Individual dose adaptation of capecitabine for reduction of severe hand-and-foot syndrome

Inès PAULE, Michel TOD, Brigitte TRANCHAND, Gilles FREYER, Emilie HENIN, Pascal GIRARD
EA3738 Ciblage Thérapeutique en Oncologie, Faculté de Médecine Lyon Sud, Université Claude Bernard - Lyon 1
ines.paule@recherche.univ-lyon1.fr

Introduction:
Capecitabine, an oral prodrug of 5-fluorouracil (5FU), used to treat metastatic or advanced colorectal cancer, is equivalently effective and better tolerated than reference intravenous treatment by an association of 5FU and leucovorin (5FU/LV), except for the hand-and-foot syndrome (HFS), which occurs in 54% patients taking capecitabine, compared to 6% of those taking 5FU/LV. This dermatotoxicity affects the palms and soles as redness, numbness and even desquamation, pain and loss of function in severe cases. Standard dose adaptation consists in dose reduction by 25% or by 50 % according to the frequency and severity of previous toxicity. This crude adaptation might by suboptimal and an individualized dose adaptation, based on all available and pertinent patient's information, combined in an appropriate longitudinal model, might allow a better control of toxicity and thus improve the therapeutic benefit.

Objectives:
To set up the methodology for individual dose adaptation on the basis of ordinal observations and evaluate its feasibility and performances, as compared to the standard approach, by randomized *in silico* clinical trials.

Methods:
Individual prediction-based dose adjustment schemes for capecitabine were derived on the basis of a longitudinal HFS toxicity model previously developed in [1]. This mixed effects transitional and proportional odds model for longitudinal ordinal data links taken doses, basal creatinine clearance and previous toxicity to the risk of (the highest) HFS grade of the week. The population model is reajusted for the particular patient before each new cycle by estimating the random (individual) effects of the model, on the basis of pertinent patient's data (taken doses, toxicity and renal function), using Bayesian techniques. The individualized model is then used to predict the risk of severe toxicity in 2 weeks and calculate the dose for the next cycle.
Proof-of-concept is given by an *in silico* clinical trial, comparing the standard and model-based adaptations in 2 x 10,000 virtual patients during 30 weeks of treatment.

Results:
The proof-of-concept simulation showed that model-based adaptation would result in reduction of severe toxicity incidence by 13% and of its average duration by 1.6 weeks (12 days), as compared to the routine adaptation. Continuous monitoring of individual toxicity risk showed to be especially beneficial for allowing earlier detection of the patients at high risk of severe toxicity and suggesting another therapy for them.

Conclusion:
Individualized dose adaptation on the basis of ordinal observations, using the developed methodology, showed to be feasible and beneficial. *In silico* results indicate that in the case of hand-and-foot syndrome induced by capecitabine, severe toxicity incidence may be reduced by 13% and its mean duration by 12 days. Moreover, estimation of individual toxicity risk showed to be especially beneficial for allowing early detection of patients intolerant to capecitabine and therefore better determination of the optimal moment to switch to another treatment.
There are several limitations to this work. Firstly, judgement of adaptation strategies is limited because impact on anti-cancer efficacy and other toxicities could not be evaluated. It should be considered that individual adaptation leads to 18% reduction of drug exposure as compared to the standard adaptation. The second restriction of this dose adaptation is related to the model which seems to assume inertia of HFS toxicity. This may be due to cumulative nature of the drug or model producing some bias for toxicity recovery. Nevertheless, this work shows that individual dose adaptation of oral anticancer drugs, performed on the basis of ordered categorical data, should be beneficial and feasible in clinical routine.

Reference:
[1] Hénin E et al. PAGE 2006; abstract No 929. http://www.page-meeting.org/?abstract=929