Toxicity with 5-fluorouracil and irinotecan: interest of genotyping in patient care

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Background

5-fluorouracile (5FU):

- Metabolize by dihydropyrimidine dehydrogenase (DPD)
- Enzymatic deficit's prevalence: incomplete for 3 to 8%, complete for 0.01 to 0.5%
- Toxicity: diarrhea, neutropenia (grade 3-4 adverse events (AE) rate increased in case of deficit)

Irinotecan:

- Metabolize by uridine diphosphate glucuronosyl-transferase 1A's (UGT1A)
- Deficit's prevalence: 15% of caucasians (homozygote for the allele UGT1A1*28)
- Toxicity: diarrhea, neutropenia, hepatotoxicity.

Despite overdoses, **side effects** and **new French recommendations**, this **preventive genetic research** is not realize systematically before begin a chemotherapy by 5FU and/or irinotecan. When one of these deficits exists, patients require **chemotherapy's dosage adjustment** in order to limit hematological and/or digestive toxicities.

Objectives

Highlight **medico-economic interest** of the **genetic screening for DPD and/or UGT1A deficits** before the initiation of chemotherapy with 5FU and/or irinotecan in order to **optimize patients' therapeutic care**.

Material & methods

- Patients of one oncologist screened between January 2015 and April 2018 (40 months).
- Data extracted: diagnosis, cancer status, prospective or retrospective screenings, screening results, type of AE, dose reductions, shifts of chemotherapy treatments, hospitalizations for AE and their costs.

Results

- 132 treated by 5FU, 2 treated by irinotecan, 176 treated by both drugs
- 20% prospective, 80% retrospective screening
- 5 DPD's deficit, 21 UGT1A's deficit, 5 combined deficit
- 18 176 € for all screenings done → cost will be decreased by more than 36% with a new externalized process

310 patients treated

51 genotyping screenings (356 €/screening)

31 positive screenings

18 toxicities

9 injections postponed

5 hospitalizations

4 toxicities observed despite a prospective screening + 14 toxicities observed before a retrospective screening

- 1 septic syndrome
- 5 gastrointestinal toxicities - 4 diarrhea, - 1 occlusive syndrome
- 12 hematological toxicities - 4 aplasia, - 7 neutropenia, - 2 thrombopenia

	Cancer status	Chemotherapy protocol	Screening	Deficit(s)	AE related	Hospitalization's length	Cost per hospitalization
Woman: 55 yo	Colon, adjuvant	FOLFOX	Retrospective	DPD + UGT1A	Septic syndrome	5	1 524 €
Man: 81 yo	Stomach, metastatic	Irinotecan alone	Retrospective	UGT1A	Febrile aplasia + diarrhea	4	5 331 €
Man: 64 yo	Colon, adjuvant	LV5FU	Retrospective	DPD + UGT1A	Febrile neutropenia	3	1 592 €
Man: 69 yo	Colon, metastatic	Avastin FOLFIRI	Retrospective	UGT1A	Aplasia + occlusive syndrome	6	6 011 €
Man: 69 yo	Colon, adjuvant	FOLFIRI	Prospective	UGT1A	Diarrhea	12	2 812 €

14 458€ of potential cost saving

Discussion/conclusion

Since December 2018, French health authority updates recommendations. It advocates a **systematic phenotyping screening** by a **dosage of uracil** for a chemotherapy with 5FU because knowledge about genotypic variant is insufficient and its use irrelevant. About UGT1A, more searches are needed to improve therapeutic care.

AE and their potential gravities have to lead oncologists to **systematically detect DPD and UGT1A deficiencies** in order to choose an **individualize' and an optimize' posology**. In oncology, to care better, all patient' characteristics (genetic, physiologic, psychologic and social) must be taken into account to target a **personalized medicine focus on patient**.