ABSTRACT 5065

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

Mathematical modeling of CA125 kinetics in recurrent ovarian cancer (ROC) patients treated with chemotherapy and predictive value of early modeled kinetic parameters in CALYPSO trial (a GCIG study)

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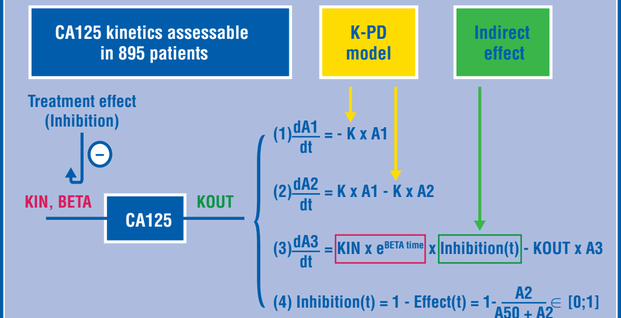
BACKGROUND

- Although CA125 kinetic profiles may be related with relapse risk in ovarian cancer patients treated with chemotherapy, no reliable kinetic parameters have been reported
- Mathematical modeling may help describe CA125 decline dynamically and determine parameters predictive of relapse

METHODOLOGY

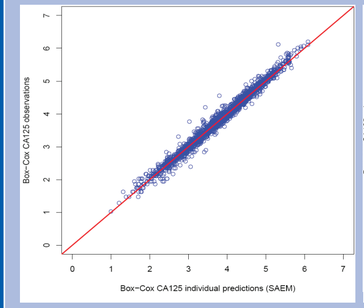
- Data from CALYPSO randomized phase III trial data comparing carboplatin-paclitaxel and carboplatin-pegylated liposomal doxorubicin in 974 ROC patients
- Population kinetic approach (Monolix™ software), semi-mechanistic model used to fit serum Box-Cox transformed CA125 concentration-time profiles with following parameters:
  - tumor growth rate constant (BETA)
  - CA 125 tumor production (KIN)
  - tumor decay rate constant (KOUT)
  - treatment indirect effect (Emax relationships with A & A50)
- The predictive values of normalized K; KIN; KOUT; BETA and A50 estimated during the first 50 treatment days were tested for progression-free survival (PFS) against other reported prognostic factors using Cox-models

DESCRIPTION OF THE MODEL

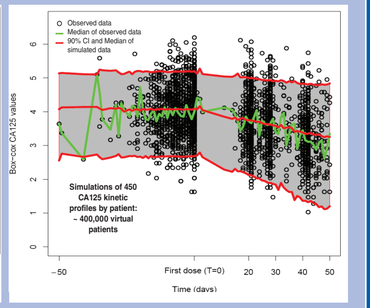


RESULTS

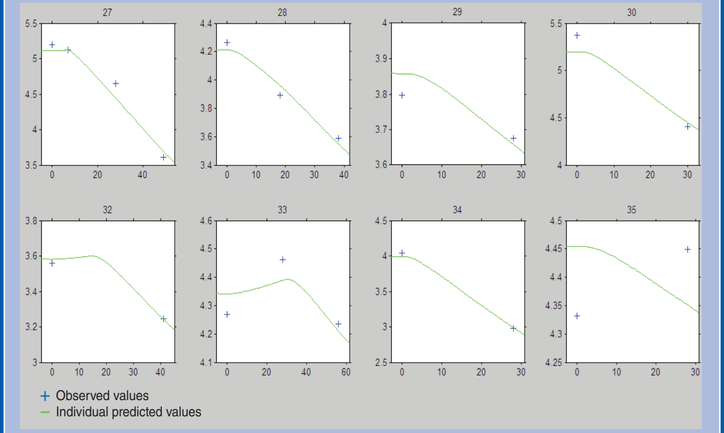
OBSERVED VS INDIVIDUAL PREDICTED TITERS



VISUAL PREDICTIVE CHECK



BOX-COX TRANSFORMED CA125 VS TIME EXAMPLE OF 8 TYPICAL PATIENTS



UNIVARIATE ANALYSIS (COX AND LOG-RANK TESTS): SELECTION OF THE BEST MODELED KINETIC PARAMETER

N = 895 patients	K (day $^{-1}$)	BETA (day $^{-1}$)	KIN (day $^{-1}$)	KOUT (day $^{-1}$)	A50	AUC	Mean residence time (MRT)	Cumulative inhibition
p	0.000251	0.323	$3.53e^{-10}$	0	0.11	$1.22e^{-05}$	$5.87e^{-05}$	0.0146
Median PFS (months)								
G1 : < med	9.18	10.43	11.68	9.01	10.56	11.32	11.12	10.43
G2 : ≥ med	10.69	9.44	9.08	11.81	9.51	9.14	9.14	9.41

MULTIVARIATE ANALYSIS (COX-MODEL)

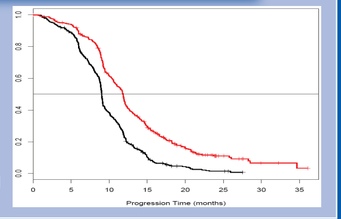
- Including the significant covariates identified using univariate analysis.
  - Predictive factors reported in the literature: platinum-free interval (PFI); metastatic site number; largest tumor size, measurable disease, GCIG decrease
  - Modeled kinetic parameters (K; BETA; KIN; KOUT; AUC; MRT, Cum Inhibition)

SIGNIFICANT INDEPENDENT PROGNOSTIC FACTORS USING MULTIVARIATE ANALYSIS

N = 891 patients	TTT (PLD vs Paclitaxel)	PFS (< 12 months vs > 12 months)	Measurable lesion (Yes vs No)	KOUT (> Median vs < median) (day $^{-1}$)	GCIG decline (Favorable vs unfavorable)
p	0.0002	$5.26e^{-11}$	$7.07e^{-05}$	$2e^{-16}$	$4.76e^{-08}$
β	-0.262	0.492	0.300	-0.643	-0.436
e^{β}	0.768	1.635	1.350	0.525	0.646
95% CI	[0.66;0.88]	[1.41;1.89]	[1.16;1.56]	[0.45;0.60]	[0.55;0.75]

PROGRESSION-FREE SURVIVAL

- The best modeled predictor of PFS was KOUT. Significant prognostic value using multivariate analysis was:
  - Continuous: HR = 5 e^{-05} 95% CI [0 – 9 e^{-04}], p < 2 e^{-10}
  - Categorial, discriminated by the median: HR = 0.52, 95%CI [0.45 – 0.60], p < 10 e^{-15}



CONCLUSION

Determination of mathematical equations describing CA125 kinetics in ROC patients treated with chemotherapy is feasible. Moreover KOUT, a modeled kinetic parameter estimated early in the first 50 treatment days, may have promising independent predictive value regarding PFS. Further validation of these results in independent cohorts is warranted.

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