Clinical validity and utility of *DPYD* polymorphisms: the present and the future of pharmacogenetic tests

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Background

The fluoropyrimidine (FL) treatment is challenging as a result of a considerable inter-patient variability in terms of efficacy and toxicity.

Recently SIF-AIOM working group published pharmacogenetic (PGx) guidelines recommending a pre-emptive pharmacogenetic tests for *DPYD*-rs3918290, *DPYD*-rs67376798, and *DPYD*-rs55886062 to prevent FL-related toxicity.

However, despite the efforts of the scientific community to thrust the introduction of these tests in the everyday clinical practice for FL treatment personalization, clinicians only occasionally decide to rely on these clinical tools.

Consequently, the first aim of our study is to demonstrate the clinical validity of testing *DPYD* SNPs to predict FL-related severe toxicity in large group of cancer patients from the current clinical practice.

Moreover, in order to assess the clinical utility of the *DPYD* pharmacogenetic tests and how the test is able to significantly improve patient outcomes, a clinical PGx service has been started up.

Material and Methods

A set of 603 unselected patients treated with FL-based chemotherapeutic regimens for different primary tumors have been retrospectively tested for eight *DPYD* polymorphisms (*DPYD*-rs3918290, *DPYD*-rs55886062, *DPYD*-rs67376798, *DPYD*-rs2297595, *DPYD*-rs1801160, *DPYD*-rs1801158, *DPYD*-rs1801159 and *DPYD*-rs17376848) for association with grade ≥3 toxicity, developed within the first three cycles of therapy.

Based on the obtained data, the Experimental and Clinical Pharmacology Unit of CRO (Aviano) has set up a clinical PGx service accessible to Medical and Radiotherapy Oncology Units.

Results

Clinical validity

Among the 603 patients, 95 (15.7%) subjects developed severe toxicity (grade ≥3).

Eighteen patients (3.0%) carried at least one variant allele for any polymorphism and eleven out of these patients (61.1%) developed grade ≥3 toxicity. *DPYD*-rs3918290 and *DPYD*-rs67376798 were associated to grade ≥3 toxicity after bootstrap validation and Bonferroni correction (P=0.003,P=0.048). *DPYD*-rs55886062 was not significant likely due to its low allelic frequency, nonetheless one out of the two heterozygous patients (compound heterozygous with *DPYD*-rs3918290) died from toxicity after one cycle of treatment. Test specificity for the analysis of *DPYD*-rs3918290, *DPYD*-rs55886062, and *DPYD*-rs67376798 was assessed to 99%.

Clinical utility

Based on the data obtained from our retrospective study and SIF-AIOM guidelines, a PGx service has set up in our unit and, up to date, 239 cancer patients candidate to a therapy with FL were referred to this service prior to treatment.

Accordingly to genotype data for *DPYD*-rs3918290, *DPYD*-rs55886062, *DPYD*-rs67376798 a starting dose adjustment was suggested for 5 patients.

Conclusion

Our data strongly demonstrate the clinical validity of the *DPYD*-rs3918290, *DPYD*-rs55886062, *DPYD*-rs67376798 genotyping test to prevent fluoropyrimidines-related grade ≥3 toxicity and to preserve treatment compliance.

Based also on the successful experience of the PGx service, we planned to organize cost-effectiveness and HTA studies to assess the clinical utility of a pre-emptive PGx approach.