PROGRAM OF "ONCOVIGILANCE" EVALUATING THE INCIDENCE AND PREVALENCE OF ADR LINKED TO THE USE OF FLUOROPYRIMIDINES-BASED CHEMOTHERAPY

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Background and aim: Fluoropyrimidines such as 5-Fluorouracil (5-FU) and capecitabine (pro-drug of 5-FU) are among the most used drugs in the treatment of solid tumors. They are cytotoxic agents that belong to the class of antimetabolites. They are very effective but their use is associated with adverse drug reactions (ADRs) of various types and degrees of severity. In addition, patients show a large variable response in term of both efficacy and safety due to the presence of some polymorphisms influencing mainly the fluoropyrimidines' metabolism. The most common ADRs are hematologic (leukopenia, thrombocytopenia), gastro-intestinal (vomiting, constipation, diarrhea) and muco-cutaneous (hand-foot syndrome, mucositis) ADRs. At the Clinical Pharmacology and Pharmacogenetics Unit of the University Hospital "San Giovanni di Dio and Ruggi d'Aragona" of Salerno, we have planned a project of active pharmacovigilance called "oncovigilance". The aim of this project, currently underway, is: 1) to monitor the safety of the chemotherapeutic regimens including fluoropyrimidines (capecitabine-oxaliplatin, Xelox; 5-FU-oxaliplatin, FOLFOX; 5-FU- irinotecan, FOLFIRI) associated or not with other drugs such as gemcitabine, cetuximab, aflibercept or bevacizumab. 2) To evaluate the genotype of each patient with reference to four polymorphisms recommended to guide the treatment with fluoropyrimidines (DPYD*2A, *13, 2846A>T and 1236G>A/haplotype B3) and other in genes involved in both pharmacodynamics and pharmacokinetics of fluoropyrimidines, oxaliplatin (e.g. GSTP1A313G) and irinotecan (UGT1A1*28) to investigate the possible association between the ADRs and such genetic variants.

Methods: We have developed a database to record patients' demographic data, blood chemistry values (leukocyte and platelet count, hemoglobinemia, creatininemia, AST and ALT, total and direct bilirubin), the type and stage of cancer, chemotherapeutic regimens and possible concomitant therapies. Particular attention has been paid to record the ADRs and their grade (I-IV) in according to the CTCAE (Common Terminology Criteria for Adverse Events). The database was updated whenever patients came to the oncological DH to have the chemotherapy cycle.

Results: We reported preliminary results concerning 53patients (31patients out of 53were affected by colorectal cancer) naive to treatment with fluoropyrimidine-based chemotherapy, who performed at least 4cycles of chemotherapy. We assigned a grade from I to IV to ADRs. Regarding haematologic ADRs, nine patients experienced grade 1neutropenia, one grade 2and another one grade 3; Six of them experienced also thrombocytopenia (grade 1in four cases and grade 2in two case), and six patient experienced thrombocytopenia alone (grade 1in five cases and grade 2in one case). In 11cases these ADRs led to the postponement of the treatment and in three most severe cases growth factors were administered. Regarding gastrointestinal ADRs, we recorded nine patients with grade 1constipation and one with grade 2; eight patients with grade 1diarrhea and four with grade 2; four patient with grade 1vomiting and one with grade 2; moreover, in 1patient we verified a grade 2diarrhea in conjunction with a grade 2mucositis that led to a 15% dose reduction of the 5-FU. All four cases of grade 2diarrhea led to the postponement of the treatment. Regarding mucocoutaneous ADRs, twelve patients experienced grade 1mucositis and two grade 2; therteen patients experienced grade 1hand-foot syndrome and six grade 2.

Conclusion: To perform an "oncovigilance" study represents a good instrument to check the occurrence and severity of ADRs in the oncological patients. The data we are collecting are available to physicians and useful to monitor the patients for the entire duration of their therapy. The pharmacogenetics analysis now ongoing will allow us to investigate the possible association between the ADRs and the aforementioned genetic variants.