Gynecologic Oncology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

A prognostic nomogram to predict overall survival in women with recurrent ovarian cancer treated with bevacizumab and chemotherapy ☆

R. Previs [a,*], K. Bevis [b], W. Huh [b], T. Tillmanns [c], L. Perry [d], K. Moore [d], J. Chapman [e], C. McClung [f], T. Kiet [e], J. Java [g], J. Chan [e], A. Alvarez Secord [a]

[a] Duke University Medical Center, Durham, NC, USA
[b] University of Alabama at Birmingham, Birmingham, AL, USA
[c] West Clinic and University of Tennessee Health Science Center, Memphis, TN, USA
[d] Stevenson Oklahoma Cancer Center at the University of Oklahoma, Oklahoma City, OK, USA
[e] UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA
[f] Stanford Women's Cancer Center, Stanford Hospital and Clinics, Palo Alto, CA, USA
[g] Roswell Park Cancer Institute, Buffalo, NY, USA

HIGHLIGHTS

- Longer treatment-free interval prior to initiation of bevacizumab combined with chemotherapy was associated with an increased progression-free survival.
- A nomogram predicted the five-year overall survival probability in recurrent epithelial ovarian cancer patients who received bevacizumab with chemotherapy.

ARTICLE INFO

Article history:
Received 7 July 2013
Accepted 20 January 2014
Available online xxxx

Keywords:
Recurrent epithelial ovarian cancer
Bevacizumab
Nomogram

ABSTRACT

Objective. To develop a nomogram to predict overall survival (OS) in women with recurrent ovarian cancer treated with bevacizumab and chemotherapy.

Methods. A multicenter retrospective study was conducted. Potential prognostic variables included age; stage; grade; histology; performance status; residual disease; presence of ascites and/or pleural effusions; number of chemotherapy regimens, treatment-free interval (TFI) prior to bevacizumab administration, and platinum sensitivity. Multivariate analysis was performed using Cox proportional hazards regression. The predictive model was developed into a nomogram to predict five-year OS.

Results. 312 women with recurrent ovarian cancer treated with bevacizumab and chemotherapy were identified; median age was 59 (range: 19–85); 86% women had advanced stage (III–IV) disease. The majority had serous histology (74%), high grade cancers (93.5%), and optimal cytoreductions (69.5%). Fifty-one percent of women received greater than two prior chemotherapeutic regimens. TFI (AHR = 0.98, 95% CI 0.97–1.00, p = 0.022) was the only statistically significant predictor in a multivariate progression-free survival (PFS) analysis. In a multivariate OS analysis, prior number of chemotherapy regimens, TFI, platinum sensitivity, and presence of ascites were significant. A nomogram to predict five-year OS was constructed and internally validated (bootstrap-corrected concordance index = 0.737).

Conclusion. Our multivariate model identified prior number of chemotherapy regimens, TFI, platinum sensitivity, and the presence of ascites as prognostic variables for OS in women with recurrent ovarian cancer treated with bevacizumab combined with chemotherapy. Our nomogram to predict five-year OS may be used to identify women who may benefit from bevacizumab and chemotherapy, but further validation is needed.

1. Introduction

Bevacizumab, a monoclonal antibody, targets vascular endothelial growth factor (VEGF), and has been shown to have anti-tumor activity in epithelial ovarian cancer (EOC). In a Gynecologic Oncology Group

☆ Disclosures: No funding was received for this work.

* Corresponding author at: Duke University Medical Center, Department of Obstetrics & Gynecology, Division of Gynecologic Oncology, Box 3079 DUMC Erwin Road, Durham, NC 27710, USA.
E-mail address: rebecca.previs@gmail.com (R. Previs).

0090-8258/$ – see front matter © 2014 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ygyno.2014.01.036

(GOG) phase II study that evaluated bevacizumab in women who had failed prior chemotherapy, Burger and colleagues reported a response rate of 21% and median response duration of 10 months with 40.3% of patients remaining progression-free at 6 months [1]. This level of activity prompted further evaluation of bevacizumab in the treatment of advanced chemo-naïve and recurrent EOC.

Two pivotal phase III trials have demonstrated an improvement in progression-free survival (PFS) and response rate (RR) for women with recurrent EOC treated with bevacizumab and chemotherapy. Aghajanian and colleagues reported that women with platinum-sensitive recurrent EOC treated with carboplatin and gemcitabine as well as concurrent/maintenance bevacizumab had a longer PFS and response rate (RR) compared to those treated with chemotherapy alone (12.4 versus 8.4 months; HR 0.484, $p < 0.0001$; 78.5% versus 57.4%; HR 0.53, $p < 0.0001$) [2]. However, the preliminary overall survival (OS) analysis revealed that the median OS in both arms was similar [3]. Pujade-Lauraine et al. demonstrated a similar improvement in PFS for women with platinum-resistant EOC treated with B + C compared to chemotherapy alone (6.7 versus 3.4 months; HR 0.48, 95% CI 0.38–0.60; $p < 0.001$) as well as an improved response rate (30.9% versus 12.6%; $p = 0.001$) [4]. Given the marginal benefit of bevacizumab, there is considerable interest to develop clinical models or biomarkers to predict which women would receive the maximal benefit from bevacizumab.

The improvement in OS and RR is of clinical interest but must be balanced against adverse effects and cost. Bevacizumab is associated with several side effects including hypertension, proteinuria, thrombosis, bleeding, compromised wound healing, encephalopathy, and gastrointestinal (GI) perforation [1,2,5,6]. In addition, the use of bevacizumab with concurrent chemotherapy followed by maintenance therapy in the front-line setting has not been shown to be cost-effective [7]. While the efficacy results are promising, the side effects and cost highlight the importance of identifying appropriate women who are candidates for anti-angiogenic therapy and avoiding the use of these therapies in those who are at high risk for adverse events or limited efficacy. Nomograms to predict PFS and survival in patients with colon, prostrate, and renal cancers treated with bevacizumab have been developed [8–11]. However, no nomograms exist for women with recurrent EOC treated with bevacizumab. The development of a predictive nomogram to identify women most likely to benefit from bevacizumab added to chemotherapy has the potential to maximize benefit while minimizing unnecessary toxicity and health care costs.

2. Methods

2.1. Eligibility

Each institution involved in the consortium obtained an Institutional Review Board approval. A database was created to identify all women diagnosed with recurrent epithelial ovarian cancer, who received bevacizumab as part of their treatment for recurrence from January 1993 to September 2011. Women who received bevacizumab at the time of any recurrence were included. From medical charts, demographic data including age; stage; grade; histology; performance status; residual disease after cytoreductive surgery; presence of ascites and/or pleural effusions; number of chemotherapy regimens; TFI, platinum-free interval (PFI) prior to bevacizumab treatment; and platinum sensitivity were extracted. Women who were lost to follow-up were excluded from analysis.

2.2. Prognostic variables

Potential prognostic variables included age; stage; grade; histology; performance status; residual disease after cytoreductive surgery; presence of ascites and/or pleural effusions; number of chemotherapy regimens; TFI; PFI prior to bevacizumab treatment; and platinum sensitivity. Residual disease was defined in one of three categories after primary debulking: residual disease ≤ 1 cm, residual disease > 1 cm, and no residual disease. Platinum-sensitive disease was defined as disease that recurred ≥ six months after front-line platinum therapy, while platinum-resistant disease was defined as disease that recurred < six months after front-line platinum therapy.

2.3. Statistical analysis

OS was estimated using the Kaplan–Meier method [12]. Because about a sixth of the women had at least one prognostic factor missing, missing values were generated by multiple imputation [13] while considering all the variables at once. Under the assumption of data missing at random (MAR), we created 10 complete data sets using predictive mean matching. Cox regression models [14] were developed for PFS and OS and fitted to each imputed data set and combined into a single model with averaged regression coefficients and variance and covariance estimates adjusted for imputation. The nonlinearity of the effect of ordinal and continuous variables was assessed using restricted cubic splines [15]. Starting from a full model containing all prognostic factors, we removed small-contribution factors by fast backward elimination [16] and kept the resulting model as the basis for the nomogram.

Validation of the nomogram included two procedures. First, model discrimination was measured quantitatively with the concordance index [17], which is similar to the area under the receiver operating characteristic (ROC) curve but for censored data. Bootstrapping provided a relatively unbiased estimate of the concordance index. Second, calibration was assessed through grouping women by their nomogram-predicted probabilities, then comparing the group mean with the actual Kaplan–Meier estimate of OS; bootstrapping was again used for bias correction.

All statistical analyses were performed using the R programming language and environment [18] with the RMS and Hmisc packages added.

3. Results

Three hundred and twelve women with recurrent EOC received bevacizumab and chemotherapy. The median age was 59 years (range: 19–85); 74% had serous cancers; 84.7% underwent primary surgery; 69.5% had optimal cytoreduction; and 96.9% received adjuvant chemotherapy with paclitaxel and carboplatin. The median and mean TFI was two and six months, respectively. 20.7% had bevacizumab in the frontline setting as either part of the primary chemotherapy regimen or as maintenance and then were retreated with bevacizumab at recurrence. The median number of chemotherapy regimens prior to receiving bevacizumab was three regimens (Table 1). The median TFI and PFI before bevacizumab were 2 and 12 months, respectively. The majority of patients had platinum-sensitive disease (75.6%). OS was estimated using the Kaplan–Meier method (Fig. 1).

A multivariate PFS analysis was conducted and TFI prior to bevacizumab (AHR = 0.98, 95% CI 0.97–1.00, $p = 0.022$) was significant (Table 2A). No clinically meaningful interactions between factors were found to be significant. A multivariate OS analysis revealed that prior chemotherapy regimens (AHR = 0.79, 95% CI 0.72–0.86, $p < 0.001$), TFI (<25 months, AHR 0.94, 95% CI 0.91–0.97; ≥25 months, AHR 0.93, 95% CI 0.89–0.96, $p < 0.001$), platinum sensitivity (AHR 0.51, 95% CI 0.36–0.72, $p < 0.001$), and the presence of ascites (AHR 2.63, 95% CI 1.84–3.76, $p < 0.001$) were significant (Table 2B). Specifically, a greater number of prior chemotherapy regimens, longer TFI, and platinum-sensitive disease were associated with longer OS, while ascites was associated with shorter OS.

3.1. Nomogram

Based on the multivariate analysis, a nomogram for OS was constructed using the following retained variables (Fig. 2): number of chemotherapy regimens prior to bevacizumab; TFI; platinum sensitivity;

Please cite this article as: Previs R, et al, A prognostic nomogram to predict overall survival in women with recurrent ovarian cancer treated with bevacizumab and chemotherapy, Gynecol Oncol (2014), http://dx.doi.org/10.1016/j.ygyno.2014.01.036