Comparison between NONMEM and NPAG to gemcitabine modelling

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Objectives

To valorate the differences between gemcitabine population pharmacokinetics parameters estimated by NONMEM (parametric method) and NPAG (Non-parametric method).

Patients and methods

A total of 512 gemcitabine samples were obtained from 49 cancer patients with solid tumors refractory to conventional treatment. They received a fixed dose rate of 10 mg/m^2/min of gemcitabine and high-dose of docetaxel (300-350 mg/m^2) using autologous stem cell transplantation. The patients were distributed in six cohorts with different times of infusion (9,12,15,18 and 20 h) and mean total dose of 10,008, 12,919, 15,990, 18,413 and 19,500 mg respectively. The samples were drawn at baseline, 30' and 3 h after the start of the infusion, 1 h and 30' before the end of the infusion, and 1h, 3h, 7 h and 14 h after the end of the infusion. Levels were assayed by HPLC.

The characteristics of patients are showed in table I. All patients gave written informed consent.

The gemcitabine concentrations were fitted to a monocompartmental model using two kinds of population kinetics programs: a parametric (NONMEM v5.0) and a non parametric program (NPAG from USCPack v.11.8. The differences between gemcitabine population pharmacokinetics parameters estimated by both methods were analyzed by Student's t-test with a statistically significant level of 0.05 using Statistica v6.8 (Stat Soft Corp.)

Table I. Characteristics of patients (n=49)

Age (mean± SD)	41.5±13.1
Weight (mean± SD)	69.7±14.5
Gender	
female	34
male	15
Diagnoses	
Breast cancer	30
Ewing's sarcoma	4
Germ-cell tumors	3
Hodgkin's disease	4
NHL	2
Others	6

Results

Table II. Gemcitabine population pharmacokinetics parameters

Parameter	NONMEM	NPAG	p
Ke (h^{-1})	3.30 ± 1.2	3.25 ±1.36	0.8258
V (L)	40.3 ± 6.3	48.2 ± 26.4	0.0215*
CL (Lh^{-1})	133 ± 23.7	132.4 ±85	0.9567

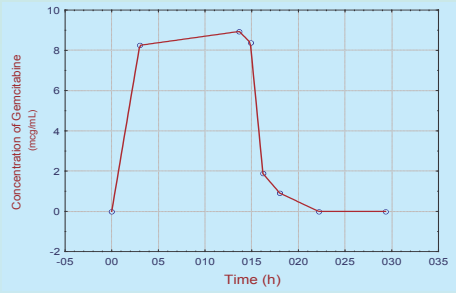

Figure 1. Concentration-time profile of mean Gemcitabine

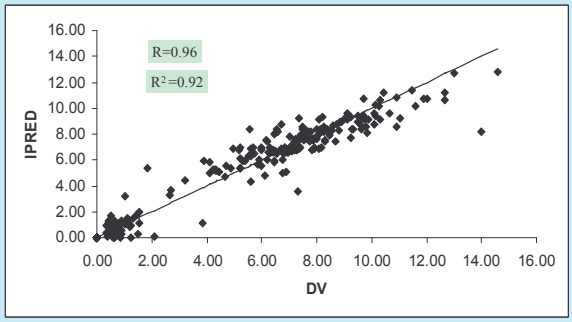

Figure 2. Observed vs Predicted concentrations estimated by NONMEM method

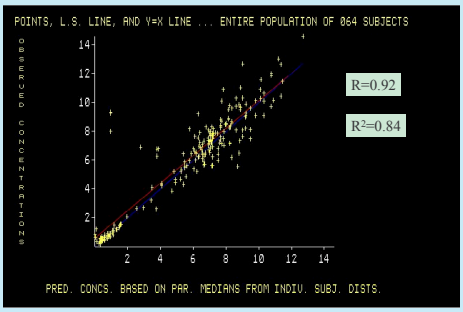

Figure 3. Observed vs Predicted concentrations estimated by NPAG method

Conclusions

With the exception of volume of distribution there aren't significant diferences between population pharmacokinetics parameters of gemcitabine estimated by NONMEM and NPAG.

The coefficient of variation for the parameters estimated by NPAG is greater than the obtained by NONMEM and for that reason the NPAG seems to be able to detect individuals that present a behaviour different to the mean population and because of this it could be more useful clinically.