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The strong prognostic value of KELIM, a model-based parameter from CA 125 kinetics in ovarian cancer: Data from CALYPSO trial (a GINECO-GCIG study)☆

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HIGHLIGHTS

- Mathematical modeling of CA-125 kinetics in ROC patients enables understanding of the CA-125 time-change components: cancer production, chemotherapy effect, elimination.
- The contradictory surrogacy of GCIG-defined CA-125 response regarding progression free survival reported by Lee et al. (JNCI 2011;103:1338) was confirmed.
- The modeled CA-125 elimination rate KELIM, potentially assessable in routine, may have promising predictive value regarding progression free survival.

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ABSTRACT

Background. Unexpected results were recently reported about the poor surrogacy of Gynecologic Cancer Intergroup (GCIG) defined CA-125 response in recurrent ovarian cancer (ROC) patients. Mathematical modeling may help describe CA-125 decline dynamically and discriminate prognostic kinetic parameters.

Methods. Data from CALYPSO phase III trial comparing 2 carboplatin-based regimens in ROC patients were analyzed. Based on population kinetic approach, serum [CA-125] concentration-time profiles during first 50 treatment days were fit to a semi-mechanistic model with following parameters: "d[CA-125] / dt = (KPROD ∗ exp (BETA ∗ t)) ∗ Effect − KELIM ∗ [CA-125]" with time, t; tumor growth rate, BETA; CA-125 tumor production rate, KPROD; CA-125 elimination rate, KELIM and K-dependent treatment indirect Effect. The predictive values of kinetic parameters were tested regarding progression-free survival (PFS) against other reported prognostic factors.

Results. Individual CA-125 kinetic profiles from 895 patients were modeled. Three kinetic parameters categorized by medians had predictive values using univariate analyses: K; KPROD and KELIM (all $P < 0.001$). Using Cox multivariate analysis, 5 independent predictors of PFS remained significant: GCIG CA-125 response (favoring carboplatin-paclitaxel arm), treatment arm, platinum free-interval, measurable lesions and KELIM (HR = 0.53; 95% CI 0.45–0.61; $P < 0.001$).

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Conclusions. Mathematical modeling of CA-125 kinetics in ROC patients enables understanding of the time-change components during chemotherapy. The contradictory surrogacy of GCIG-defined CA-125 response was confirmed. The modeled CA-125 elimination rate KELIM, potentially assessable in routine, may have promising predictive value regarding PFS. Further validation of this predictive marker is warranted.

Introduction

The monitoring of CA-125 decline profile during chemotherapy as a way of predicting treatment efficacy, risk of relapse or survival has been extensively investigated in ovarian cancer patients. Many patients with ovarian cancer do not have measurable disease; therefore, tumor response cannot be frequently assessed using Response Evaluation Criteria in Solid Tumors (RECIST) [1]. Many studies have demonstrated the prognostic or predictive values of single values (e.g., thresholds at a time t, nadirs, or normalizations) [2–7] or of kinetic parameters based on a minimum of 2 time points such as the percentage decreases [8,9], half-lives [10–14], or area-under-the-curve (AUC) [15]. In 2004, the Gynecologic Cancer Intergroup (GCIG) defined CA-125 response as a 50% reduction in CA-125 levels maintained for at least 28 days [1]. However the actual predictive value of GCIG-defined CA-125 response has been questioned in a recent analysis of CALYPSO phase III trial, in which two carboplatin-based regimens were compared in patients with platinum-sensitive relapsed/recurrent ovarian cancers (ROC) [16]. Lee et al., analyzed CA-125 decline profiles from patients enrolled in this trial, and reported paradoxical outcomes about the prognostic value of GCIG-defined CA-125 response [9]. The analysis showed that CA-125 early decline (defined as rate of CA-125 decrease of at least 50% per month) or CA-125 early responses (complete or partial response) were more frequent in the carboplatin-paclitaxel arm. These outcomes were contrary to expectations as carboplatin-pegylated liposomal doxorubicin (PLD) regimen was superior to carboplatin-paclitaxel regimen in terms of progression-free survival (PFS) [9,16].

Mathematical modeling based on population kinetic approach may enable assessment of individual CA-125 kinetic profiles dynamically [17]. Indeed this commonly implemented strategy in pharmacokinetic studies presents several advantages for analysis of serum tumor markers kinetics. Application of this method has been described in studies evaluating of the kinetics of other serum tumor markers [18–21]. Results were promising and confirmatory studies are ongoing [22,23].

Dynamic investigation of CA-125 kinetics during chemotherapy using semi-mechanistic models, which are able to separately assess: 1) tumor marker production rate by cancer; 2) the indirect effect of chemotherapy on CA-125 production and 3) the marker elimination rate, is a rational strategy to understand the components of CA-125 time-changes. The present study is aimed at building a population kinetic-based semi-mechanistic model of CA-125 kinetics in patients enrolled in CALYPSO trial to search for potential prognostic factors of relapse.

Patients and methods

Patients and objectives

CALYPSO was a randomized, multicenter, phase III non-inferiority trial to test the efficacy and safety of the combination of carboplatin with PLD (CD) compared with carboplatin and paclitaxel (CP) in patients with platinum-sensitive ROC (NCT00189553). A total of 976 patients were randomized, 467 to CD and 509 to CP. Details have been previously published [16]. The primary objective of the present study was to show the feasibility of characterizing CA-125 kinetics from patients using a population kinetic semi-mechanistic model. The secondary objective was to identify modeled kinetic parameters, related to CA-125 tumor production, treatment effect, or CA-125 elimination, which might harbor early predictive value regarding treatment efficacy.

Model building

Individual CA-125 data were analyzed using a population kinetic approach with a non-linear mixed effect model (Fig. 1) [17][24]. Basic details of population kinetic approach which enables estimation of model parameters in sparse sampling conditions with a few time points per patient are presented in Appendix A. To normalize CA-125 titer distribution, data were Box–Cox transformed [25] (Appendix A). A semi-mechanistic model based on kinetic-pharmacodynamic (K-PD) approach was used to fit serum CA-125 values measured during the first 50 treatment days [26]. This strategy is commonly used for pharmacokinetic studies when no drug concentration data are available [26]. This time frame was arbitrarily selected such that early predictive factors of efficacy were identified, which could be used for treatment adjustment in routine. Treatment kinetics were assumed to be described by a 2-virtual-compartment model: central (C1) receiving chemotherapy dosing (doses set to 1) and a transit compartment (C2) to describe the treatment lag-time effect (Fig. 1) [27]. CA-125 production inhibition induced by treatment was expressed by an indirect effect model using an Emax relationship [28]. This model is expressed as follows:

$$\frac{dC1}{dt} = -K \times C1 \tag{1}$$

$$\frac{dC2}{dt} = K \times C1 - K \times C2 \tag{2}$$

$$\frac{dCA125}{dt} = KPROD \times e^{BETA \times time} \times EFFECT - KELIM \times CA125 \tag{3}$$

$$EFFECT = 1 - \frac{C2}{A50 + C2} \epsilon [0;1] \tag{4}$$

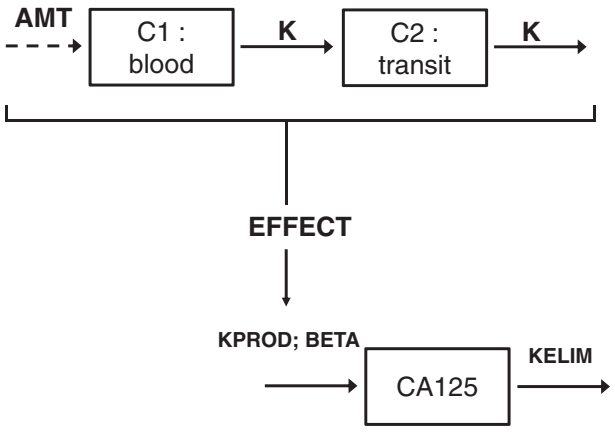

Fig. 1. Description of the semi-mechanistic model. AMT: Unknown CA-125 dose amount; K: treatment kinetics; KPROD: CA-125 tumor production rate; BETA: tumor growth rate; KELIM: CA-125 elimination rate; EFFECT: production inhibition; C1: central compartment receiving chemotherapy dosing; and C2: transit compartment to describe the treatment lag-time effect.