Time to event models of survival in cancer of pancreas : confirmation of explanatory variables pre-selected by bootstrap analysis

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OBJECTIVES

Treatment of pancreas cancer often involves protocols out of references. These are argued by phase 2 studies, small cohorts studies or case reports. Important goal is to rank these protocols according to efficacy and safety.
This ranking and associated statistical models are of potential interest for patient, help to proritize phase 3 studies to undertake, help to design phase 3 studies. Multivariate statistical analysis lead to select appropriate explanatory variables, with events of interest like progression free survival, tumor size kinetics, score of toxicity, and for this study time to death. Here modelisation involve Weibull model, in order to confirm explanatory variables pre-selected by 2-stage bootstrap analysis.

METHODS

▪ The population multivariate analysis was performed using NONMEM based on datas from a cohort of 42 unselected patients. Weibull model was implemented in NONMEM with prediction of probability of death . Confirmation of explanatory variables pre-selected was test on individuals predictions : possible correlations between these variables and individual median time to event were explored using the three step approach described by Maitre et al (3), incorporating use of Tanagra* software for PLS (Partial least squares) regression (to take into account prospective correlation between covariates).**

RESULTS

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SPRED
BASE=THETA(1)
EMAX=THETA(3)
EC50=THETA(4)
E=(EMAX*VAR)/(EC50+VAR); Effect model
GAM=THETA(2)
TMED=(E+BASE)*EXP(ETA(1)); Median Time to Event
IF (TMED.LE.0) EXIT 1 300
LAM=LOG(2)
R=DV/TMED
A=LAM*R**GAM
DENS=GAM*A/DV*EXP(-A); probability density to observe event
SURV=EXP(-A)
IF (SURV.LE.0) EXIT 1 100
IF (SURV.GE.1) EXIT 1 200
Y=(1-CENS)*DENS+CENS*SURV
STHETA 6 (0.1,2.5,9) 3 5 NOABORT
SOMEGA 9
SEST NOABORT PRINT=5 MET=COND LAPLACE LIKE POSTHOC SIGDIGITS=3
MAX=1000
SCOV
STABLE NOPRINT ID GENR AGE META LIG CYC TMED CHIR DENS SURV CENS
DV
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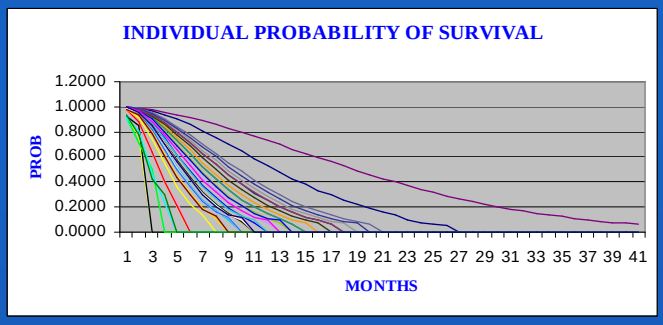

42 patients were analysed, with combinations of 12 different protocols of chemotherapy. Pre-selected variables were : age , stage at diagnosis (local or metastatic) , number of treatment lines, first protocol schedule, prior surgery, global dose , platinium salt introduction, gemcitabin-oxaliplatin protocol exposure, erlotinib exposure.
From the the three steps approach, PLS regression lead to variable important in projection for dose, platinium salt, gemcitabin-oxaliplatin, stage at diagnosis, number of treatment lines, but not for age. Proportion of variance explained was : 81.39% on input covariates, 78.9% on target variable.

▪Variable	OBJ	ETA on Median Time to Event
▪None	264.547	39.37%
▪Lines	256.474	29.73%
▪Global dose	247.921	18.54%
▪Pt salt	259.360	34.78%
▪Erlotinib	254.235	19.50%
▪Age	263.428	38.99%

Effects on OBJ value and decreases in the interindividual variability on TMED confirm these effects.

**eric.univ-lyon2.fr/~ricco/tanagra/fr/tanagra.html*
**** Clin Pharmacokinet 44(4) 417-418**

CONCLUSION

▪ Such pre-selection of statistical and clinical pertinent variables seems to be an interesting prerequisite to time to event modelisation under Weibull or Cox approaches. Such approaches are efficient for sparse and heterogenous datas like outliers of references in cancer treatment, and could improve determination of prognostic factors during data mining analysis, where number of covariates can be superior to number of patients and when potential correlation between covariates exist.