Gynecologic Oncology 140 (2016) 193–198

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Endpoints in clinical trials: What do patients consider important? A survey of the Ovarian Cancer National Alliance

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HIGHLIGHTS

- Clinicians have debated the selection of ovarian clinical trial endpoints.
- Optimal endpoint selection should reflect true patient benefit.
- We surveyed patients to discern what constitutes meaningful clinical trials outcomes.

ARTICLE INFO

Article history:
Received 7 September 2015
Received in revised form 23 November 2015
Accepted 25 November 2015
Available online 26 November 2015

Keywords:
Patient-reported outcomes
Clinical trial endpoints
Progression free survival
Overall survival

ABSTRACT

Objective. In order to understand the patient's perspective in regards to meaningful surrogate clinical trial endpoints and the impact of treatment-related toxicity, and quality of life, we surveyed women with gynecological cancers to ascertain their preferences.

Methods. A 28-question anonymous online survey was posted on the OCNA website (www.ovariancancer.org). Survey questions included demographic factors, tumor data, and patients' preference regarding side effects and therapy endpoints. Data was analyzed for frequency and percentage of each response. Student t-test, Fisher's exact test and Wilcoxon rank sums were preformed.

Results. There were 1413 survey responses. Participants reported that for a new agent to be meaningful, the minimum extension of progression-free survival (PFS) and overall survival (OS) should be five or more months, 77% and 85% of the time, respectively. Most subjects (55%, $n = 612$) were interested in an agent that would keep tumor growth relatively static without change in OS. Addressing the impact of adverse aspects from a hypothetical new agent as a function of response, there was significant migration ($p < 0.0001$) to acceptance of greater toxicity and cost under the scenario of a 5–6 months OS gain, despite three-fold higher neurotoxicity, as compared to a PFS gain of 3–4 months/no OS gain without toxicity. Response patterns weren't altered by recurrence status.

Conclusions. Herein, we show that magnitude of outcome is a desired effect, even given the prospect of significant toxicity and cost. However, these preferences appear to differ between those with primary and recurrent disease.

1. Introduction

Ovarian cancer is a highly lethal malignancy comprised of epithelial ovarian, primary peritoneal and fallopian tube carcinoma [1–2]. After initial therapy, most ovarian cancer patients have undetectable disease and are considered to be in clinical remission. However, the majority of these women will experience recurrence and ultimately succumb to disease [3–5]. Thus, only modest gains have been realized in 5-year survival and cure rates have not significantly improved.

Well-designed and executed randomized clinical trials utilizing overall survival (OS) as the primary endpoint provide the most incontrovertible data upon which to establish new standards of care, but are challenged by cost and long reporting times. In addition, extended post-progression survival, large patient enrollment requirements, and common use of effective subsequent and crossover treatments challenge the concept of OS as the optimal endpoint for all ovarian cancer

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http://dx.doi.org/10.1016/j.ygyno.2015.11.030
0090-8258/

trials. Further, rapid discovery of potentially important and targetable molecular aberrations in ovarian carcinogenesis has created a groundswell of opportunities that surpasses the ability to investigate these targets in large, prolonged clinical trials [6,7].

To address these issues, the Society of Gynecologic Oncology (SGO) convened a meeting and initiated ongoing dialogue with the Food and Drug Administration (FDA) originally in March of 2014, and explored the concept of considering alternative primary clinical trial endpoints to OS. A principle concern was the lack of development of more effective drugs for ovarian cancer patients. This dialogue culminated in an FDA workshop co-sponsored by the SGO, American Society of Clinical Oncology (ASCO), and American Association for Cancer Research (AACR) that included patient advocates. In preparation for this workshop, the SGO proposed consideration of progression-free survival (PFS) as a viable endpoint either alone or in combination with relevant clinical endpoints other than OS in select circumstances with the expectation that this change would reduce some of the limitations associated with OS as the primary endpoint [8–10]. Specifically, the adoption of PFS would eliminate the post-progression survival effect, and confounding data complexity when subjects receive cross-over and subsequent active treatments. With the recent FDA approvals of bevaciumab and olaparib based on PFS and objective response, respectively, these alternatives to OS represent a new precedent for regulatory approval in ovarian cancer.

The discourse of surrogate endpoints in clinical trials has largely centered upon OS, which is the most objective of the clinical trial endpoints. It is difficult to justify the use of surrogate endpoints such as patient reported outcomes (PRO's) in certain patient cohorts, such as those without overt symptoms. Health professionals, clinical investigators, and regulatory officials have directed most of the discussion on alternative endpoints. Our objective was to better understand the perspective of patients in regard to what defines meaningful clinical benefit within the context of a clinical trial. Thus we surveyed women with ovarian or other gynecologic cancer about their treatment preferences that provide meaningful benefit, in multiple clinical scenarios. In addition, we evaluated patient preferences' regarding the impact of treatment related toxicity and quality of life. Finally, we sought to explore patient preferences' for relevant trade-offs of efficacy versus toxicity commensurate with contemporary clinical trial outcomes in both the front-line and recurrent disease states.

2. Methods

This study was conducted in accordance with the regulations set forth by the institutional review board of the University of Texas M.D. Anderson Cancer Center. A 28-question anonymous online survey was created (Supplemental Fig. 1). All questions were original, and neither prior items nor instruments were included in this survey. Survey questions were constructed to query patient preferences regarding treatment side effects and meaningful benefit. Questions were not pretested before online posting; however, survey content was base upon patient interactions with the Ovarian Cancer National Alliance (OCNA) and interviews conducted at the Foundation for Women's Cancer survivorship courses. Demographic data points of surveyed information included: current age, ethnicity, sexual orientation, and parental status. Tumor data collected included: tumor site, treatment status, recurrence status, number of chemotherapy regimens experienced, and prior participation in clinical trials.

Following elucidation of our cohort's demographics and clinical experience, we evaluated their expectations and desires for therapy based on PFS and OS. For clarity, consistency, and clinical relevance based on contemporary data, we defined these endpoints prior to questioning. Anticipating a diverse upper limit of expectations, we structured these questions so as to elicit the minimal amount acceptable by which they would consider a new agent's result meaningful. Additionally, hypothetical scenarios were created to clarify patient tolerance of toxicity in a planned course of treatment. Using hypothetical treatment regimens employing a novel experimental agent, subjects selected between two options: option A, a new agent that impacted PFS by 3–4 months without any significant toxicity, but without any gain in OS, or option B, an improvement in OS of 5–6 months, but with a three-fold higher rate of neurotoxicity, defined as significant interference with activities of daily living and pain/numbness in extremities.

In order to understand how treatment related toxicity was perceived, we queried the impact of common adverse events from exposure to a hypothetical new agent as a function of response (stable disease as its best response versus tumor response and "extended life"). Using the Likert scale from 0 (no toxicity) to 4 (severe, debilitating toxicity, corresponding to the Common Toxicity Criteria for Adverse Events [CTCAE] v4 grade 0–4), symptoms surveyed included nausea/vomiting, febrile neutropenia, joint pain, neuropathy ("numbness, tingling or weakness in hands/feet"), and treatment costs.

Participants ranked eight quality of life factors ranging from most impactful to least impactful. Also, participants ranked eight treatment outcomes from most important to least important. Scores were assigned 1–8 with 8 points for the most frequent response down to 1 for least frequent, and rank sum scores were calculated for each variable. QOL factors included: feeling well, fewer interruptions to daily activities, less frequent hospital and doctor office visits, more favorable drug schedule (administered less frequently), less pain, normal levels of intimacy with partner, low treatment costs, and other. Outcome factors included: cure, extending interval between chemotherapy, reduced chemotherapy induced symptoms, reduced cancer induced symptoms, live longer even tough not cured, feel healthier, affordable treatment cost, and response to treatment. Responses were reported by weighted ranking and rank sum scores.

This survey was constructed and posted online by Zoomerang (Palo Alto, CA) after an announcement at the OCNA National Meeting in Washington DC (July 2012). A follow-up reminder email was distributed to OCNA members with the inclusion criteria and general goals of gaining the patients' perspective. No further information as to goals was mentioned so as to not bias the responses. The survey link was live for a 6 week period on the OCNA website (www.ovariancancer.org). Consent was intrinsic to participation in the survey at initial registration. Survey participation was anonymous, and no compensation was offered for survey participation. After the defined study period, the survey was closed and no longer available for online access.

Data was organized and analyzed for frequency of each response, and percentage of responses. Student t-test was calculated to determine statistical significant differences between response patterns when assumptions of normality were assured. All data elements were evaluated by descriptive statistics. Point estimates and 95% confidence intervals were calculated for estimated proportions. Variables meeting criteria for normality were compared by parametric methods; those not meeting the assumptions of normality were compared by Fisher's Exact test for nominal variables and Wilcoxon rank sums test for continuous variables. p values <0.05 were considered statistically significant unless multiple comparisons required the use of a Bonferroni adjustment.

3. Results

3.1. Survey response

Response to the survey was robust with 2218 visits to the website and 1413 unique site visitors providing responses. Of these, 1063 completed the survey in full with an additional 366 partially completing the survey, for an overall completion rate of 75%. The majority of participants ($n = 1204$, 85%) reported a personal history of ovarian cancer. The remaining 15% were composed of the following diagnoses: endometrial cancer, cervical cancer, other, or unspecified. In this report we limited our analyses to those identified as having ovarian, fallopian tube or primary peritoneal cancer (Fig. 1).