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Pharmacokinetics of idelalisib and outcomes

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BACKGROUND and RATIONALE: The use of idelalisib, a PI-3 kinase delta inhibitor (PI3KI), is currently highly regulated by recommendations due to adverse effects. Yet, other PI3KIs could benefit from further development for the treatment of lymphoproliferative disorders. Limited information is available on the pharmacokinetics (PK) of idelalisib. This open, prospective, non-randomized study was carried over two years (registered at clinicaltrials as NCT02824159) in Toulouse University Hospital between April 2016 and April 2019. The study had planned a cohort of 57 patients, but, due to the safety alerts mentioned above, ultimately included 15 patients with CLL, 11 with FL and 1 with Waldenström macroglobulinemia (total n=27).

Patients and Methods

Over the first year of treatment, 169 AE were recorded in the 27 patients, 56 were clinically significant adverse events (CSAE: serious AE and/or CTCAE grade ≥3 and/or leading to dose concession) observed in 19 patients: gastro-intestinal (35%), hepatic (28%) or haematological (18%). Notably, very few AE were respiratory (2%).

At month 1 of treatment, a one-day PK study was performed, with plasma collection before idelalisib intake, then at 30 minutes, 1, 2, 4 and 6 hours for 26 patients. Plasma concentration was assessed using a validated (according to FDA and EMA guidelines) U-HPLC-MS/MS method (chromatography plus mass spectrometry as detector). The parameters measured were: i) Trough concentration(Ctrough); ii) maximal concentration (Cmax); and iii) area under the curve (AUC) reflecting drug exposure.

PK analyses results: No correlation with clinically significant AEs

Table 1. Pharmacokinetics of idelalisib after one month of treatment according to the occurrence of CSAE (Mean ± SD).

PK parameters	Whole cohort N=26	CSAE N=18	No CSAE N=8	P value
Ctrough ng/mL	1077 ± 416	1138 ± 475	939 ± 199	0.4
Cmax ng/mL	2886 ± 900	2820 ± 956	3033 ± 796	0.8
AUC ng*h/mL	13307 ± 5152	13652 ± 5697	12530 ± 3872	0.8

Ctrough : trough concentration resC; Cmax: maximal concentration; AUC (t ss): area under the curve

An important inter-individual variation was observed with mean (±SD) values of 1077±416 ng/mL for Ctrough, 2886±900 ng/mL for Cmax and 13307±5152 ng/mL for AUC. No difference in these parameters appeared to be associated with CSAE. Not shown: no difference observed in PK values between patients who responded to idelalisib therapy (n=17) and those who did not (n=8). However, considering the median AUC as cutoff, significant survivals differences were shown.

PK analyses results: Higher AUC correlates with shorter PFS and OS

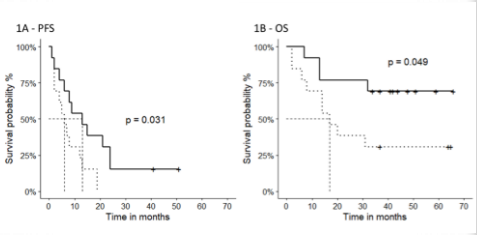

Figure 1. Survival curves (1A progression free survival; 1B overall) according to idelalisib pharmacokinetics (area under the curve, AUC) after one month of treatment, comparing patients with AUC below the median (solid line) to those with AUC equal to or above the median (dotted line). The dashed lines indicate the time to reach median survival (not reached for OS).

AUC and Survivals

The hazard ratio (HR) for progression-free survival (PFS) was 2.65 (95% confidence interval [CI] 1.08-6.52), yielding a statistically significant difference (p=0.031) in favour or AUC below the median (Figure 1A). The difference was also statistically significant for overall survival (OS, p=0.049) for the group with lower AUC values (Figure 1B), characterized by an HR of 3.09 (95% CI 0.94-10.1). It is worth noting that median OS was not reached (vs. 18 months) for the group of patients with better OS.

Conclusion: Using data from a PK study conducted in 27 patients undergoing idelalisib treatment, we showed that patients exhibiting lower exposure (with an area under the curve below the median) demonstrated significantly improved progression-free survival and also better overall survival. This suggests that tumour drug monitoring of PI3KIs could help to improve their efficacy and tolerance. It is of utmost importance that real-world PK analyses should be conducted for the brand new generation of PI3KIs