Kantonsspital St.Gallen

Fluoropyrimidine chemotherapy: recommendations for DPYD genotyping and therapeutic drug monitoring of the Swiss Group of Pharmacogenomics and Personalised Therapy

Seid Hamzic,Stefan Aebi,Markus Joerger,Michael Montemurro,Marc Ansari,Ursula Amstutz & Carlo Largiadèr

Fluoropyrimidines (FPs), mainly 5-fluorouracil (5-FU) and its oral prodrug capecitabine (Cap), remain the backbone of the treatment of many different solid tumors. Despite their broad use in clinical routine, 10–40% of patients experience severe, and in rare cases (0.2–0.5%) even lethal, FP-related toxicity in early chemotherapy cycles. Today, there is a plethora of evidence that genetic variants in the gene encoding for the 5-FU catabolising enzyme dihydropyrimidine dehydrogenase (DPD, encoded by DPYD) are predictive of severe FP-related toxicities, and international clinical practice recommendations for DPYD genotype-guided FP dosing and therapeutic drug monitoring (TDM) are available. In spite of this strong evidence and DPYD genotyping becoming standard practice in other countries, it is has not been widely adopted in Switzerland to date. Here, we discuss current guidelines on genotype-guided FP dosing and TDM, and propose recommendations tailored to the situation in Switzerland to facilitate their clinical uptake for the further individualisation of FP chemotherapy. We recommend preemptive testing of four DPYD variants (c.1905+1G>A (rs3918290), c.1679T>G (rs55886062), c.2846A>T (rs67376798) and c.1129-5923C>G (rs75017182, c.1236G>A/HapB3)) in patients with an indication for FP-based chemotherapy, with the costs reimbursed through the compulsory health insurance in Switzerland. Carriers of these variants (6.5% in the Swiss population) have a 40–50% risk of developing severe early-onset toxicity when treated with standard FP doses. In these patients, we therefore recommend the use of a reduced starting dose, based on a dose adjustment scheme provided herein. Furthermore, we recommend the use of infusional 5-FU in patients with a DPYD risk genotype in order to enable TDM-based dose escalation. Only if the use of an infusional 5-FU regimen is not feasible should a slow titration of Cap, starting with the recommended reduced dose and basing further doses on monitoring of toxicity, be considered. Given that several studies have shown that TDM in 5-FU treatment improves not only the therapy's safety, but potentially also its efficacy, we also include detailed TDM-based dosing guidelines and discuss the pre-analytical aspects of 5-FU TDM.

Kantonsspital St.Gallen

type	journal paper/review (English)
date of publishing	24-11-2020
journal title	Swiss Med Wkly (150)
ISSN electronic	1424-3997
pages	w20375