Severe Fluoropyrimidines Toxicities: a simple and effective way to avoid them. Screen Effectively for DPD Deficiencies

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BACKGROUND

Severe, even fatal toxicities which occur during the first course of chemotherapy treatments using fluoropyrimidines pose a serious public health problem. This family of chemotherapy molecules is used in over 60% of protocols, in adjuvant and metastatic settings. Even protocols using orally-administered molecules cause the same toxicities.

PATIENTS

11,351 patients were screened for the risk of severe toxic reaction (April 2001-December 2011).
11,104 before treatment, 247 after toxicities (grade III-IV or death).
Chemotherapy protocols: FEC, LV5FU2, FOLFOX, FOLFIRI, Capecitabine, UFT.

METHODS

Toxicity risk evaluation combines genotyping (1) (24 mutations) by pyrosequencing (Qiagen, Paris, France) and phenotyping (UH_2/U ratio) (2). Multiparametric risk calculations (genotyping + phenotyping + physiological + physiopathological parameters) were done via ODPM Tox™ (ODPM, Angers, France). Patients deemed at risk before treatment received an individually-adapted dose via ODPM Protocol™ (ODPM, Angers, France).

RESULTS

► Results for the total population (11,351 patients) are presented in Figure 1 (A).

- 346 patients (3%) had one or more mutations.
- The most frequent mutation is the 2846 A>T (1.6%)

► Results for the population screened before treatment (11.104 patients) are shown in Figure 1 (B).

- % of patients with one or more mutations among the 24 sought is the same as in the general population (2.4%).
- The mutation most frequently found is the 2846 A>T (1.3%).
- 1 patient was a homozygote DPYD2A and one was doubly mutated.

Pre-treatment screening saved their lives.

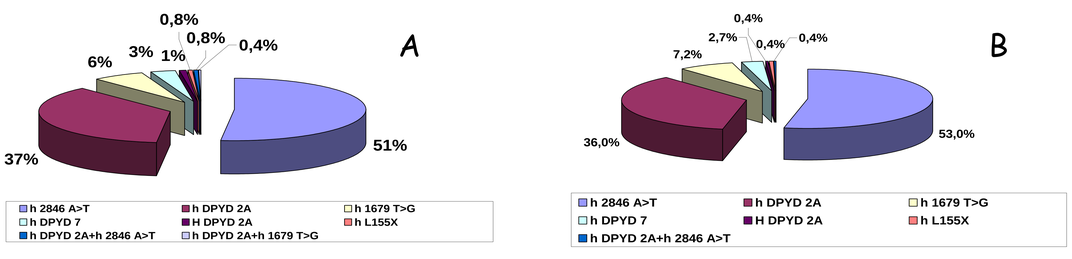

Figure 1: Mutation frequency in the total population (11,351 pts) (A) and in the population screened before treatment (11,104 pts) (B)

► Results for the patients screened after toxicities (247 patients)

- 27 patients (11%) died (5FU, Xeloda, UFT,…)
- 220 patients (89%) showed grade III-IV toxicities (diarrhea, febrile neutropenia, coma, multi-organ toxicity.

The distribution of mutations in this population is shown in Figure 2: Total population (A), Patients who died (27 patients) (B).

- 60% of patients who died had one or more mutations

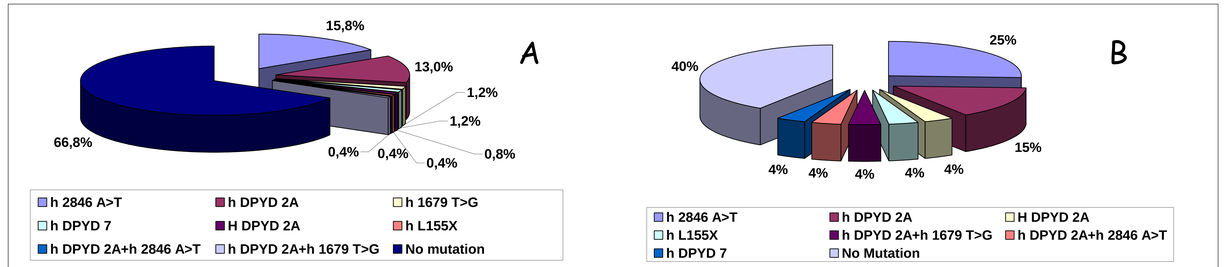

Figure 2: Mutation frequency: (A) Total population (247 pts), (B) Patients who died (27pts)

EFFECTIVE SCREENING FOR DPD DEFICIENCY

Patients N	One or plus mutations N (%)	Deficient phenotypic status* N (%)	Multiparametric approach (ODPM Tox™)* N (%)
247	82 (33%)	211 (85%)	242 (98%)
27	16 (59%)	24 (89%)	27 (100%)

*Deficient phenotypic status = UH_2/U
*Multiparametric approach (ODPMTox™) = genotyping + phenotyping + physiological + physiopathological characteristics

CONCLUSION

Multiparametric approach (ODPM Tox™) is the key to avoiding 100% of mortalities related to toxicities and 98% of severe toxicities. Neither genotyping nor phenotyping alone are sufficient predictors of early onset toxicity.
Currently 2,000 patients screened annually using this approach (ICO, France).
Clinical practice: 1 blood sample 10 days before starting treatment. Results in 8 days.
Even DPD deficient patients can be treated using pharmacokinetic monitoring and appropriate dose adjustment (ODPM Protocol™).

References

Morel et al., Mol Cancer Ther. 2006; Morel et al. Clin Biochem 2007
Boisdron Celle M et al. Cancer Lett. 2007; Patents : 0503616, O6290592.2