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Predictive value of serum CA-125 levels in patients with persistent or recurrent epithelial ovarian cancer or peritoneal cancer treated with bevacizumab on a Gynecologic Oncology Group phase II trial☆,☆☆,★

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ABSTRACT

Objective. To compare two methods of determining therapeutic response and disease progression — modified Gynecologic Cancer Intergroup (GCIG) criteria based on CA-125 and Radiographic Evaluation Criteria in Solid Tumors (RECIST), in a phase II trial of bevacizumab for patients with recurrent or persistent epithelial ovarian and peritoneal carcinoma.

Methods. Patients were treated with bevacizumab 15 mg/kg every 21 days. Modified GCIG definitions of progression and response were retrospectively applied and compared to RECIST-defined progression and response. The prognostic significance of CA-125- and RECIST-defined responses and progressions were explored.

Results. Sixty-two patients were evaluable by RECIST, 59 for progression by CA-125, and 45 for response by CA-125. Median progression-free survival (PFS) by RECIST and progression-free interval (PFI) by CA-125 were 4.7 and 5.2 months respectively. However, 12.9% of those with CA-125 defined progression remained progression-free according to RECIST for at least 8 months. Thirteen of 62 patients (21%) had response by RECIST and 14/45 (31%) by CA-125. Time dependent analyses indicated that progression by CA-125 was associated with a 5.2 fold increased risk of progression by RECIST, and response by CA-125 had a 5 fold decrease in risk of progression by RECIST. Landmark and time dependent analyses showed prognostic value of responses by CA-125 and RECIST.

Conclusions. In this study, disease assessment by RECIST and CA-125 appears to correlate in general. However, approximately 10% of patients might demonstrate progression earlier by CA-125.

Introduction

In clinical trials for solid tumors, National Cancer Institute Response Evaluation Criteria in Solid Tumors (RECIST) represent the gold standard for response determination [1]. Although epithelial ovarian and peritoneal cancers are often assessed radiographically according to RECIST, clinical management is often guided by the less invasive and more cost-effective serum CA-125 level as a surrogate to RECIST. Gynecologic Cancer Intergroup (GCIG) CA-125 criteria have demonstrated a reasonable association with RECIST-defined response and progression in retrospective studies of patients treated with cytotoxic therapies [2–6]. Therefore, over the last decade, CA-125 has been incorporated into the assessment of disease in some clinical trials examining cytotoxic agents. It is unclear whether newer biologic targeted therapies, such as anti-angiogenic agents,

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could have an impact on CA-125 levels independent of tumor burden. If so, the accuracy of CA-125 in disease assessment could be compromised. Incorrect assessment of disease status by surrogate measures such as CA-125 might lead to premature discontinuation of, or rejection of, active therapy.

Gynecologic Oncology Group (GOG) Protocol 170-D was a phase II evaluation of single-agent bevacizumab in patients with persistent or recurrent ovarian or peritoneal carcinoma with primary endpoints of progression-free survival (PFS) at 6 months and response as determined by RECIST [7]. CA-125 measurements were collected, but these values were only required to confirm RECIST-defined complete responses.

The primary objective of this study was to assess the interactive and independent values of serum CA-125 and RECIST as measures of disease response or determinants of progression in the context of treatment with anti-angiogenic agent, bevacizumab, whose mechanism of action is unlike traditional cytotoxic agents. The secondary objective was to explore the prognostic significance of CA-125 and RECIST-defined responses and progressions.

Patients and methods

This is a retrospective analysis of serum CA-125 measurements recorded in patients enrolled on GOG Protocol 170-D. Details regarding the design and results of this study have been previously published [7], but in summary, GOG 170-D was a multi-center phase II evaluation of single-agent bevacizumab at 15 mg/kg intravenously every 21 days in patients with histologically-confirmed recurrent or persistent ovarian or peritoneal carcinoma. The original study received local Institutional Review Board (IRB) approval. Patients with 1–2 prior regimens, of platinum-free interval $\leq$12 months with 1 prior platinum regimen or any interval with 2 such regimens, and measurable disease were eligible. The study's primary endpoints were the proportion of patients responding or who were progression-free (PFS) at 6 months as determined by RECIST [1]. CA-125 measurements were only required to confirm a complete response in patients who had complete disappearance of disease on imaging. The final cohort consisted of 62 evaluable patients, 41 (66%) of whom had received 2 prior regimens and 26 (42%) of whom were considered platinum-resistant (platinum-free interval<6 months). The overall response rate by RECIST for the entire cohort was 21% (2 complete and 11 partial responses), and 25 (40.3%) patients were PFS at 6 months. These results exceeded the thresholds of 10 responses and 13 patients with PFS at 6 months, supporting further investigation of bevacizumab in patients with epithelial ovarian and related cancers.

CA-125 levels were measured within 14 days before study entry and prior to each cycle of bevacizumab, and were not recorded after treatment was discontinued for either RECIST-defined disease progression or unacceptable toxicity. Details regarding the methodology of CA-125 measurement such as assay type and reference ranges were not available. Therefore, the upper limit of normal (ULN) was defined as a serum CA-125 concentration of 35 units/mL. Modified GCIG criteria were applied to CA-125 values to determine both progression and response. Specifically, progression was defined as a two-fold increase in the ULN if the nadir value was less than the ULN, a two-fold increase in the nadir value if the nadir value was greater than the ULN or death [3,4].

Response was defined as at least a 50% reduction in baseline CA-125 sustained over 28 days [5,6]. Response by CA-125 was further refined in this report. Patients with CA-125 reduction below 35 units/mL, sustained for at least 28 days, were deemed to have a complete/full response. Otherwise, patients meeting the response criteria were classified as having partial responses. Patients who progressed by CA-125 within 8 weeks were categorized as having progressive disease and those who had at least 2 serum measurements (for at least 56 days after study entry), indicating none of the above categories were classified as having stable disease. Patients whose baseline CA-125 levels were less than twice the ULN prior to treatment were considered not evaluable by CA-125 criteria, and were excluded from response evaluations. Some evaluable patients did not submit enough data to determine a response classification, so they were classified as "Indeterminate for Response" and included in the calculation of the proportion responding (in the denominator as treatment failures).

Statistical methods

Time at risk for overall survival (OS) was assessed from study entry until death or date last seen. Time at risk for PFS was assessed from study entry until date of progression (by either RECIST or CA-125) or death (which ever occurred first), or date last seen. The estimate of PFS by CA-125 is potentially biased since collection of serum was stopped in patients who progressed by RECIST. The time at risk for the PFI by RECIST was determined by standard procedures and defined from study entry until the date of progression or date last seen. For all of these measures, the date of last follow up was used to determine a censored observation period in cases where the endpoint was not observed. In contrast, the time at risk for PFI by CA-125 was from study entry until progression by CA-125 or the date of last serum collection (for censored cases).

Time dependent covariate analyses were conducted with the hazard of disease progression (by RECIST) modeled though a Cox proportional hazards (PH) model as a function of the patients' state of disease progression (or response) by CA-125, using the method outlined by Buyse and Piedbois [8]. At an event time, patients within the risk set were categorized as being in a state of progression if their CA-125 values were greater than twice the ULN or maximum of their nadir value. In a separate analysis, patients were likewise categorized to be in a state of response if their most recent CA-125 values were no greater than 50% of their baseline levels. All 62 patients were included in the analysis of progression whereas only patients evaluable for response by CA-125 were included in the analysis of response.

A similar time dependent covariate analysis was done for the hazard of death. The covariates in these analyses were response as well as progression (by both RECIST and CA-125) [9,10]. The 4 types of analyses were conducted separately. A patient's covariate was initially set to zero until the outcome of interest was met (e.g. response by CA-125). Then the variable was permanently set to the value 1. The analyses were conducted in this manner because many patients survive well beyond the timeframe of a clinical trial. In addition to univariate covariate analyses, multivariate analyses were conducted to assess the significance of these factors in the presence of potential confounders (performance status and platinum sensitivity).

A landmark analysis is often considered a survival analysis where the starting point for time at risk is reset from the time of study entry to a later time when most (or all patients) have observed the response of interest. Those patients who die before the start point are excluded from the analysis. Then OS can be examined by stratifying on response without issues involved in causal ordering [11]. A landmark analysis could not be conducted with RECIST tumor response since the time until tumor responses was unusually long with this treatment. This would require a significant proportion of patients to be excluded from the analysis. However, CA-125 responses were quickly observed, enabling an easy comparison of these groups through relatively standard techniques.

Results

Sixty-two patients were eligible and evaluable on clinical protocol [7]. Serum CA-125 levels over time were highly variable, and in