

HIGH DOSE METHOTREXATE : COVARIATES OF INTEREST TO ANTICIPATE

RESPONSE AND TOXICITIES

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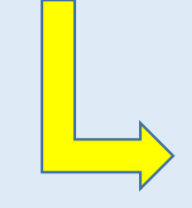
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INTRODUCTION

High-dose methotrexate (HDMTX) : **antimetabolite** that interferes with the metabolism of folic acid, inhibiting the **dihydrofolate reductase (DHFR)**.

Approximately **2 to 10%** of patients receiving HDMTX → suffer **Acute Kidney Injury**, despite appropriate supportive care measures during HDMTX administration.

Prolonged renal impairment → **systemic methotrexate exposure**



Potential myelosuppression and hepatotoxicity



CONTEXT / OBJECTIVES

Monocentric longitudinal study, data collected over **9 years**. Population: Only adult patients with a **hematological** indication were included.

Endpoints :

- Determine covariates that may **influence** patient **exposure** to HDMTX
- Identify covariates associated with **increased toxicities**

MATERIALS AND METHODS

Database → generated in Microsoft Office Excel by collecting datas using softwares available at APHM (Axigate, Pharma, Chimio...)

Data Treatment :

- 1) Datas in excel format (.xlsx) converted in .csv format to be analyzed with R software.
- 2) Script redacted in R with some covariates recoded
- 3) Script ok → exploratory data analysis



RESULTS / DISCUSSION

Characteristic	N = 152 ¹
Concentration 24h (µM)	5 (11)
Concentration 48h (µM)	0.44 (1.15)
Concentration 72h (µM)	0.23 (0.97)
Creatinine Clearance 24h (mL/min)	105 (45)
Creatinine Clearance 48h (mL/min)	109 (51)
Creatinine Clearance 72h (mL/min)	106 (62)
Dose (g)	4,821 (3,570)
Sex	
Male	82 / 148 (55%)
Female	66 / 148 (45%)
Age (years)	52 (16)
Weight (kg)	70 (18)
Height (cm)	169 (11)
BSA (m ²)	1.78 (0.21)
Prolonged anemia (>72h)	
Yes	12 / 151 (7.9%)
No	139 / 151 (92%)
Prolonged thrombopenia (>72h)	
Yes	41 / 151 (27%)
No	110 / 151 (73%)
Prolonged neutropenia (>72h)	
Yes	24 / 151 (16%)
No	127 / 151 (84%)
Anemia grade	
Grade < 2	63 / 152 (41%)
Grade ≥ 2	89 / 152 (59%)
Thrombopenia grade	
Grade < 2	139 / 152 (91%)
Grade ≥ 2	13 / 152 (8.6%)
Neutropenia grade	
Grade < 2	144 / 152 (95%)
Grade ≥ 2	8 / 152 (5.3%)

¹ Mean (SD); n / N (%)

Table 1 : Population characteristics

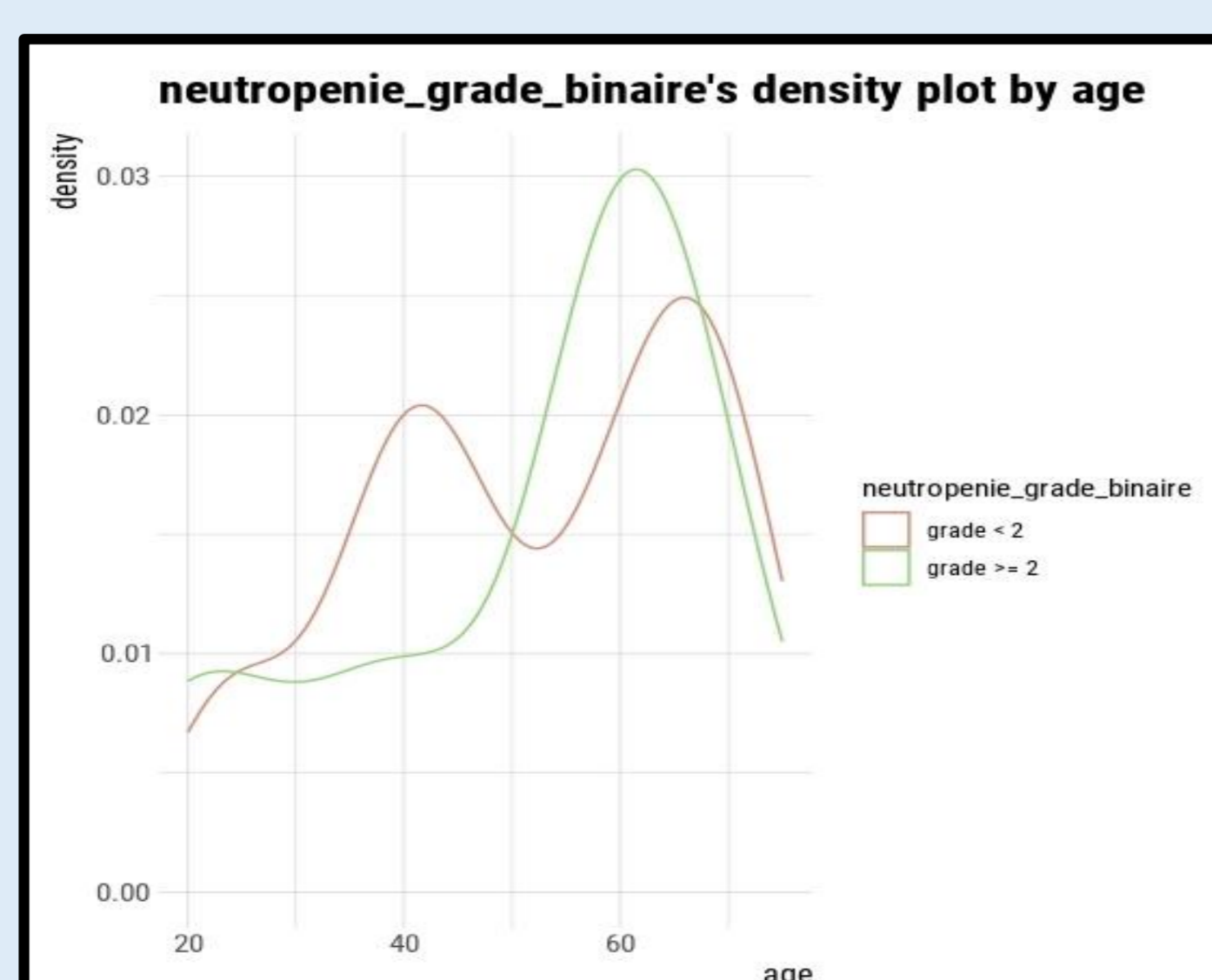


Figure 1 : Neutropenia density plot by age



Intra & inter individual variability PK

Characteristic	Prolonged Neutropenia (> 72h)		p-value ²
	0, N = 24 ¹	1, N = 127 ¹	
Concentration 24h (µM)	3 (1, 8)	1 (1, 2)	0.2
Concentration 48h (µM)	0.14 (0.10, 0.52)	0.16 (0.10, 0.28)	0.2
Concentration 72h (µM)	0.07 (0.05, 0.18)	0.07 (0.05, 0.12)	0.3
Creatinine Clearance 24h (mL/min)	86 (69, 104)	101 (82, 134)	0.014
Creatinine Clearance 48h (mL/min)	86 (60, 106)	109 (84, 134)	0.012
Creatinine Clearance 72h (mL/min)	96 (80, 110)	97 (69, 125)	0.3
Dose (g)	4,663 (2,488, 6,000)	4,825 (1,988, 5,913)	0.4
Sex			0.2
Male	15 (68%)	66 (53%)	
Female	7 (32%)	59 (47%)	
Age (years)	60 (52, 66)	49 (39, 66)	0.069
Weight (kg)	67 (58, 80)	69 (52, 81)	0.6
Height (cm)	172 (165, 176)	170 (162, 177)	0.7
BSA (m ²)	1.78 (1.64, 1.98)	1.84 (1.61, 1.99)	0.8

¹ Median (IQR); n (%)
² One-way analysis of means (not assuming equal variances); Pearson's Chi-squared test; Fisher's exact test

Table 2 : Covariates tested in the presence of prolonged neutropenia (>72h)

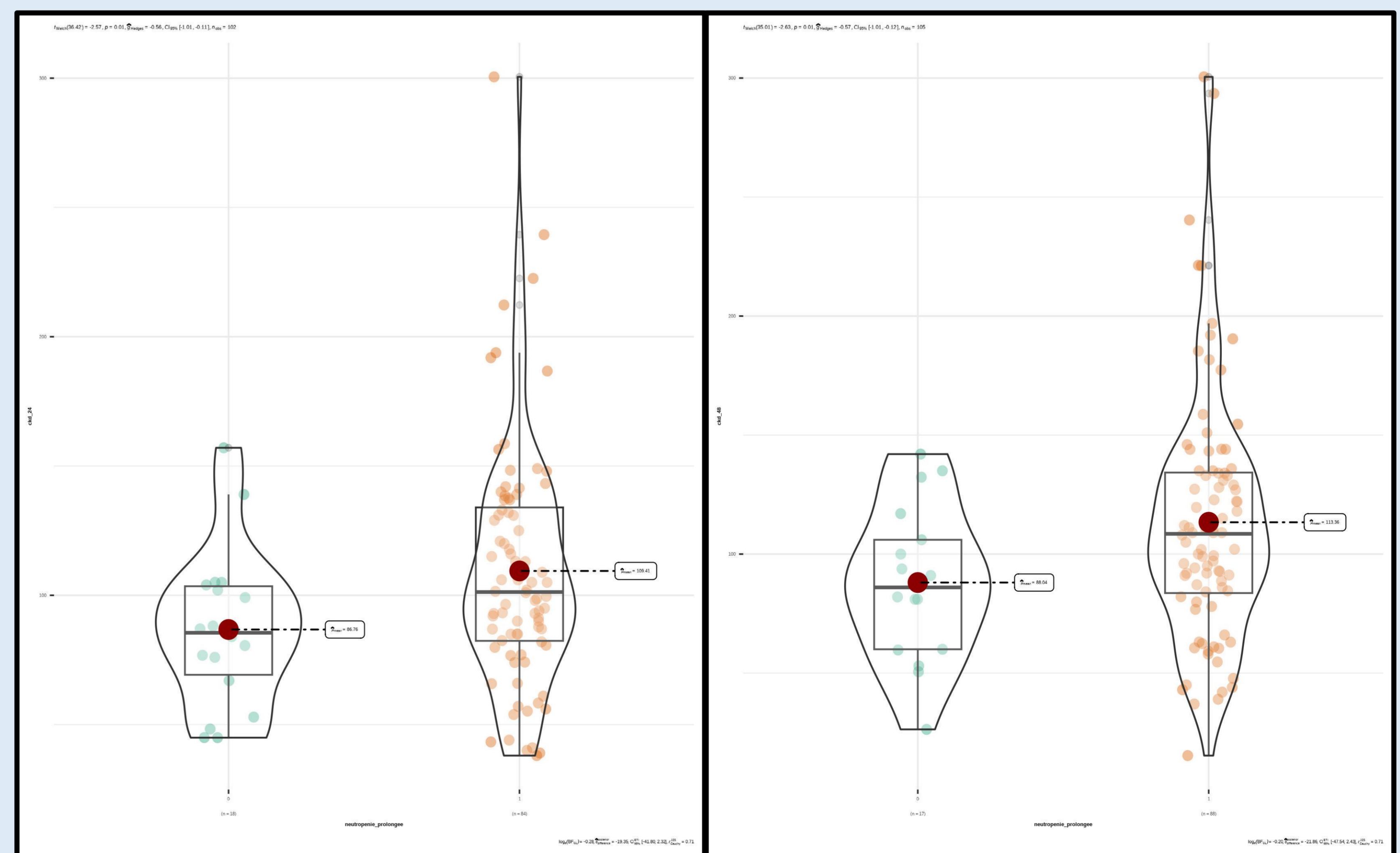


Figure 2 : Violin plots representing neutropenia density of probability with CrCl at 24h and 48h

CONCLUSION

The results show us many clues to know more about toxicities in patients receiving HDMTX. First, by analysing concentrations at 24h, 48h and 72h, we can see a large intra- and inter-individual variability in MTX pharmacokinetics. Then we decide to focus on neutropenia. With univariate tests, prolonged neutropenia (>72h) seems to be associated with creatinine clearance (CrCl) at 24h and 48h. Age also seems to be associated with the risk of developing prolonged neutropenia. Next step in our work is to determine whether the delayed elimination of methotrexate could affect CrCl and then induce further toxicities. Impact of exposure on response will be explored too.