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

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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 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.

Background

**5-fluorouracil (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 1As (UGT1A)
- Deficit’s prevalence: 15% of caucasians (homozygote for the allele UGT1A*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

4 toxicities observed despite a prospective screening

14 toxicities observed before a retrospective screening

5 gastrointestinal toxicities
- 4 diarrhea, - 1 occlusive syndrome

12 hematological toxicities
- 4 aplasia, - 7 neutropenia, - 2 thrombopenia

5 hospitals

310 patients treated

51 genotyping screenings (356 €/screening)

31 positive screenings

18 toxicities

9 injections postponed

14,458€ of potential cost saving

<table>
<thead>
<tr>
<th>Cancer status</th>
<th>Chemotherapy protocol</th>
<th>Screening</th>
<th>Deficit(s)</th>
<th>AE related</th>
<th>Hospitalization’s length</th>
<th>Cost per hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woman: 55 yo</td>
<td>Colon, adjuvant</td>
<td>FOLFOX</td>
<td>Retrospective</td>
<td>DPD + UGT1A</td>
<td>Septic syndrome</td>
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<tr>
<td>Man: 81 yo</td>
<td>Stomach, metastatic</td>
<td>Irinotecan alone</td>
<td>Retrospective</td>
<td>UGT1A</td>
<td>Febrile aplasia + diarrhea</td>
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<tr>
<td>Man: 64 yo</td>
<td>Colon, adjuvant</td>
<td>LV5FU</td>
<td>Retrospective</td>
<td>DPD + UGT1A</td>
<td>Febrile neutropenia</td>
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<tr>
<td>Man: 69 yo</td>
<td>Colon, metastatic</td>
<td>Avastin FOLFIRI</td>
<td>Retrospective</td>
<td>UGT1A</td>
<td>Aplasia + occlusive syndrome</td>
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<tr>
<td>Man: 69 yo</td>
<td>Colon, adjuvant</td>
<td>FOLFIRI</td>
<td>Prospective</td>
<td>UGT1A</td>
<td>Diarrhea</td>
<td>12</td>
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