Prevention of 5-FU-induced health-threatening toxicity by pretherapeutic DPD deficiency screening. Medical and economic assessment of a multiparametric approach.

Boisdron-Celle, M.1; Capitain, O.2; Faroux, R.3; Borg, C.4; Metges, J.P.5; Galais, M.P.6; Kaassis, M.7; Bennouna, J.8; Bouhier-Leperrier, K.9; Francois, E.10; Baumgartner, I.11; Guerin-Meyer, V.12; Cojocarasu, O.1; Roemer-Becuwe, C.14; Stampfli, C.15; Rosenfeld, L.16; Lecomte, T.17; Berger, V.18; Campion L.19; Morel, A.1; Gamelin, E.20


Background:

5-FU is the backbone of most chemotherapy regimens in GI oncology. Patients with DPD deficiency can experience early highly severe (5%) even fatal (0.2%) toxic side-effects. Recently, Boisdron-Celle et al.9 demonstrated that a multiparametric approach (5-FU±ODPM™, Angers, France) is the key to avoid 100% of deaths related to toxicities and 98% of severe toxicities in a group of 11,351 patients. Neither genotyping nor phenotyping alone are sufficient predictors of early-onset toxicity. Our purpose is to confirm the medical and economic interest of pretherapeutic screening of DPD deficiency by the same multiparametric approach in a multicenter prospective cohort study (Eudrac t n°2008-000026-39).

Methods:

Two parallel cohorts (Arm A and Arm B) of patients treated with 5-FU-based chemotherapy for colorectal carcinoma were compared. Enrollment in either group was based on 5-FU administration guidelines of each institution.

The DPD deficiency screening was accomplished using a comprehensive approach including genotyping (DPYD) and phenotyping (ratio UHβJ/UF). This multiparametric risk calculation (genotyping + phenotyping + physiological + physio-pathological parameters) was done using the solution 5-FU±ODPM™ (ODPM, Angers, France). The first aim of this study was to compare the 2 arms in terms of early 5-FU-induced toxicity grade, whereas the secondary aim was an economic evaluation of the related costs of the severe toxicities versus the cost of DPD screening.

Results:

1130 patients were included from to 09/01/2008 to 07/31/2012. All patients were screened for DPD deficiency (Table 1), prospectively (Arm A) or retrospectively (Arm B). Clinical data were available for 1077 patients (Table 2).

Table 1: screening for DPD deficiency

<table>
<thead>
<tr>
<th>Arm</th>
<th>DPD screening</th>
<th>N. of patients</th>
<th>Partial deficiency (%)</th>
<th>Complete deficiency (%)</th>
<th>5-FU induced toxic death</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>yes</td>
<td>720</td>
<td>17 (2.4%)</td>
<td>1 (0.14%)</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>no</td>
<td>410</td>
<td>Ongoing evaluation</td>
<td>1 (0.25%) retrospective confirmation</td>
<td>1 (0.25%)</td>
</tr>
</tbody>
</table>

Table 2: Clinical characteristics of patients

<table>
<thead>
<tr>
<th>Arm</th>
<th>N. of patients</th>
<th>Age – years (range)</th>
<th>Adjuvant chemotherapy</th>
<th>Toxicity Grade 2±, cycles 1-3**</th>
<th>Toxicity Grade 5, cycles 1-3**</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>692</td>
<td>64,7±11.1 (24-88)</td>
<td>356 (51%)</td>
<td>690 (99.7%)</td>
<td>692 (100%)</td>
</tr>
<tr>
<td>B</td>
<td>385</td>
<td>63,6±10.9 (24-88)</td>
<td>195 (51%)</td>
<td>379 (98.4%)</td>
<td>384 (99.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>0.105</td>
</tr>
</tbody>
</table>

* The completely deficient patient was treated without 5-FU avoiding the toxic death. ** Arm A patients found to be partially deficient had treatments adapted with 5-FU±ODPM Protocol™.

Conclusion:

One complete deficiency occurred in both groups: arm A patient had safe treatment whereas arm B patient died due to 5-FU-related toxic death.

Pre-therapeutic DPD deficiency detection (5-FU±ODPM™) represents a SIMPLE and EFFECTIVE way to avoid severe toxicity and death due to toxicity.

The enrollment was prematurely closed for ethical reasons after unanimous experts’ decision (5-FU-induced proven toxic death).

In this study, we confirmed the data previously presented by Traoré et al.9 regarding the micro-economic evaluation of pretreatment DPD deficiency screening demonstrating that the per-patient cost of the test was lower (196€ – 261$) than that of toxicity medical care following severe toxicity (509€ - 678$).

NOTES:

Arm A

** DDP screening: Among the 720 patients included in this group, we have found 17 patients with partial DPD deficiency and 1 with complete deficiency.

** 5-FU treatment: for each of the 17 partially deficient patients the 5-FU dosages were continually adapted using the PK-monitoring solution, 5-FU±ODPM Protocol™ (ODPM, Angers, France). The only patient with complete deficient treatment was replaced by replacing 5-FU with another TS inhibitor.

** Clinical data: Only 2 (0.28%) patients showed severe toxicity (grade 3-4). No Grade 5 toxicities were evidenced. The only completely deficient patient did not show toxicity, because he was not treated with 5-FU, after having been screened.

Arm B

** DDP screening: Among the 410 patients included in this group, 1 patient died due to 5-FU early-onset toxicity, and was retrospectively confirmed to be completely DPD deficient.

** 5-FU treatment: all patients were treated with 5-FU based protocol.

** Clinical data: 6 (1.56%) patients showed severe toxicity (grade 3). Only one Grade 5 toxicity occurred in the completely DPD deficient patient treated with adjuvant FOLFOX 4. He developed a 5-FU-induced SAE on day 6 including febrile neutropenia G4, septicemia, diarrhea, mucositis and secondary dehydration, renal failure, then death. 5-FU imputable Grade 5 SAE was declared by the investigator.

This patient, complete DPD deficient, developed a lethal 5-FU induced toxicity.

In this study, we confirmed the data previously presented by Traoré et al.9 regarding the micro-economic evaluation of pretreatment DPD deficiency screening demonstrating that the per-patient cost of the test was lower (196€ – 261$) than that of toxicity medical care following severe toxicity (509€ - 678$).

The enrollment was prematurely closed for ethical reasons after unanimous experts’ decision (5-FU-induced proven toxic death).