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DPD deficiency: Medico-economic evaluation of pre-treatment screening of 5-FU toxicity

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Purpose

The objective of this study was to assess the cost-effectiveness of a dihydropyrimidine dehydrogenase (DPD) deficiency screening test, combining 2 complementary assays, genotyping and phenotyping, before fluoropyrimidine administration.

Introduction

5-FU remains the back bone of most chemotherapy regimens in digestive cancers. Though, it can provoke severe, even lethal, toxic side effects. The frequency of treatment-related deaths with the standard protocols of 5-FU is between **0.3%** and **1.2%** and frequency of WHO grade III-IV toxicities is between **25%** and **30%**. Furthermore, these toxicities mobilize significant resources. DPD, the 5-FU key metabolic enzyme is submitted to a genetic polymorphism. Acute and early 5-FU toxicity is mostly due to DPD deficiency. We developed a screening test with the objective to assess DPD activity and detect metabolic deficiency. Our aim was to provide a pretherapeutic detection of 5-FU metabolic deficiency and to individually adapt 5-FU dosing ($5\text{-FU}^{\text{ODPM, Tox + Protocol}}$, ODPM, France). This test consists of a comprehensive approach coupling DPD genotyping and phenotyping (didrouracil/uracil : UH_2/U). On the one hand, this screening helps to prevent severe toxicities and their related costs. On the other hand, by itself, it is an additional cost to the treatment.

Methods

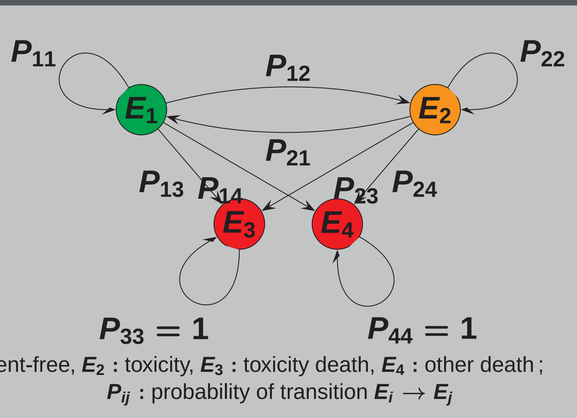
Patients and medico-economic design

- Retrospective data from a population of patients treated for colorectal cancer :
  1. Arm A standard protocol (2400 mg/m^2) : no screening test n=886 patients
  2. Arm B $5\text{-FU}^{\text{ODPM Protocol}}$: with screening $5\text{-FU}^{\text{ODPM Tox}}$ test n=856 patients
- Cost-effectiveness study
- The main point of view was society perspective
- The time horizon was 2 cycles of chemotherapy

Model and outcomes

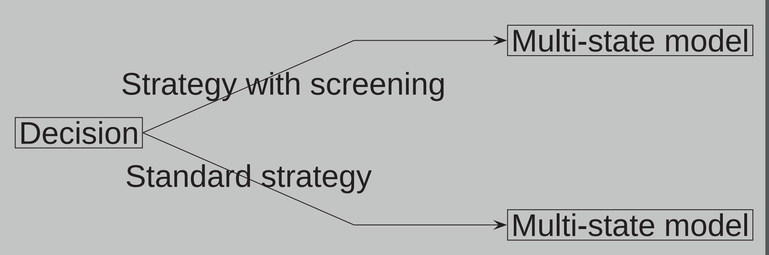
- **A multi-state Markov-type model** was used to estimate the mean cost and effectiveness for each of the two strategies.
- **Costs** :
  - Cost of the standard strategy $COST_{\text{Standard}} = COST_{\text{treatment of toxicities}}$
  - Cost of the screening strategy $COST_{\text{With Screening}} = COST_{\text{screening test}} + COST_{\text{treatment of toxicities}}$
- **Effectivenesses** were cumulative prevalences of no toxicity : E_{Standard} and $E_{\text{With Screening}}$
- **Incremental cost-effectiveness ratio (ICER)** :

$$ICER = \frac{\left(COST_{\text{Standard}} - COST_{\text{With Screening}}\right)}{\left(E_{\text{Standard}} - E_{\text{With Screening}}\right)}$$



E_1 : event-free, E_2 : toxicity, E_3 : toxicity death, E_4 : other death ;
P_{ij} : probability of transition $E_i \rightarrow E_j$

The Decision Tree :



Statistical method & Probabilistic analysis

- Summary statistics for outcomes (costs, prevalences and ICER)
- Non-parametric bootstrap for outcomes : 5,000 iterations
- 95% Confidence Interval for costs, prevalences and ICER

Results

Costs

	Screening strategy	Standard strategy
Cost of screening test	153€	0€
Cost of treatment	X€	X€
Cost of toxicities TN	42€	508€
Total	195€	508€

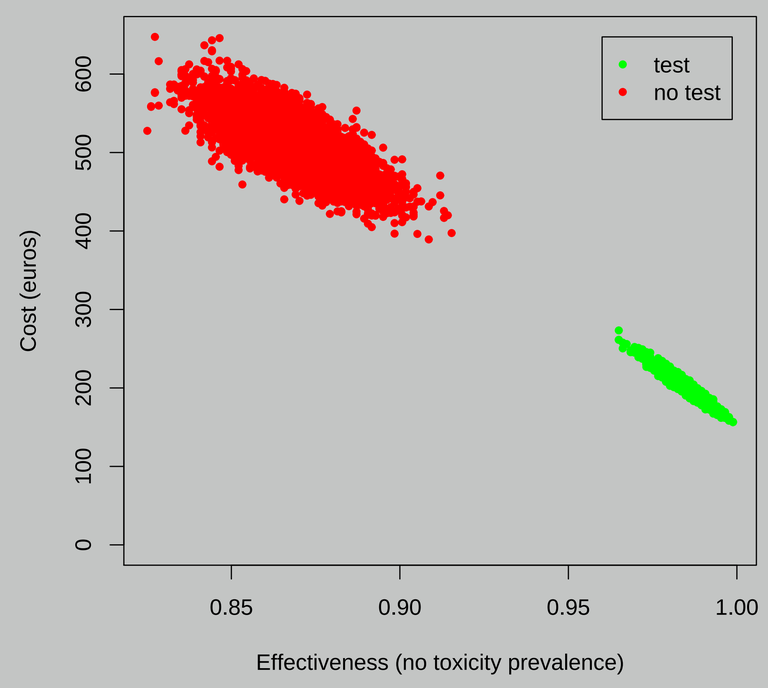
Effectiveness

Cycle 1	99.5%	94.2%
Cycle 2	99.1%	93.1%
Cumulative prevalences prevalences	98.6%	87.3%

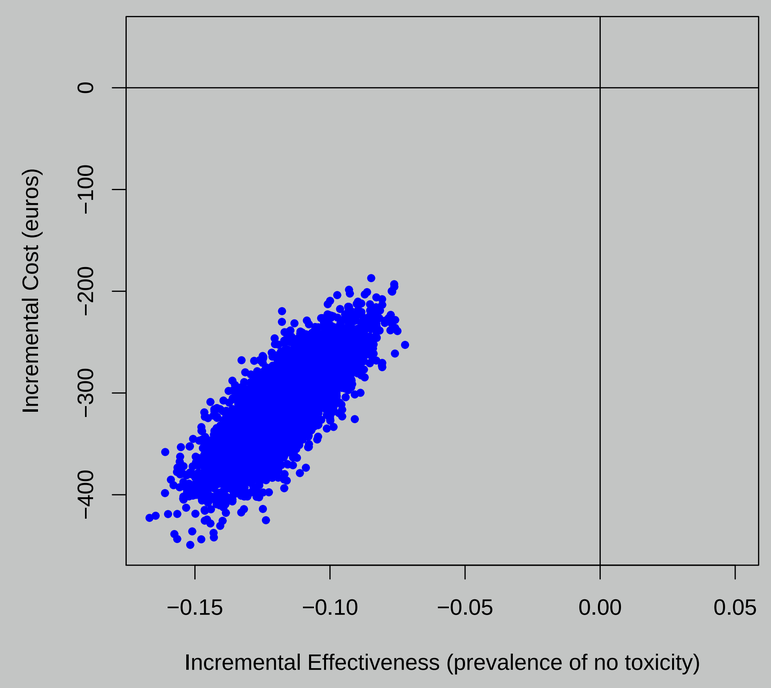
ICER

Incremental Cost	-313€
Incremental Effectiveness	-11.30%
ICER	2770€/toxicity

(a) Cost-effectiveness scartterplot



(b) ΔCost and ΔEffectiveness distributions



		Cost (€)	Effectiveness (%)	Incremental Effectiveness%	Incremental Cost (€)	ICER (€/toxicity)
Standard strategy	mean	509	13.08			
	CI	(508 ;510)	(13.04 ;13.11)			
Screening strategy	mean	196	1.38	-11.69	313	2680
	CI	(195.5 ;196.5)	(1.37 ;1.39)	(-11.73 ;-11.65)	(312 ;314)	(2674 ;2686)

CI : 95% confidence interval for mean value

Conclusions

Pre-treatment screening test ($5\text{-FU}^{\text{ODPM, Tox + Protocol}}$, ODPM) combining DPD genotyping and phenotyping reduced 5-FU-induced severe toxicities and prevented induced deaths. Its cost was lower than that of toxicity medical care that it prevented, even when not taking in account other related costs (death...). It should be recommended before 5-FU administration.

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