ToxNav® germline genetic testing and PROMinet digital mobile application toxicity monitoring: Results of a prospective single centre clinical utility study – PRECISE

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Introduction

5-fluorouracil (5-FU) and its oral pro-drug capecitabine are the most commonly prescribed chemotherapeutic agents for treating colorectal cancer (CRC). A significant proportion (20-30%) of patients treated with these drugs develop severe side-effects [1,2], often resulting from inborn deficiencies of enzymes or drug transporters used by the body for drug break down and deactivation [1,3]. Germline polymorphisms in one such enzyme, Dihydropyrimidine dehydrogenase (DPYD), results in reduced enzyme activity, toxic metabolite accumulation and subsequent toxicity which in severe cases can lead to hospital admission and/or toxic death [4,5].

In addition, patient reported chemotherapy toxicity data is often highly variable leading to poor chemotherapy toxicity recognition by clinicians [6,7].Therefore, in the PRECISE study, we assess the clinical utility of a germline DNA sequencing-based test (ToxNav) for mutations in DPYD and ENOSF1 genes to alter clinician prescribed fluoropyrimidine doses and use of a digital application (PROMinet) to accurately record patient reported chemotherapy toxicity.

Methods

Adult patients with a histological diagnosis of CRC who consented to fluoropyrimidine-based chemotherapy and genetic testing were recruited prospectively and given a digital application to monitor and record associated toxicities.

Table 1: Risk classification criteria to fluoropyrimidine - based toxicities based on patient ToxNav test result.

Risk	Risk Criteria
Standard	No copies of DPYD deficiency or HFS-associated alleles.
Standard with high HFS risk	No copies of DPYD deficiency alleles but one or more HFS-associated alleles.
High	One copy of a DPYD deficiency allele.
Critical	Homozygous for one or heterozygous for two DPYD deficiency alleles.

DNA was extracted from whole blood samples collected from each patient, and subsequently analysed for 18 germline coding variants in DPYD and 1 ENOSF1 variant. A risk report result based on the known penetrance of DPYD/ENOFS1 variance to chemotherapy toxicity was made available to the treating physician designating them into one of four categories (Table 1).

A risk report result based on the known penetrance of DPYD/ENOFS1 variance to patient reported toxicity was monitored through the use of the PROMinet digital mobile app, developed by Oxford Medical Intelligence. The app functions through a daily questionnaire of toxicity data as the patient proceeds through chemotherapy. App responses were averaged across treatment for each patient for each week and across the 12 week monitoring period.

Results

ToxNav germline genetic testing was performed for 60 patients and risk classification in Table 1 followed. Uptake of genetic testing was high and results were available on average 17 days from initial clinical encounter. One patient was identified with high-risk variant A551T (DPYD Exon 13). Variants were frequently found in the ENOSF1 (rs2612091) and DPYD intronic regions, rs7548189 and rs12132152 (Table 2) [5]. One patient received a ToxNav test that suggested predisposition to a high risk of 5-FU-based chemotherapy toxicity. This patient had their initial chemotherapy dose reduced to 80% and subsequently experienced minimal/mild side-effects.

ToxNav also identifies patients at potential risk of developing “hand-foot reactions/syndrome” (HFS). To assess utility, ToxNav HFS risk scores were compared to digital mobile app responses for HFS. For patients classified as “high risk HFS”, there was a trend for app-recorded HFS severity to be higher during weeks 1 and 2 of the app monitoring period, though this did not reach statistical significance ($p > 0.05$).

PROMinet app responses for 13 symptom toxicities were also compared with clinician-determined patient toxicity severity. Patient reported data for “tiredness” was positively correlated with clinician graded toxicity (clinician reported “severe” vs. “moderate” or “mild”, $p<0.05$ for both). Analysis of app responses was also performed for patients receiving either CAPOX/single agent CAP (n=27), or FOLFOX/FOLFIRI (n=6). The incidences of hand-foot reactions and sore mouth were higher in patients receiving CAPOX/CAP ($P<0.01$ for both) whereas constipation was lower ($P<0.001$) (Figure 1).

Table 2: Germline variants analysed and frequencies observed using the ToxNav test.

Variant	Gene	Allele count	Allele freq %	Patient freq %
rs12132152	DPYD Intronic	4	3.39	6.78
rs7548189	DPYD Intronic	15	12.71	23.73
A551T	DPYD Exon 13	1	0.85	1.69
rs2612091	TYMS/ENOSF1	54	45.76	66.10

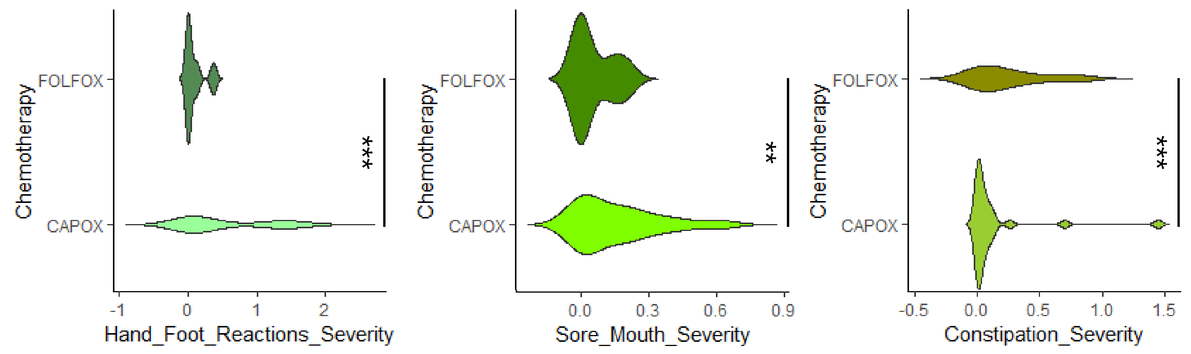

Figure 1: Toxicity severity for patients receiving oral capecitabine vs. intravenous 5-fluorouracil chemotherapy. Hand foot reactions and sore mouth were significantly more severe for CAPOX/CAP whereas constipation was less severe. *** p <0.001, ** p<0.01.

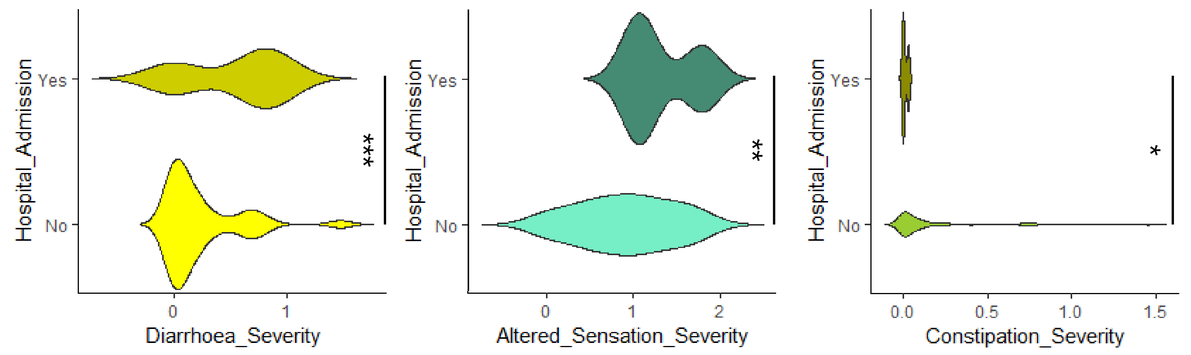

Figure 2: Toxicity severity for patients requiring a hospital admission vs. those that did not. Diarrhoea was significantly more severe in patients admitted to hospital whereas constipation and sore mouth were less severe. *** p <0.001, ** p<0.01, * p<0.05.

Patients with severe toxicities often require chemotherapy dose reduction and/or acute hospital admission. We therefore analysed app toxicity profiles for patients requiring dose reduction and/or admitted to hospital. “Hand-foot reaction” was inversely correlated with subsequent need for dose reduction whereas “vomiting” and “diarrhoea” were higher ($P<0.05$ for all). In addition, the severity of “diarrhoea” and “altered hand foot sensation” were significantly elevated in patients requiring hospitalisation, with lower scores for “constipation” and “sore mouth” (Figure 2).

Conclusions

The ToxNav germline DNA sequencing-based test has the ability to provide clinically relevant information to assist or affect clinician treatment decision-making in patients receiving 5-FU-based chemotherapy, such as altering the initial prescribed 5-FU dose. A novel digital mobile application (PROMinet) for recording patient reported toxicity successfully obtained a high volume of patient toxicity data with high granularity which in turn might allow the improvement and personalisation of chemotherapy management.

The accurate pharmacogenomic prediction and monitoring of severe toxicity and toxic deaths among chemotherapy-receiving patients has the potential to reduce morbidity and mortality. In the PRECISE clinical utility study, we demonstrate that a genomic ToxNav test with concurrent monitoring using the PROMinet app provides potentially useful information to treating physicians and warrants further larger scale studies.

References: **1:** Froehlich, T. K. et al. Clinical importance of risk variants in the dihydropyrimidine dehydrogenase gene for the prediction of early-onset fluoropyrimidine toxicity. Int. J. Cancer 136, (2014). **2:** Lee, A. M. et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). J. Natl. Cancer Inst. 106, (2014). **3:** Amstutz, U. et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin. Pharmacol. Ther. 103, (2018). **4:** Latchman, J. et al. 5-Fluorouracil Toxicity and Dihydropyrimidine Dehydrogenase Enzyme: Implications for Practice Case Study HHS Public Access. Clin J Oncol Nurs 18, (2014). **5:** Rosmarin, D. et al. Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: investigation in the QUASAR2 study, systematic review, and meta-analysis. J. Clin. Oncol. 32, (2014). **6:** Richardson, A. et al. The experience of fatigue and other symptoms in patients receiving chemotherapy. Eur. J. Cancer Care (Engl). 5, (1996). **7:** Pearce, A. et al. Incidence and severity of self-reported chemotherapy side effects in routine care: A prospective cohort study. PLoS One 12, e0184360 (2017).

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