Modelling change in tumour size, survival and new lesions appearance in patients with ovarian cancer treated with carboplatin monotherapy or in combination with gemcitabine

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ABSTRACT

Objectives:
Change in tumour size (CTS) is a marker of cytotoxic drug effects and there is growing interest in using this metric as primary endpoint [1], allowing earlier evaluation of treatment outcome compared to conventional metrics such as overall survival (OS). The objective of this study is to develop a model to quantify CTS during therapy and to investigate the predictive value of CTS, lesions location on trial enrolment and time of new lesion appearance on OS in metastatic ovarian cancer (MOC).

Methods:
Data from a Phase III randomized study, comparing the efficacy of gemcitabine plus carboplatin versus carboplatin monotherapy in patients with recurrent MOC, was available for analysis [2]. The database included 336 patients, (173 followed up until death, 163 censored). A modelling approach was applied to characterise the CTS time course, evaluating several exposure measures to describe drug effects. Parametric time-to-event (TTE) models were investigated to predict appearance of metastasis, OS and dropout probability as functions of CTS and other covariates.

Results:
The CTS model [3,4,5] successfully described the data. Resistance to treatment was however not statistically significant and the two drugs promoted tumour shrinkage with independent additive effects. Drug exposure was incorporated as the per-cycle AUC predicted from the doses and literature PK models [6,7]. Metastasis appearance, OS and dropout probabilities were described using parametric TTE models, with a Weibull hazard increasing with time. Two time-varying covariates, describing tumour evolution during treatment, were included in the OS model: the predicted relative CTS up to week 12 (and thereafter $rCTS_{week12}$), and the appearance of new lesions. Other included (time-constant) covariates were tumour size and ECOG status at baseline. The rCTS at the end of the first treatment cycle was a significant predictor in the metastasis appearance model.

Conclusions:
Metrics from the developed CTS model, quantifying the effect of carboplatin monotherapy and when combined with gemcitabine, could successfully predict metastasis appearance and OS probability in MOC. In addition to appearance of new lesions, predicted rCTS(t) up to week 12 was a significant predictor of OS probability and better than rCTS at fixed time points such as week 6 or 8. Predicted rCTS after first treatment cycle was the best predictor for appearance of new metastasis.

BACKGROUND

- In oncology, for a drug to be considered superior to the standard of care, it must demonstrate significant improvement in Overall Survival (OS). The use of surrogate endpoints (e.g. overall response rate) may allow regulatory submission before the survival dataset matures.
- Change in Tumour Size (CTS) is a marker of cytotoxic drug effects and there is growing interest in using this metric as a measure of treatment response and as a surrogate/ primary endpoint[1].
- CTS(t) has been demonstrated to be predictive of OS in Non Small Cell Lung Cancer[8], colorectal cancer[3], thyroid cancer[4] and, recently, metastatic breast cancer[9].

OBJECTIVE

- To model CTS(t) in patients with metastatic ovarian cancer.
- To predict OS probability and to investigate its relationship with
  - patient characteristics at beginning of treatment
  - CTS as a time-varying variable and as a fixed time-point measurement
  - appearance of new lesions during treatment
- To model the appearance of new lesions during treatment.

MATERIAL

- A randomized phase 3 study comparing Carboplatin (Cb) monotherapy vs Gemcitabine (G) plus Carboplatin in patients with advanced epithelial ovarian carcinoma who failed first-line platinum-based therapy.
- 336 treated patients (168 GCb Arm, 168 Cb Arm), 1358 total TS measurements. Lesions assessed at baseline and every other therapy cycle (approx every 6 weeks).
- 173 deaths (51%) (91 Cb arm, 82 GCb arm).
- Patients were allowed to be treated for up to six 21-day cycles.
  - Cb administered intravenously on day 1 (target AUC=5.0 [4.0] mg/mL·min in the Cb [GCb] arm)
  - G administered intravenously on days 1 and 8 (Dose=1000 mg/m^2)
- Treatment postponed for up to 2 weeks in case of toxicity, and restarted immediately after recovery with dose reduction.
- Patients discontinued from the study in case of disease progression (RECIST1) or if the beginning of a cycle had to be postponed for more than 2 weeks.
- Tumour size was defined as the Sum of Longest Diameter (SLD) of target lesions (max n=10).
- New lesions do not contribute to the SLD.

METHODS & RESULTS

Model for CTS(t)

$$\frac{dy(t)}{dt} = k_G y(t) - \left(k_{D_{Cb}} Exposure_{Cb}(t) + k_{D_G} Exposure_G(t)\right) y(t)$$

$$y(0) = SLD(0) = SLD_{screening}$$

$$Exposure_x(t) = \frac{AUC_x(t)}{\Delta t_{Doses\ x}}$$

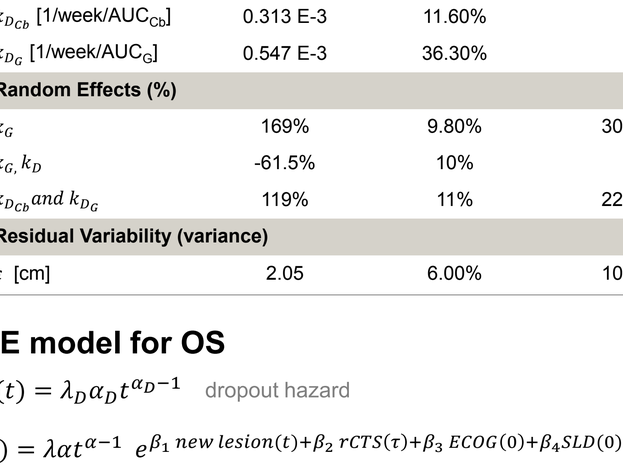

Figure 1. CTS(t) model. Drug exposure is predicted from the doses and literature PK models[6,7]. The two treatments promote tumour death with independent additive effects.

- Dose, drug concentration and AUC (from literature PK models) were investigated as exposure metrics in the SLD model.
- Development of drug resistance during treatment was non-statistically significant.
- In the simulation, drop-out from TS assessment in case of progressive disease was taken into account. Currently we are investigating a logistic regression model for simulating the probability of dropout from TS assessment.

Table 1. Parameter estimates for the CTS(t) model.

Parameter	Estimate	RSE (%)	Shrinkage
Fixed Effects			
k_G[1/week]	1.70 E-3	23.30%	
$k_{D_{Cb}}$ [1/week/AUC_{Cb}]	0.313 E-3	11.60%	
k_{D_G} [1/week/AUC_G]	0.547 E-3	36.30%	
Random Effects (%)			
k_G	169%	9.80%	30%
k_G, k_D	-61.5%	10%	
$k_{D_{Cb}} and\ k_{D_G}$	119%	11%	22%
Residual Variability (variance)			
ε [cm]	2.05	6.00%	10%

TTE model for OS

$h_D(t) = \lambda_D \alpha_D t^{\alpha_D - 1}$ dropout hazard

$h(t) = \lambda \alpha t^{\alpha - 1}\ e^{\beta_1 new\ lesion(t) + \beta_2 rCTS(\tau) + \beta_3 ECOG(0) + \beta_4 SLD(0)}$ death hazard

$$rCTS(\tau) = \begin{cases} \frac{TS(t) - SLD(0)}{SLD(0)}, & t < week12 \\ \frac{TS(week12) - SLD(0)}{SLD(0)}, & t \geq week12 \end{cases}$$

- significant covariates determined with the forward inclusion (p-val=0.01) - backward elimination (p-val=0.001) algorithm.
- Simultaneous estimation of the parameters of the CTS and OS models.

Table 2. Parameter estimates for the TTE model for OS and dropout from OS.

Parameter	Estimate	RSE (%)
Dropout hazard		
λ_D	0.256 E-3	25%
α_D	2.68	3%
Death hazard		
λ	1.10 E-3	29%
α	1.99	5%
β_1 (new lesion(t))	1.22	13%
β_2 (rCTS(τ))	0.619%	12%
β_3 (ECOG(0))	0.533%	28%
β_4 (SLD(0))	0.244%	26%

TTE model for appearance of new lesions

$h_D(t) = \lambda_D \alpha_D t^{\alpha_D - 1}$ dropout hazard

$h(t) = \lambda \alpha t^{\alpha - 1}\ e^{\beta_1 rCTS(week3)}$ new lesion appearance hazard

Table 3. Parameter estimates for the TTE model for appearance of new lesions and dropout from new lesions assessment.

Parameter	Estimate	RSE (%)
Dropout hazard		
λ_D	0.0056	3%
α_D	2.73	7%
New lesion hazard		
λ	0.0042	8%
α	2.18	8%
β_1 (rCTS(week3))	2.96	36%

RESULTS

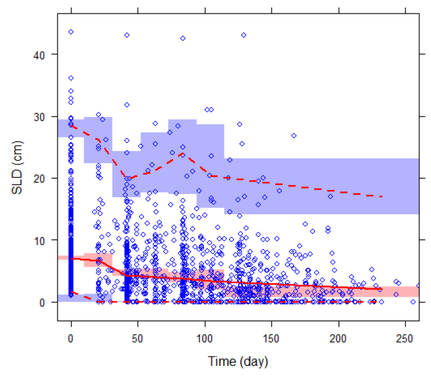

Figure 2. Visual predictive check for the CTS(t) model. Median (solid line), 10th and 90th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals (shaded areas) for the median, 10th and 90th percentiles of the simulated data (based on 1000 simulations).

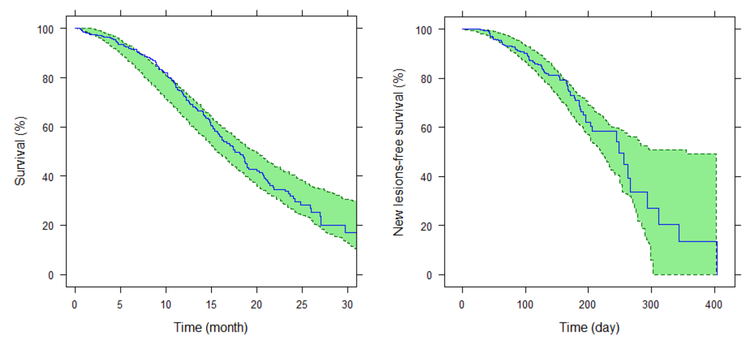

***Figure 3.* Visual predictive check for the Kaplan-Meier survival (left) and new lesion –free survival (right) curve.** The observed Kaplan-Meier curve (solid line) is compared to the 95% confidence interval (shaded area) derived from model simulations (based on 1000 samples) of the survival and new lesion appearance models, respectively.

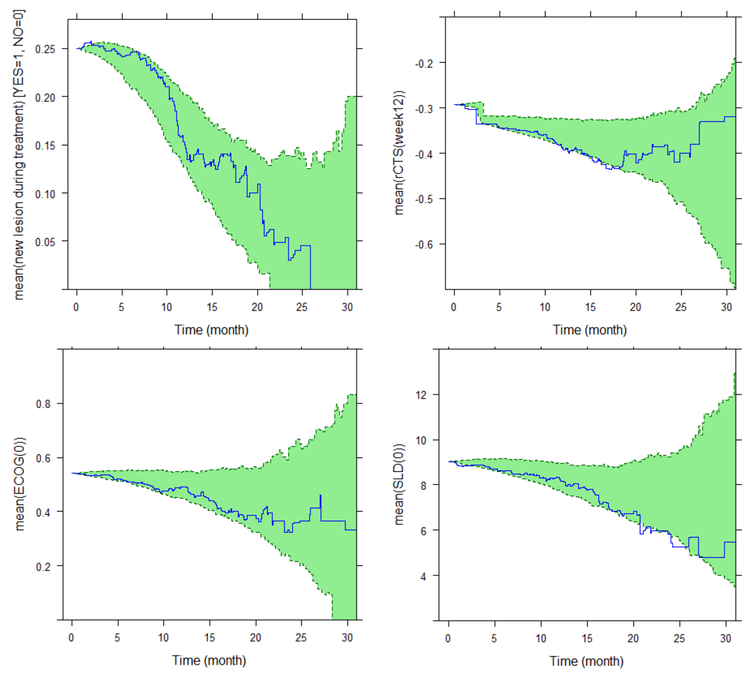

Figure 4. Kaplan Meier Mean Covariate plot for the final OS model. The mean of the covariate is computed based on all of the individuals still in the study at every inflection point of the Kaplan Meier survival curve. Observed mean (solid line) is compared to the 95% confidence interval (shaded area) of the mean derived from model simulations (based on 1000 samples).

CONCLUSIONS

- The CTS(t) during drug treatment data were successfully described by a modified Claret model. Drug exposure was incorporated as the per-cycle AUC and the two drugs had independent additive effects in promoting TS reduction. Resistance to treatment was not statistically significant.
- The OS probability was described by a TTE model with a Weibull hazard and covariates:
  - appearance of new lesions during treatment
  - rCTS(t) up to week12 and rCTS(week12) afterwards
  - ECOG status at baseline
  - SLD at baseline
- The appearance of new lesions was preliminarily described by a TTE model with a Weibull hazard and covariate rCTS(week3).
- Future works will include the validation of the CTS(t) and OS models on independent ovarian cancer studies.

Acknowledgements:

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115156, resources of which are composed of financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. The DDMoRe project is also financially supported by contributions from Academic and SME partners. This work does not necessarily represent the view of all DDMoRe partners.

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