekly) paclitaxel.^{41,42} Essentially, any regimen that challenges standard of care on the basis of non-inferiority should have demonstrated improved QoL outcomes.

Some phase 3 maintenance/consolidation trials have collected QoL end points, including treatment-associated toxicity with maintenance paclitaxel therapy,^{41,43–45} bevacizumab,^{41,46} and ongoing investigations with novel therapies (GOG 212).⁴¹

The setting of recurrence is arguably the most important stage along the ovarian cancer continuum to consider QoL data. If recurrent ovarian cancer is managed as a chronic disease, these considerations are crucial in determining when, if, and which treatment should be administered.^{47,48} There may be additional comorbidities in a patient who is now older, and perhaps less robust, following her initial treatments, cumulative toxicities and end-organ damage, increased risk of platinum hypersensitivity reactions, and financial and social stressors. Recently completed (eg, CALYPSO) and ongoing trials (eg, OVM 0818) have attempted to address some of these concerns in the patient with recurrent disease.^{41,49}

One of the few trials to address QoL in the long-term (>5 year) survival stage of the continuum was conducted in survivors of early-stage ovarian cancer. Telephone interviews were used to assess QoL, sexual health, psychosocial status, and treatment effects (late) in the cohort. Despite reporting that QoL was good in these cancer-free patients, fear of recurrence and anxiety associated with follow-up persisted in 20% and 30% of the cohort, respectively. Twenty-five percent of patients entered menopause early (surgical or secondary to treatment) and reported distress with menopausal symptoms. Sexual dysfunction was common. Survivors expressed a desire for increased counseling and support, both during treatment and over the long term, but also described personal growth and resilience stemming from their cancer diagnosis.³⁵ Thus, it is necessary to expand investigations in long-term survivors and during the other nonactive treatment stages of the ovarian cancer continuum.

SURVIVORSHIP PLANS FOR LONG-TERM FOLLOW-UP IN CANCER PATIENTS

In 2006, in the United States, the Institute of Medicine issued a report recommending that every cancer patient receive an individualized survivorship care plan that includes guidelines for monitoring and maintaining their health. Insight into long-term survivorship has been provided through studies of pediatric and adolescent cancer survivors, many of which have shown that these survivors are at increased and ongoing risk for many types of hospital-related late morbidity, suggesting that long-term follow-up on many health issues is essential.^{50,51} Furthermore, outpatient visits to both generalists and specialists were markedly increased in survivors of childhood cancer (diagnosed age <20 years), with 64% more visits compared with age- and sex-matched members of the general population. This translated to a 92% higher probability of seeing a general practitioner and 158% higher likelihood of a specialist visit.⁵² Long-term follow-up of cancer survivors is feasible in health care systems where population-based registries are established and is a cost-effective and comprehensive means to assess (1) late effects of treatment in cancer survivors, (2)

utilization of health care resources (individual and societal costs), and (3) the role of long-term support and intervention programs.^{53,54} Such a system of evaluation could be brought to the ovarian cancer cohort, arguably a much more attainable task than in the childhood cancer cohort, as disease-specific and overall survival will be much lower in ovarian cancer patients. The training of oncologists does not traditionally include education and clinical practice guidelines surrounding many of these long-term health issues. Similarly, training of generalists and/or family practitioners does not always encompass the special needs of cancer survivors.^{30,36,55–57} Patients and physicians often have discordant expectations with respect to the role of the oncologist and the role of the primary care provider pertaining to cancer surveillance, screening guidelines, and preventive health.⁵⁸ Despite this discordance, and the lack of formalized cancer survivorship training for physicians, the majority of cancer survivors report satisfaction with posttreatment medical care. However, psychosocial needs, in the short and long terms, were not met. Patients, physicians, and nursing staff felt that a formalized follow-up plan for cancer survivors would be extremely helpful.^{30,55,57–64}

The National Cancer Institute has taken a lead in the research, development, and implementation of survivorship care plans, and more information can be found at <http://www.cancer.gov/cancertopics/factsheet/Therapy/followup>.⁶⁵ Survivorship care plans specific to breast and colorectal cancer are available through the American Society of Clinical Oncology Web site at <http://www.cancer.net/patient/Survivorship/> ASCO+ Cancer+ Treatment+Summaries.⁶⁶ The American Society of Cancer gives general guidelines for follow-up care after cancer treatment and provides specific links to other institutions where care plans are available (<http://www.cancer.org/Treatment/SurvivorshipDuringandAfterTreatment/SurvivorshipCarePlans/index>).⁶⁷ These resources provide an excellent template from which an ovarian cancer survivorship care plan can be derived in the future.

SURVIVORSHIP TOOLS OF MEASUREMENT AND ISSUES OF TIMING AND DATA COLLECTION

Clinicians and researchers need to be familiar with the tools used to collect QoL data and know how and when to collect measurements and how to interpret the data specific to the ovarian cancer population. Consideration must be given to the collection of a baseline assessment at the time of initial cancer diagnosis in all ovarian cancer patients. This provides a reference for comparison of QoL at later time points along the ovarian cancer continuum and truly reflects an individual's health status before cancer treatment.

With the integration of QoL data in cancer clinical trials, opportunities for psychosocial interventions to improve QoL for the individual patient have been unveiled. Success of psychosocial interventions may, however, go beyond a change in QoL parameters.^{68–75} Behavioral, immune, and survival benefits have been observed following psychological intervention in postsurgical breast cancer patients.^{69–71} Interventions in patients with newly diagnosed breast cancer have been successful in reducing depressive symptoms with an indirect effect of reduction in inflammatory markers.⁷⁶ In cervical cancer patients, a randomized clinical trial was undertaken in the patients 13 months or longer after time of

diagnosis (until 22 months) comparing psychosocial telephone counseling intervention to usual care. Patients in the intervention group had improved QoL outcomes, a favorable shift in their immune marker profile, and a decrease in serum parameters associated with chronic stress.⁷⁷ In meta-analyses, the impact of psychosocial interventions on survival has been discordant^{78–80}; however, this is likely secondary to the very diverse study populations and measured end points in the included intervention studies.

Intervention strategies can also take the form of patient education and conceptual change. The WRITE (Written Representational Intervention to Ease Symptoms) symptom trial is an ongoing study (GOG 0259) assessing whether educational interventions can ease symptoms and QoL in women with recurrent ovarian cancer. The WRITE symptom review is offered through self-directed symptom review (interactive computer module) versus nurse-delivered symptom review (interactions with a study nurse). For patients comfortable with Internet technology, it allows them to expand on symptom character and duration, focus their questions to RN staff, and follow or retrace a thread of information back for details^{81,82} may prove to be very helpful.

Assessment of QoL parameters and focused intervention during the end-of-life supportive care stage of the ovarian cancer continuum has traditionally been nonexistent. However, one can be inspired by a recent report where utilization of hospice services in patients with metastatic lung cancer resulted in an improved QoL, less depression, and longer survival.⁶⁸ It needs to be acknowledged that the majority of patients with epithelial ovarian cancer will reach this stage along the continuum and therefore we should not lose the opportunity to learn from and support this group of women.

There are several established measures that have proven to be reliable, valid, and sensitive to change over time in the ovarian cancer population. These include the FACT-O,⁸³ the QLQ-C30, and QLQ-OV28.^{16,84–86} A description of many of the scales utilized in gynecologic oncology can be found in the review of Penson et al³⁸ (FACT-G, FACT-O, QLQ-C30, QLQ-OV28) and in the assessment of Wenzel et al of long-term QoL in survivors of early-stage ovarian cancer.³⁵

More recent patient-reported outcome measurement contributions include the FACT-GOG Neurotoxicity 4-item scale,⁸⁷ the FACT-GOG Abdominal Discomfort (AD), and the NCCN-FACT Ovarian Symptom Index 18 (NFOSI-18). The FACT-GOG Neurotoxicity 4-item scale is a reliable and valid tool to assess chemotherapy-related peripheral neuropathy.⁸⁷ The FACT-GOG AD is useful in evaluating abdominal symptoms frequently associated with advanced epithelial ovarian cancer. This 4-item AD subscale reliably and validly assesses ovarian cancer-specific abdominal discomfort and has captured abdominal symptom responses to intravenously administered and intravenously/intraperitoneally administered cisplatin/paclitaxel treatments.³⁹ The NFOSI-18 is a new ovarian cancer-specific symptom index composed of symptoms rated as highest priority by both oncology clinical experts and women with advanced ovarian cancer. It includes 3 subscales: disease-related symptoms, treatment-related symptoms, and general function/well-being. The NFOSI-18 shows strong preliminary evidence for reliability and validity as a brief assessment of the most important symptoms associated with treatment for advanced ovarian cancer.⁸⁸

Timing of data collection is equally important in guiding the utilization of these tools and interpretation of results. A questionnaire that is filled out 3 months after completion of therapy will not reflect severity or frequency of symptoms experienced during treatment. However, optimal timing and frequency of QoL data collection specific to ovarian cancer depend on hypotheses to be tested (eg, benefits of treatment; toxicities of treatment) or long-term survivorship concerns.

CONCLUSIONS

Through increased use of the aforementioned tools in ovarian cancer patients and the sharing of results, the quantity and the quality of ovarian cancer survivorship literature will increase, thus improving the ability to guide collection, timing, and interpretation of QoL data. In short, expansion of intervention studies in ovarian cancer is long overdue. Resources need to be allocated (research and development, staff to execute) to achieve this expansion. There is an opportunity to study the success of interventions along various stages of the ovarian cancer continuum and to incorporate recommended changes into a survivorship care plan.

Although formal guidelines cannot be made until this body of literature is available, it is hoped that by the time the GCIG reconvenes for the fifth OCCC, such guidelines will be possible, and QoL data will be implemented in all international clinical trials. To that end, these cumulative results could be useful in guiding an ovarian cancer survivorship care plan.

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FIGURE 1.
Quality-of-life considerations over the course of the ovarian cancer care continuum.