Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Objective response rate is a possible surrogate endpoint for survival in patients with advanced, recurrent ovarian cancer☆

Mohammed Kashif Siddiqui [a], Jerzy Tyczynski [b,1], Ankit Pahwa [a], Ancilla W. Fernandes [c,*]

[a] PAREXEL International, Chandigarh, Chandigarh, India
[b] Global Medical Evidence and Outcomes Research, AstraZeneca, Gaithersburg, MD, USA
[c] Health Economics and Outcomes Research, AstraZeneca, Gaithersburg, MD, USA

HIGHLIGHTS

- ORR is a possible surrogate for OS in recurrent OC with ≥2 lines of therapy.
- Each 10% increase in ORR, predicts an increase of OS by 2.83 months.
- A 10% increase in odds ratio of ORR predicts a 2.5% reduction in the HR of OS.

ARTICLE INFO

Article history:
Received 5 October 2016
Received in revised form 29 March 2017
Accepted 31 March 2017
Available online xxxx

Keywords:
Ovarian cancer
Survival
Response rate
Odds ratio

ABSTRACT

Objective. Evaluate literature to assess response rate as a surrogate endpoint of survival in ovarian cancer (OC).

Methods. Systematic review consistent with PRISMA criteria, identified randomized, controlled trials reporting overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in recurrent OC. MEDLINE® and Embase® searches (year 2000–March 23, 2015) were augmented by bibliographic screening. Proposed surrogate measures (independent variables) were ORR and disease control rate. True clinical outcomes (dependent variables) were median OS and PFS. Analyses were performed on unweighted and weighted data using correlation analysis, linear regression, and surrogate threshold effect (STE). Smaller STE indicates greater predictive precision with magnitude of STE dependent on variance of prediction.

Results. Thirty-nine studies were included for review, representing 9223 platinum-sensitive and resistant patients. Objective response rate ($r = 0.82$; $P < 0.001$) was a better predictor than disease control rate ($r = 0.58$; $P < 0.001$) and strongly correlated with PFS ($r = 0.85$; $P < 0.0001$). Weighted-regression analysis demonstrated that for each 10% increase in ORR, PFS increased by 1.20 months and OS by 2.83 months. Regression analysis of treatment effects (odds ratio of response, hazard ratio of survival) suggests that a 10% increase in odds ratio of ORR would result in 2.5% reduction in the hazard ratio of OS. Based on weighted data, STE indicated that an ORR of ≥1% is needed to achieve nonzero OS benefit.

Conclusion. This systematic review supports ORR as a possible surrogate clinical trial endpoint for OS in recurrent OC with at least second-line therapy.

1. Introduction

Ovarian cancer (OC) is the fifth leading cause of female death due to cancer in the United States. It was estimated that 21,280 new cases would be reported in 2016 and 14,240 deaths would occur due to OC [1]. Overall, five-year survival rates among women with OC range between 44% for all stages combined and 27% for advanced disease [2]. Standard care for advanced OC comprises a combination of surgical cytoreduction and platinum-based chemotherapy, and although a large proportion of women with advanced OC experience remission following these interventions, disease recurrence occurs in approximately 75% of responders to initial treatment [3,4].

As a result, treatments after recurrence are focused on prolonging survival and improving quality of life. To that end, phase III clinical studies are designed to ascertain whether new treatments are superior to

☆ Portions of this review were presented in a poster at the SGO Annual Meeting on Women's Cancer in San Diego, California, March 19–22, 2016.

* Corresponding author.
E-mail address: Ancilla.Fernandes@astrazeneca.com (A.W. Fernandes).

[1] Current affiliation is Pharmacovigilance & Patient Safety, AbbVie Inc., North Chicago, IL, USA.

http://dx.doi.org/10.1016/j.ygyno.2017.03.515
0090-8258/

standard therapy, positively affect patient quality of life, or both. Historically, overall survival (OS) has been considered a "gold standard" endpoint in oncology studies because it is clinically relevant, objective, easily interpreted, and reflects the ultimate goal for therapeutic comparisons [5,6]. However, use of OS as a clinical endpoint has several caveats: large sample sizes may be required in tumor types with more favorable prognoses; extended follow-up is necessary for some populations; and because measurement may be diluted by nonmalignant causes of death, treatment crossover, and by multiple lines of therapy for recurrent or advanced disease. Surrogate endpoints are endpoints typically observed before the occurrence of a true endpoint, such as mortality, and are used to draw conclusions about the effect of a therapeutic intervention on a true endpoint. Consequently, validated surrogate endpoints in OC may lead to smaller or shorter cancer studies. Yet surrogate endpoints have the disadvantage of relying on extrapolation to an unobservable effect of therapy on the true endpoint, with potentially misleading results [7].

Ensuring that a valid analysis of the surrogate endpoint is indeed a representation of the true clinical endpoint is necessary to the validation of surrogate endpoints [8]. The Prentice criterion (Fig. 1a) is a set of specifications that stipulate the independence of the impact of a treatment on the true endpoint for a surrogate endpoint [9]. Analysis using a surrogate endpoint is based on hypothesis-testing where the null hypothesis is; the intervention has no effect on the surrogate endpoint. The decision taken to reject the null hypothesis using the surrogate endpoint is extrapolated to reject the null hypothesis using the true endpoint (i.e., no effect of the intervention using the true endpoint). For the treatment under consideration, there is a single pathway from treatment to a true endpoint that goes through a surrogate endpoint. Thus, if the surrogate endpoint is known, determination of the distribution of the true endpoint requires no further information.

For any treatment effect, the null hypothesis on a surrogate endpoint is rejected, which extrapolates to the true endpoint and concludes no effect of the intervention [7]. The surrogate threshold effect (STE) (Fig. 1b) permits estimation of the minimum effect on a surrogate endpoint that predicts a nonzero, statistically significant treatment effect on a true clinical endpoint [10,11]. The purpose of this study was to evaluate the literature to assess response rate as a surrogate endpoint of survival in OC.

2. Methods

The investigators conducted a systematic review consistent with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria, inclusive of literature published from January 1, 2000, through March 23, 2015. A targeted search was performed to identify clinical studies that reported survival for both responders and non-responders in patients with OC, to establish any difference in OS and/or progression-free survival (PFS) of responders and non-responders (validation/proof-of-concept). The results of proof-of-concept validation suggested that patients with OC who responded to chemotherapy (platinum or non-platinum based) tend to have higher median OS compared with non-responders. As a result, response could represent a potential surrogate measure for survival in OC. However, due to the exploratory nature of this study, and the few studies of this nature in OC, disease was not specified as a confounding factor.

During this analysis, it was necessary to overcome the susceptibility to deviation from the Prentice criterion necessary for extrapolation, which would result in variation of the probability of the true endpoint from the surrogate endpoint. For this reason, the STE (Fig. 1b) was employed at the individual study level to estimate the minimum effect on the surrogate endpoint that predicts a nonzero, statistically significant treatment effect on the true clinical endpoint in a future study [10,11]. Due to the paucity of literature in this area, and to assess the utility of STE in overcoming the limitations of surrogate endpoints, a more comprehensive literature review was performed.

The primary inclusion criterion was adult women with advanced OC who failed first-line therapy. The literature search was delimited by applying the following parameters: 'non- responder' OR non*response*, survival*, 'ovarian cancer'/exp OR 'ovarian cancer'. Studies included in the current analysis met these additional pre-defined eligibility criteria (Table 1). Eligible randomized controlled studies (RCTs) of second-line treatment or above in OC were identified, and data extracted for objective response rate (ORR) or disease control rate (DCR) and survival (PFS, OS). Literature searches included databases and sources to identify studies published in journals indexed by Excerpta Medica Database (Embase®), Medical Literature Analysis and Retrieval System Online (MEDLINE®), and bibliographic screening of systematic reviews and meta-analyses. Citations retrieved through the literature search were initially screened for inclusion based on their title and abstract. Full-text copies were obtained for citations that met the inclusion criteria, and in instances where it was not possible to determine whether the study fulfilled inclusion criteria based on the abstract alone. Data extractions were carried out by a single reviewer, with a 100% quality check of the extracted data by an independent reviewer. Data were quantitatively assessed based on the relationship between response rate and survival endpoint, using standard methodology.

The independent variables were the proposed surrogates: ORR expressed as complete response (CR) + partial response (PR); DCR defined as CR + PR + stable disease (SD). The dependent variables were the true clinical outcomes that included median OS and median PFS.

2.1. Statistical approach

All analyses were performed on weighted and unweighted data. For the primary analysis, the data summarized across studies were analyzed by weighting each treatment group proportional to its sample size divided by the total number of patients across all treatment groups from all studies used in the meta-analysis. This was done to compensate for the variability in sample sizes across studies.

$$W_i = n_i/N$$

where, W_i is the weight of the ith treatment group, n_i is the same size of the ith treatment group, and N is the sum of all the sample sizes (i.e., the total number of patients across all treatment groups from all studies used in the meta-analysis).

For secondary analyses, the same analysis was repeated for the unweighted data, which means that each study treatment group contributed equally to the analysis. In addition to using fixed effect model, a random effect model was also used for both primary and secondary analysis. In the random effects model, 'study' was used as a random effect. This helped to further explore the association between a proposed surrogate measure (PSM; independent variable) and a target clinical outcome (TCO; dependent variable) by taking into account the variance between and within studies.

The correlation coefficient to identify relationships between PSM and TCO was determined. Linear regression was conducted to identify direction of association.

The use of STE based on a linear relationship was to determine relevance and strength of surrogate measure. The STE value was determined by incorporating the regression line, 95% confidence interval (CI), and the 95% prediction interval. The cut point of lower prediction limit with the 0 value from y-axis and the corresponding nonzero value of the x-axis determines the required STE [10,12,13]. The smaller STE, the higher the precision of prediction (narrower prediction limits), and the more useful the proposed surrogate.

Analyses were based on data from individual studies. Statistical relationships were assessed based on strength of correlation coefficients: 0.1 to 0.3, small/weak; >0.3 to ≤0.5, medium/moderate; >0.5, large/strong. Individual treatment arms across studies were used as the "unit of analysis." To preserve randomization between studies, the

Please cite this article as: M.K. Siddiqui, et al., Objective response rate is a possible surrogate endpoint for survival in patients with advanced, recurrent ovarian cancer, Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.03.515