Genetic polymorphisms as a stratification factor that contributes to identify patients at high risk of developing Anthracycline-induced cardiomyopathy

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Anthracyclines (ANT) represent a class of cytotoxic agents widely used in the treatment of a broad spectrum of malignancies. The use of ANT, however, is limited by the onset of cardiotoxicity (CTOX), that is usually cumulative and dose-dependent[1]; however there are numerous reports of CTOX after administration of doses below those considered 'safe', and even after a single dose of ANT. The occurrence of these unexpected episodes has led to investigate the possible role of the patient genetic profile. In the present study, we attempted to find an association between single nucleotide polymorphisms (SNPs) variants in genes involved in the ANT pharmacology and the risk of CTOX.

Based on published literature[2,3], we identified 3 putative genes involved in CTOX: UGT1A6[4], that encodes the hepatic UDP-glucuronsyltransferase enzyme; SLC28A3[5], a concentrative nucleoside transporter, that plays an important role in mediating the cellular entry of a broad array of physiological nucleosides and anticancer nucleoside analogs and ABCB4[6], an ATP-binding cassette transporter, involved in the multidrug resistance phenomenon and localized as well at the canalicular membrane of hepatocytes.

The study was approved by the Local Ethics Committee. Consecutive patients diagnosed with breast cancer, scheduled fordrug therapy that includes ANT, were included in the study, after the written informed consent was obtained. Before ANT treatment, a comprehensive clinicalevaluation and theechocardiographic assessment were performed. Plasma level of cardiac Troponin I (cTnI) was measured at baseline, 1 week after each chemotherapy and every 3 months during the follow up, using the LOCI method on a Dimension Vista system (Siemens Healthcare Diagnostic). Any cTnI value exceeding 45 pg/mL was considered elevated. Genomic DNAwas extracted from blood using QIAamp DNA purification system (QIAGEN, Milano, Italy). DNA samples were genotyped for single-nucleotide polymorphisms (SNPs) by TaqMan®SNP genotyping assay (Life Technologies, Monza MB, Italy), which was designed to detect variants of a single nucleic acid sequence, without quantifying the target. SNP analyses of the chosen genes(2 SNPs for each: the UGT1A6 glucuronidase and the transporters SLC28A3 and ABCB4) were conducted using ViiATM Software (Applied Biosystem, Streetsville, Ontario, Canada).

Only pts who completed 6 months follow-up were considered (n=87; mean age 51.7±11.7y; 15% with more than 3 CV risk factors). During treatment, 10 pts (group 1) showed an increase in cTnI, while in 77 pts (group 2) cTnI concentration remained undetectable. Comparison between the two groups revealed that, although using the Wilcoxon Two-Sample Test, differences do not reach the statistical significance, group 1 pts presented a younger age: 45.3±11.8 vs 52.5±11.5y (p=.09) and a higher basal heart rate (84.6±14.9 vs 76.6±12.6bpm; p=.07). Interestingly, SNP analysis of the chosen genes showed that only 2 pts of group 1 (20%) are homozygous for the protective allele in at least 3 SNPs, while 20 pts of group 2 (26%) are homozygous for the protective allele in more than 3 SNPs (p=.007).

Present results, although limited by the low patient number, allow to design a working hypothesis to identify the risk level to develop CTOX in patients undergoing ANT chemotherapy. The existence of genetic variants at risk and their inclusion in predictive models, together with a clinical, echocardiographic and neurohumoral evaluation, may allow to customize the ANT-based protocols, to limit the incidence of cardiotoxicity.

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