A case of QT prolongation during therapy with tamoxifen and trastuzumab: pharmacogenetic analysis to clarify the occurred event

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Introduction

Tamoxifen (TAM), the standard in adjuvant therapy for pre-menopausal women with hormone-sensitive breast cancer, is a pro-drug metabolised into more active 4-hydroxytamoxifen (4OHT) and endoxifen mainly by CYP2D6, CYP3A4/5, while UDP glucuronosyltransferases (UGTs) 2B7 and 1A1 play a role in inactivation of TAM and its metabolites.
Some polymorphisms in these CYPs genes affect the corresponding enzymes; 5-10% of Caucasian are poor metabolisers for CYP2D6 while polymorphims on CYP3A4/5 genes lead to intermediate or poor enzyme activity in 72% or 8% of Caucasian, respectively. Among UGTs genes, UGT2B7*2 variant allele results in 2 and 5-fold decreases of activity against 4OHT and endoxifen, respectively, as compared to UGT2B7*1 reference allele and, UGT1A1*28 is associated to reduced enzyme activity.
We describe a case of QT prolongation in a woman treated with standard doses of TAM and co-treated with trastuzumab. Since QT prolongation is reported in TAM summary of product characteristics as a side effect in overdose, her pharmacogenetic profile was investigated.

Case report

A 42 year old woman with HER-2 positive breast cancer received radiotherapy and adjuvant chemotherapy with no significant side effects. Echocardiograms (ECGs) before and at the end of chemotherapy showed a normal QT corrected for hearth rate (QTc= 0.46 seconds (s)). Sequential to chemotherapy, adjuvant trastuzumab and TAM were started. Because of a mild hypertension and some extrasystoles, an additional ECG performed showed a QT prolongation (QTc= 0.53s), ventricular extrasystoles, and no specific ST alterations. On the basis of evidence of correlation between QT prolongation and TAM, the drug was withdrawn, hypertension controlled with ramipril and a beta-blocker added for extrasystoles. Another ECG showed a reduction of the QT interval (QTc= 0.48s) however it never returned to the pre-TAM values. After completion of trastuzumab therapy, TAM was reintroduced and a further QT prolongation (QTc= 0.52s) was noted. TAM was definitively withdrawn and the patient started letrozole and LHRH analogue with QT interval slightly over the upper normal value (QTc= 0.48s).
Pharmacogenetic analysis of the well known functional genetic variants associated to altered TAM metabolism was performed. The patient was found to carry the CYP2D6*4 null allele and UGT2B7*2 defective allele in heterozygousity, and the CYP3A5*3 and UGT1A1*28 in an homozygous status. Phenotypes resulting by this analysis correspond to an intermediate metaboliser for CYP2D6 and CYP3A and a poor metaboliser for, UGT2B7 and UGT1A1.

Discussion

We describe the case of a patient that showed a prolongation of the QTc, during a therapy with tamoxifen associated to trastuzumab. Our analysis, showing defective alleles in many genes involved in the metabolic pathway of TAM, supports the possibility of an accumulation of this drug and its more active metabolites leading to an event occurring in cases of overdose. Moreover, this is the first report describing TAM adverse effects due to the UGT1A1*28 allele. Two case of QT prolongation hypothesized increased TAM plasma levels after administration of therapeutic doses, however no pharmacogenetic nor pharmacokinetic tests were performed. Our results are consistent with recent findings showing high doses of TAM and 4OHT alter myocytes cardiac contractility and $Ca2^{+}$ handling; moreover an excessive inhibition by tamoxifen on cardiac human ether-a-go-go-related gene (HERG) potassium channels can lead to acquired long QT syndrome. Finally, we cannot exclude an additive effect between TAM and trastuzumab that is known to induce cardiotoxicity.

Conclusion

This observation should be further confirmed in additional studies, but the possibility of QT prolongation in patients receiving these drugs should be already taken into account, to be monitored by periodic ECGs.