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Dynamic modeling in ovarian cancer: An original approach linking early changes in modeled longitudinal CA-125 kinetics and survival to help decisions in early drug development ☆

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HIGHLIGHTS

- Early predictors of clinical benefit during drug development are needed.
- The links between early changes in CA125 and PFS in ovarian cancer were quantified.
- Early changes in CA125 may be an early predictive tool of the expected gain in PFS.

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ABSTRACT

Objective. Early prediction of the expected benefit of treatment in recurrent ovarian cancer (ROC) patients may help in drug development decisions. The actual value of 50% CA-125 decrease is being reconsidered. The main objective of the present study was to quantify the links between longitudinal assessments of CA-125 kinetics and progression-free survival (PFS) in treated recurrent ovarian cancer (ROC) patients.

Methods. The CALYPSO randomized phase III trial database comparing two platinum-based regimens in ROC patients was randomly split into a "learning dataset" and a "validation dataset". A parametric survival model was developed to associate longitudinal modeled CA-125 changes (ΔCA125), predictive factors, and PFS. The predictive performance of the model was evaluated with simulations.

Results. The PFS of 534 ROC patients were properly characterized by a parametric mathematical model. The modeled ΔCA125 from baseline to week 6 was a better predictor of PFS than the modeled fractional change in tumor size. Simulations confirmed the model's predictive performance.

Conclusions. We present the first parametric survival model quantifying the relationship between PFS and longitudinal CA-125 kinetics in treated ROC patients. The model enabled calculation of the increase in ΔCA125 required to observe a predetermined benefit in PFS to compare therapeutic strategies in populations. Therefore, ΔCA125 may be a predictive marker of the expected gain in PFS and an early predictive tool in drug development decisions.

Introduction

More than 225,900 new cases of ovarian cancer are diagnosed worldwide each year [1]. Ovarian cancer accounts for the leading cause of death among all invasive cancers of the female gynecological system [1]. The objective of treating patients with advanced ovarian cancer is to lengthen overall survival. However, the time required to observe a significant gain in survival during clinical trials is too long. Consequently, early predictors of clinical benefits that are able to reduce the time line required to evaluate new treatments are needed [2].

Change in tumor size as assessed by discrete RECIST criteria is the outcome traditionally used to evaluate treatment efficacy in phase I

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It was also presented in a general poster session at the annual American Society of Clinical Oncology (ASCO) meeting: Wilbaux M, et al.: Benefit in progression-free survival (PFS) to expect based on CA125 reduction at week 6 in recurrent ovarian cancer (ROC) patients: CALYPSO phase III trial data (a GINECO-GCIG study). J Clin Oncol (suppl; abstr 5547 (112408)) 2013.

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and phase II studies [3]. More recently, this endpoint has been suggested to have a more predictive value when considered as a continuous outcome. Following the Critical Path Initiative recommendations by the US Food and Drug Administration, mathematical and statistical models demonstrated that early changes in tumor size are predictors of survival in a variety of tumors, including metastatic breast cancer, colorectal cancer, and non-small cell lung cancer [4–6].

In advanced ovarian cancer patients, monitoring the decline in CA-125 titers in conjunction with the assessment of tumor size (using RECIST criteria) during chemotherapy is a strategy for characterizing treatment efficacy recognized by Gynecologic Cancer InterGroup (GCIG) [7]. However, the relevance of the binarized CA-125 response criterion (e.g., at least a 50% reduction from a pretreatment sample and maintained for at least 28 days) was strongly questioned by Lee et al. in 2011 [8]. Recent studies have suggested that longitudinal assessment of CA-125 values using mathematical algorithms will be more accurate than a single threshold-based strategy for analyzing CA-125 kinetics but the relationships to treatment benefit have never been assessed [9–11].

The actual predictive value of CA-125 dynamics during treatment in patients with advanced ovarian cancer is to be determined. In a previous study, we showed that quantifiable links exist between CA-125 kinetics and tumor size changes using a mathematical model, but the association with progression-free survival (PFS) remained to be elucidated [12]. The objectives of the present study were to establish the quantitative relationships between longitudinal modeled CA-125 kinetics and PFS in patients with recurrent ovarian cancer who are treated with chemotherapy, and to predict the expected PFS based on the patient-modeled CA-125 response. In addition, we aimed to identify the potential changes in CA-125 required to observe a predetermined improvement in PFS. This model could provide a useful tool for assessing the reliable prediction of PFS and support early drug development decisions.

Materials and methods

Trial and patients

The CALYPSO trial was a randomized, multicenter, phase III non-inferiority trial to test the efficacy and safety of the combination of carboplatin and pegylated liposomal doxorubicin (CD) compared to the standard combination of carboplatin and paclitaxel (CP) in patients with platinum-sensitive recurrent ovarian cancer (ROC). A total of 976 patients were randomized, 467 to CD and 509 to CP. Pujade et al. reported the superiority of CD regarding PFS and safety, and the details of this study were published previously [13].

Data management

Patients with non-measurable lesions were excluded from our analysis. For computational reasons, patients who had all their CA-125 values consistently lower than 25 $U \cdot mL^{-1}$, resulting in flat kinetic profiles, were removed. The whole patient dataset was randomly split into: (i) a learning dataset including two-thirds of patients to build the model and estimate parameters and (ii) a validation dataset with the remaining one-third of patients for an advanced evaluation of the model. Due to the skewness of the distribution of dependent variables, CA-125 concentrations were Box–Cox transformed (Supplementary S1, online only) and tumor size values log-transformed, to meet normality assumption [14]. Tumor size was reported as the sum of the longest dimensions of all target lesions, and a limit of quantification of 10 mm was utilized [3].

Model building procedure

A five-step scheme was used to relate changes in CA-125 titers, tumor size and PFS (Fig. 1). The previously reported model, meant to link CA-125 and tumor size changes, was combined with a parametric model of PFS [12].

First, modeled fractional changes in tumor size and CA-125 longitudinal changes were assessed from baseline to week 6. The selected 6 week length of time for CA125 kinetic modeling relates to 2 cycles of carboplatin–paclitaxel, which was considered as suitable for early prediction of treatment benefit. Next, several covariates potentially associated with PFS were screened. A parametric survival model meant to associate longitudinal CA-125 kinetics, significant predictive factors, and PFS was developed using the approach described by Claret et al. for colorectal cancer [6]. After internal and advanced internal evaluations, practical applications were modeled; the expected PFS was predicted based on the patient CA-125 response, and the increase in modeled fractional changes in CA-125 required to observe a predetermined PFS improvement was calculated.

1) Assessment of modeled fractional changes in tumor size and CA-125
   Tumor sizes and CA-125 titers were used to calculate fractional changes in tumor size (ΔTS) and CA-125 (ΔCA125) modeled continuously from baseline (BL) to week 6, as described in Supplementary S2 (online only).
   Of note, tumor size and CA-125 titers predicted at baseline and week 6 by the longitudinal model were used to calculate ΔTS and ΔCA125 [12]. The model structure is presented in Supplementary S3 (online only). The model was implemented using the CA-125 concentrations, tumor size values, and chemotherapy dates available in the CALYPSO database.
2) Screening for significant predictive factors
   Several covariates potentially associated with PFS were tested: ΔTS, ΔCA125, baseline tumor size, baseline CA-125, patient therapy-free interval (≤12 months vs. >12 months), age, treatment type (CP vs. CD), lesion number (=1 vs. >1)… Significant predictive factors for PFS were determined using Kaplan–Meier curves (log-rank test) and univariate Cox regression analyses (likelihood ratio test) with a two-sided alpha risk of 0.05 [15,16]. All significant factors in the univariate analysis were integrated in a multivariate analysis using the parametric survival model.
3) Development of the parametric survival model
   A parametric survival model was developed to describe the distribution of PFS as a function of longitudinal changes in CA-125 and tumor size and significant predictive factors [17]. The median PFS (months) was calculated for all patients from the date of the first administration of chemotherapy until the date of progressive disease or death, whichever occurred first. Different PFS distributions (i.e., exponential, Gaussian, log-normal, Weibull, logistic, and log-logistic) were tested using adequate statistical and graphical tests (i.e., likelihood comparison and assumption testing) before selecting the best distribution. Significant predictive factors were included in the parametric model one-by-one using forward selection (alpha = 0.05). Backward stepwise elimination procedures were then carried out to exclude non-significant covariates (alpha = 0.01).
   The Akaike Information Criteria (AIC) were calculated to compare different models [18]. The final model was internally evaluated and its ability to predict PFS was tested using simulations on learning and validation datasets (Supplementary S4, online only).
4) Practical applications of the model
   The model was applied to predict expected median PFS based on the patient-modeled CA-125 response. Individually modeled ΔCA125 was dichotomized on the medians in order to discriminate between two groups of patients: rapid-responders (ΔCA125 greater than the median) and slow-responders (ΔCA125 lower than the median). The median PFS was computed using individual values for significant covariates and ΔCA125. The predicted median PFS along with 95% CI was compared to the observed median PFS.
   The model was also used to predict the increase in the modeled fractional change in CA-125 required to observe a predetermined PFS benefit for the purpose of comparing therapeutic strategies.