Tercera Reunión Anual del grupo:

Grupo de Farmacia Oncológica de la SEFH

sefh
Sociedad Española
de Farmacia Hospitalaria

fefh
Fundación Española
de Farmacia Hospitalaria

ATENCIÓN FARMACÉUTICA
AL PACIENTE
ONCOHEMATOLÓGICO

GENOTIPADO DE LA DPyD y UGT EN CCR

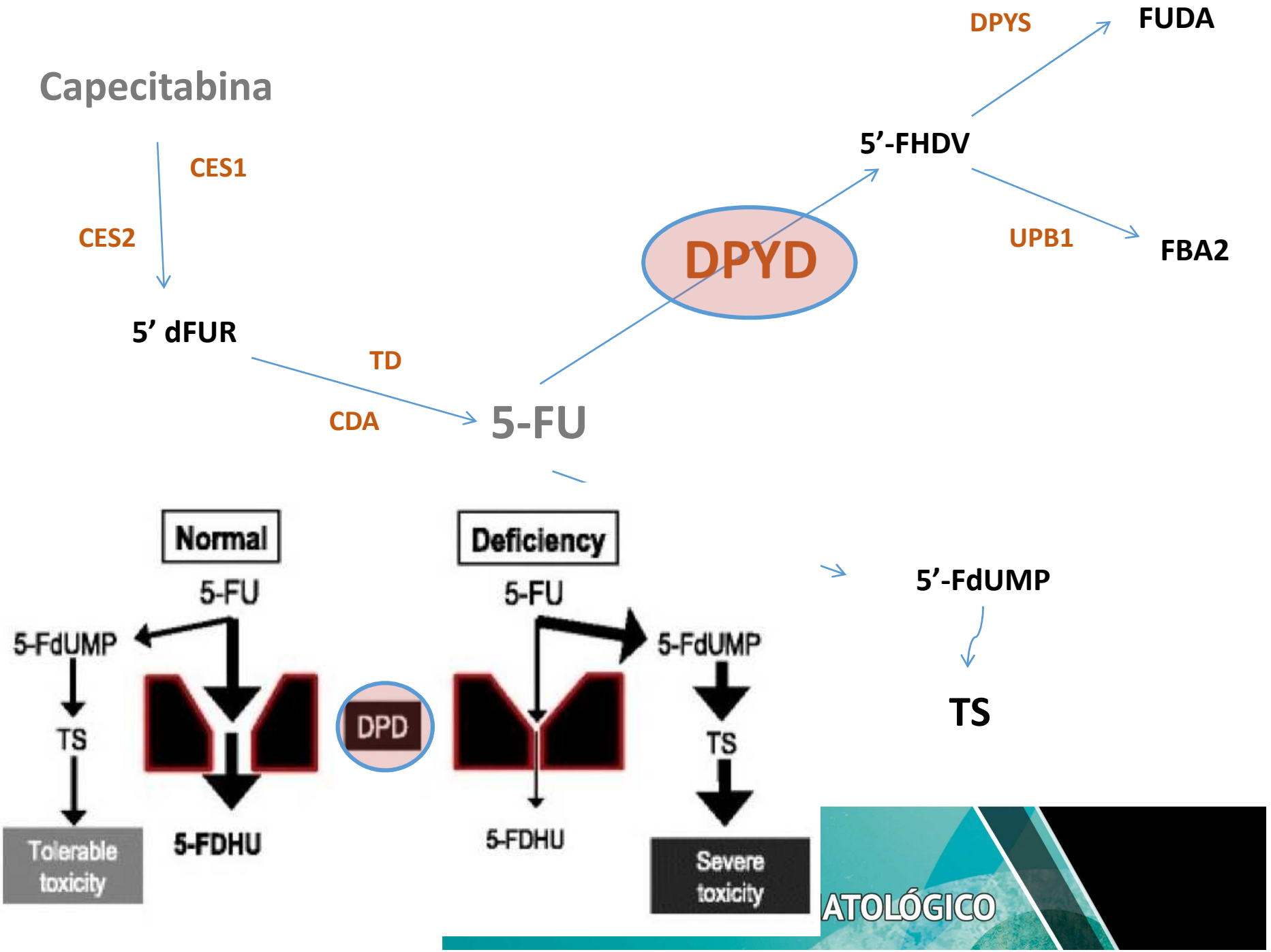
Fernando Gutiérrez Nicolás

Papel las fluoropiridimidinas en el tratamiento del CCR

Tercera Reunión Anual del grupo:

GEDEFO

Grupo de Farmacia Oncológica de la SEFH


Capecitabina
CES1
CES2
5' dFUR
TD
CDA
5-FU
DPYD
5'-FHDV
DPYS
FUDA
UPB1
FBA2
5'-FdUMP
TS
Normal
5-FU
5-FdUMP
TS
Tolerable toxicity
5-FDHU
DPD
Deficiency
5-FU
5-FdUMP
TS
Severe toxicity
5-FDHU
ATOLÓGICO

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[564,565] Irinotecan is inactivated by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which is also involved in converting substrates such as bilirubin into more soluble forms through conjugation with certain glycosyl groups. Deficiencies in UGT1A1 can be caused by certain genetic polymorphisms and can result in conditions associated with accumulation of unconjugated hyperbilirubinemias, such as types I and II of the Crigler-Najjar and Gilbert syndromes. Thus, irinotecan should be used with caution and at a decreased dose in patients with Gilbert syndrome or elevated serum bilirubin. Similarly, certain genetic polymorphisms in the gene encoding for UGT1A1 can result in a decreased level of glucuronidation of the active metabolite of irinotecan, resulting in an accumulation of the drug and increased risk for toxicity,[565-567] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[567] Results from a dose-finding and pharmacokinetic study suggest that dosing of irinotecan should be individualized based on UGT1A1 genotype.[568] The maximum tolerated dose of intravenous irinotecan every 3 weeks was 850 mg, 700 mg, and 400 mg in patients with the *1/*1, *1/*/28, and *28/*28 genotypes, respectively.

NCCN National Comprehensive Cancer Network®

practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[567] although guidelines for use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on patients who experience irinotecan toxicity is not recommended, because they will require a dose reduction regardless of the UGT1A1 test result.

4.3 Contraindicaciones

- Antecedentes de reacciones graves e inesperadas al tratamiento con fluoropirimidinas,
- Hipersensibilidad a capecitabina, a alguno de los excipientes incluidos en la sección 6.1 o a fluorouracilo,
- En pacientes con probada deficiencia de dihidropirimidina dehidrogenasa (DPD) (ver sección 4.4),
- Durante el embarazo y la lactancia,
- En pacientes con leucopenia, neutropenia o trombocitopenia graves,
- En pacientes con insuficiencia hepática grave,
- En pacientes con insuficiencia renal grave (aclaramiento de creatinina por debajo de 30 ml/min),
- Tratamiento con sorivudina o sus análogos químicamente relacionados, tal como la brivudina (ver sección 4.5),
- Si existen contraindicaciones a cualquiera de los medicamentos del régimen combinado, no se

La dihidropirimidina deshidrogenasa (DPD) desempeña un papel importante en el metabolismo del fluorouracilo. Ha habido informes de mayor toxicidad del fluorouracilo en pacientes con actividad reducida/deficiencia de DPD. Si procede, está indicada la determinación de la actividad de la enzima DPD antes del tratamiento con 5-fluoropirimidinas.

Association francophone de défense des victimes du 5-FU et analogues présentant un déficit en DPD

Chaque année en France, 200 patients* atteints d'un cancer meurent, non pas à cause de leur maladie, mais à cause d'un médicament anticancéreux, le 5-Fluorouracile (5-FU), qui s'est avéré toxique pour eux car ils présentaient un déficit enzymatique, le déficit en DPD (Dihydropyrimidine déshydrogénase).**

Un test à partir d'une simple prise de sang pré-thérapeutique pourrait éviter ces drames ; malheureusement c'est la roulette russe, car tous les oncologues ne le font pas.

Pour que les choses changent, des parents de victimes françaises et québécoises se sont regroupés au sein de l'**ASSOCIATION FRANCOPHONE DE DÉFENSE DES VICTIMES DU 5-FU ET ANALOGUES PRÉSENTANT UN DÉFICIT EN DPD.**

---

* Il est impossible de connaitre le chiffre exact à cause du secret médical et des médecins qui ne déclarent pas les causes réels des décès ou "oublient" de faire les signalements aux centres de pharmacovigilance.

** JFHOD mars 2016

Casos cercanos

250 nuevos casos al año

4-6 ingresos/año **1/año**

¿Por qué no?

Por una cuestión de farmacoeconomía

Should DPD analysis be required prior to prescribing fluoropyrimidines?

*Jane L. Yen, Howard L. McLeod**

mains the best solution for improving patient outcomes. Still, with the currently available clinical laboratory assays, it is not yet possible to screen cancer patients with a high level of predictive accuracy. However, as an understanding of the molecular basis of 5FU-related toxicity continues to improve, and the techniques for assessing DPD deficiency are further refined, there is hope that screening will become practicable in the future.

0,8-1,9%

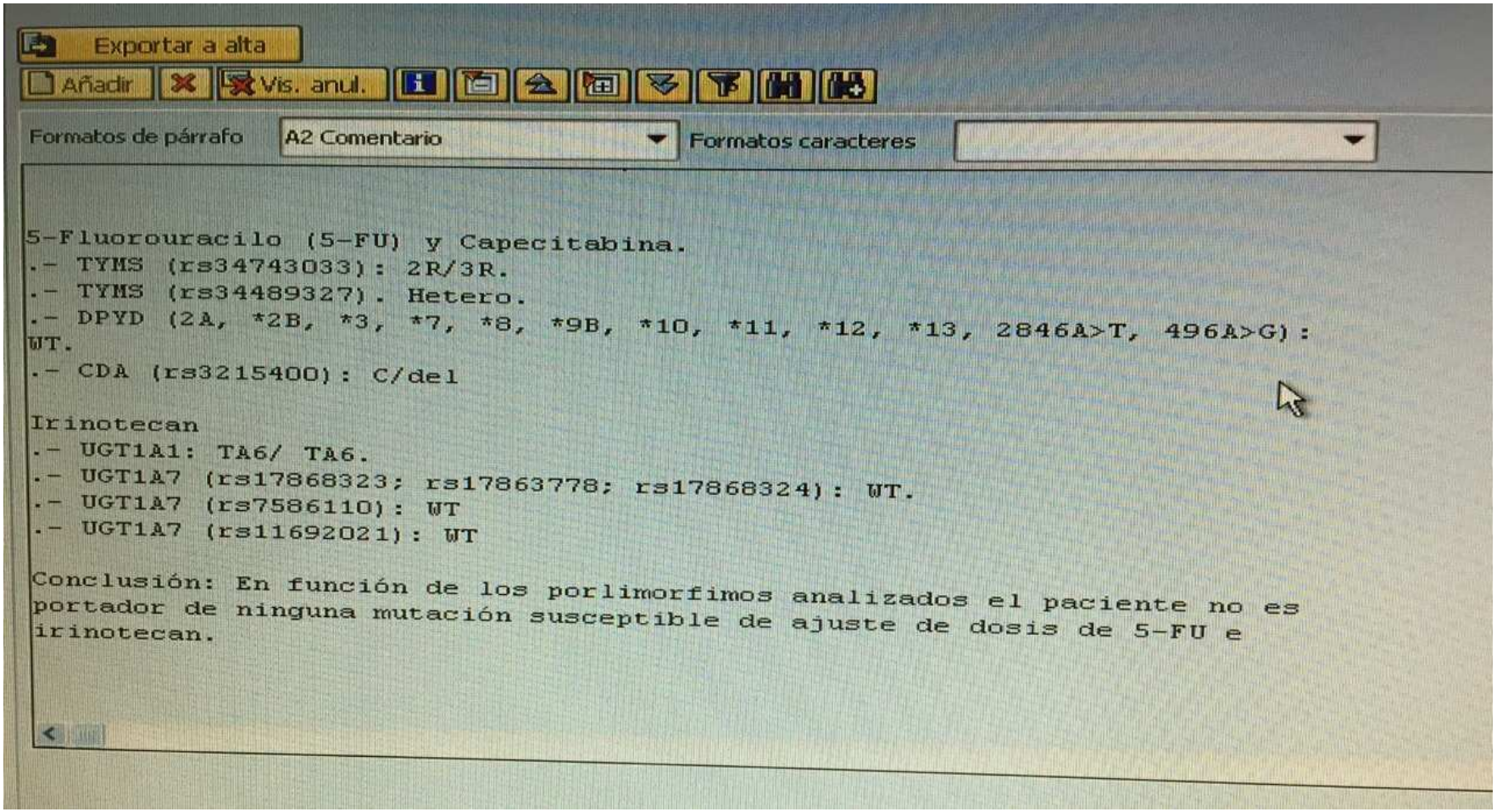
¿Por qué si?

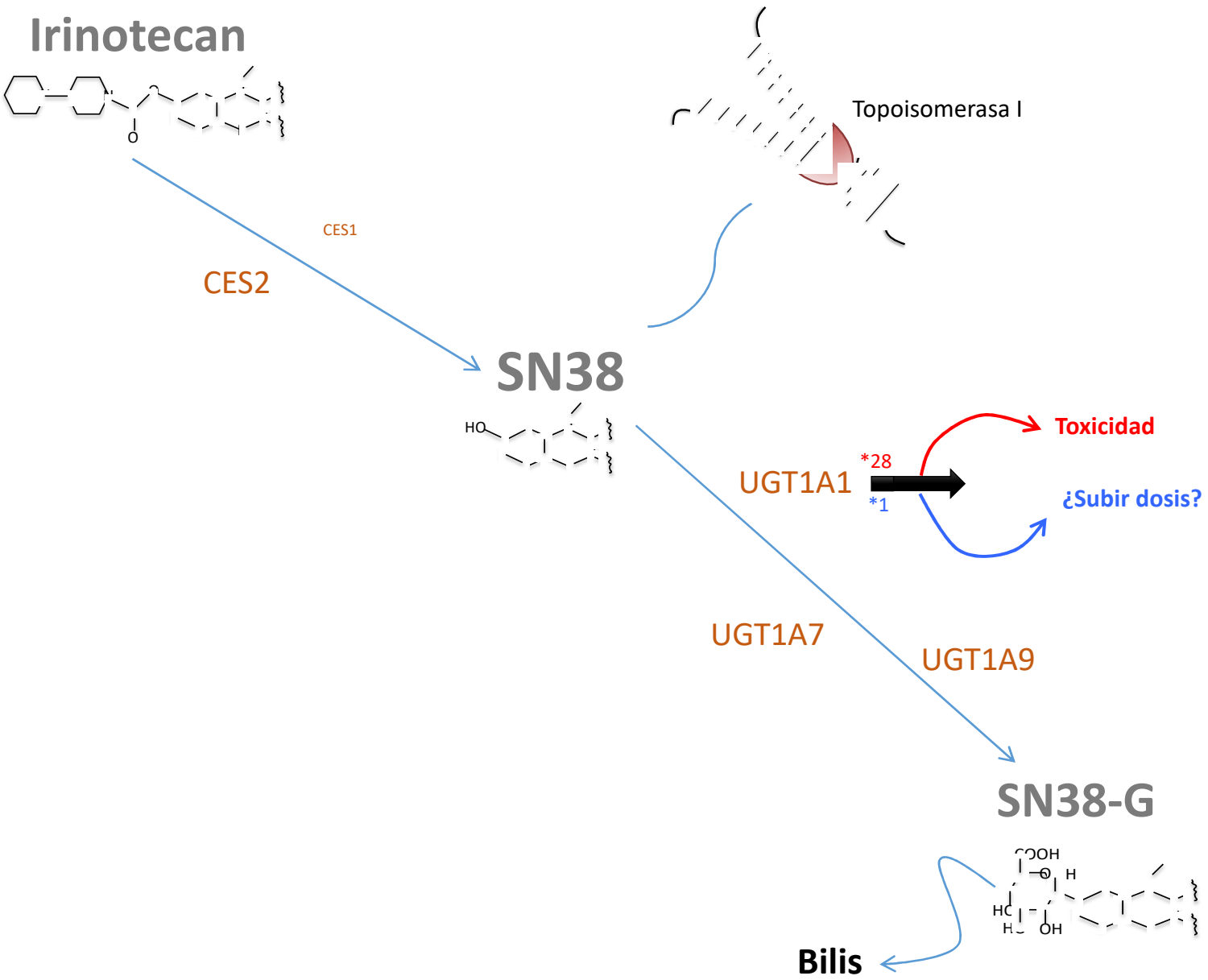
DPYD genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: call for a drug label update

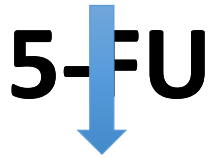
Table 1. Initial dose recommendations for heterozygous *DPYD* variant allele carriers [ ]

***DPYD* variant**	**% of standard fluoropyrimidine dose[a]**
*DPYD**2A (rs3918290)	50
c.1679T>G (rs55886062)	50
c.2846A>T (rs67376798)	75
c.1236G>A/HapB3 (rs56038477)	75

[a]For patients with complete DPD deficiency (for example homozygous *DPYD* variant allele carriers) selection of alternative treatment is recommended.


Exportar a alta
Añadir
Vis. anul.
Formatos de párrafo
A2 Comentario
Formatos caracteres
5-Fluorouracilo (5-FU) y Capecitabina.
.- TYMS (rs34743033): 2R/3R.
.- TYMS (rs34489327). Hetero.
.- DPYD (2A, *2B, *3, *7, *8, *9B, *10, *11, *12, *13, 2846A>T, 496A>G):
WT.
.- CDA (rs3215400): C/del
Irinotecan
.- UGT1A1: TA6/ TA6.
.- UGT1A7 (rs17868323; rs17863778; rs17868324): WT.
.- UGT1A7 (rs7586110): WT
.- UGT1A7 (rs11692021): WT
Conclusión: En función de los porlimorfimos analizados el paciente no es
portador de ninguna mutación susceptible de ajuste de dosis de 5-FU e
irinotecan.

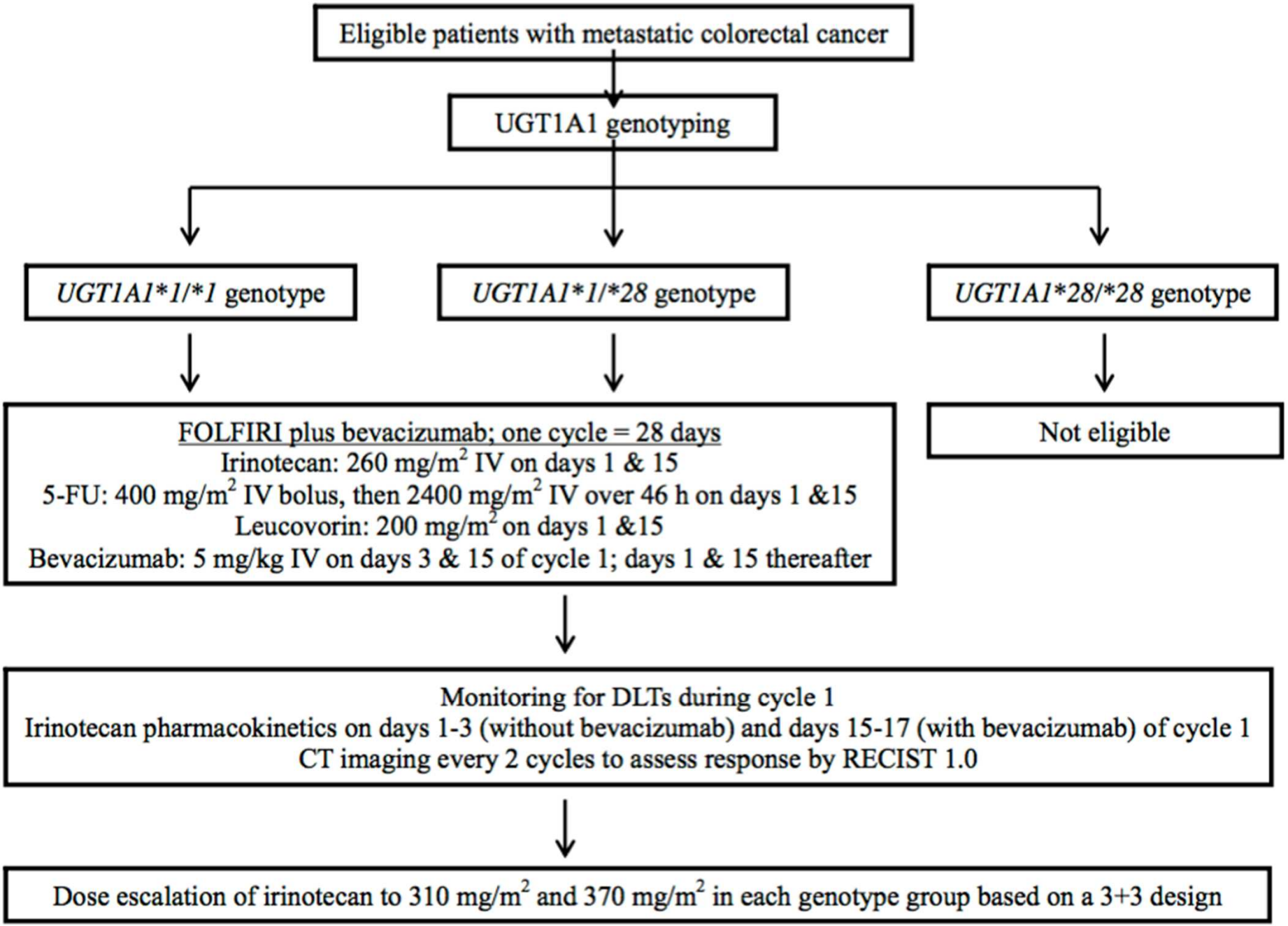

Irinotecan
Topoisomerasa I
CES1
CES2
SN38
UGT1A1
*28
*1
Toxicidad
¿Subir dosis?
UGT1A7
UGT1A9
SN38-G
Bilis



Baja frecuencia

Alta frecuencia

Figure 1. Schema of the study.



ANNALS OF ONCOLOGY

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

531P

Prognostic factors and specific populations in the pharmacogenetic randomized phase II trial of FOLFIRI with high-dose (HD) of irinotecan vs standard doses in metastatic colorectal cancer (mCRC) patients (pts) according to UGT1A1 genotype

Methods: Chemotherapy-naïve patients with the UGT1A1 *1/*1 or *1/*28 genotypes were randomized to receive HD-FOLFIRI vs FOLFIRI every two weeks. Irinotecan doses for UGT1A1 *1/*1 and *1/*28 pts in the experimental group were 300mg/m^2 and 260mg/m^2 respectively. The standard irinotecan dose of 180mg/m^2 was administered in the control group. Main clinical-pathological characteristics and clinical outcomes of pts included were analysed.

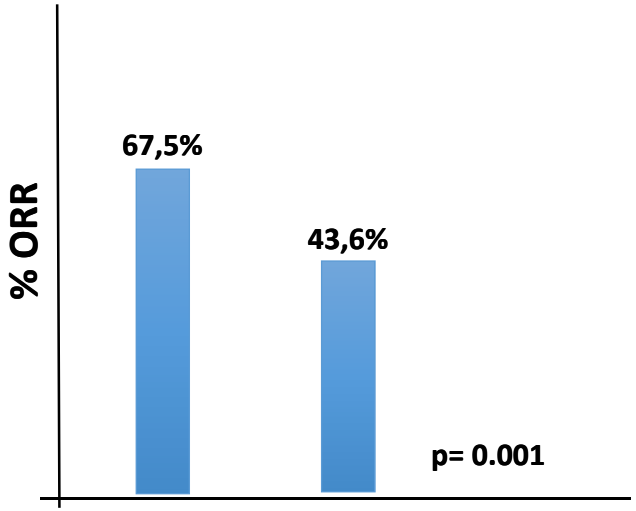
Results: Between Jun-12 and Oct-16 82 pts were included. The ORR was significantly higher in the experimental group (67.5% vs 43.6%; p = 0.001). There were not interactions between ORR and clinical characteristics (sex, age, ECOG, tumour location, synchronous disease) and RAS/BRAF status. However, when BRAF mutation was considered, no objective response was observed in the control group compared with 41.7% of pts treated with HD-FOLFIRI (p = 0.003). Metastatic surgical resection was performed in 15 pts (22.5% in HD-FOLFIRI and 15.4% in FOLFIRI) and was associated with ORR (29.5% vs 5.7%; p = 0.007). Median PFS and OS were 8.6 and 26 months (m) (HD-FOLFIRI) and 8.2 and 29 m (FOLFIRI). ECOG 0/1(9.9 vs 7.2 m) and metastatic resection (15.5 vs 7.8 m) were significantly associated with PFS. In terms of OS pts with metastatic surgery (not reach vs 18.4 m) achieved better outcome. Multivariate analysis showed significant association between metastatic resection with both, PFS and OS.

1*/1* **1*/28*** **28*/28***

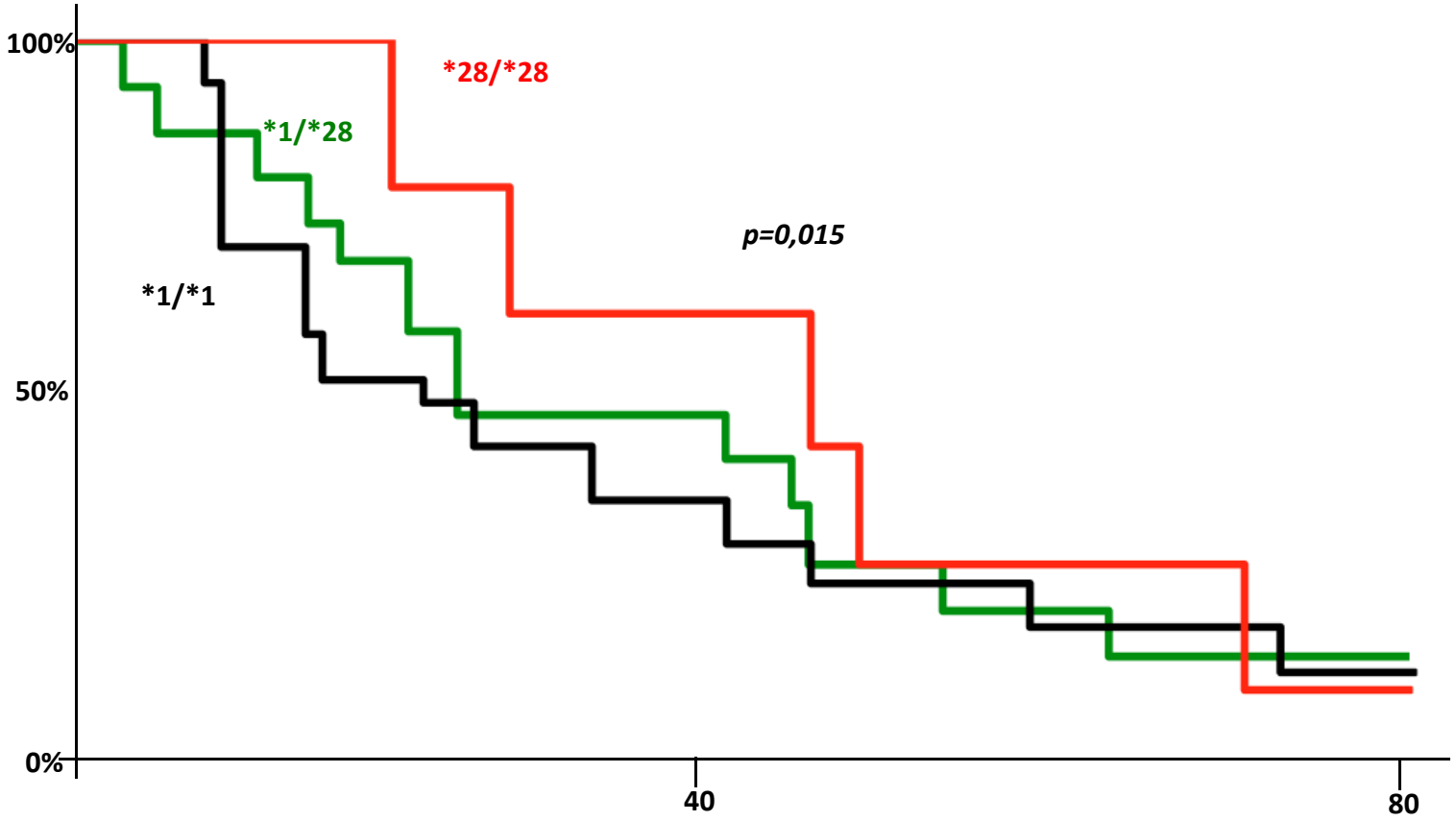
- **1*/1*** **1*/28***
  - **Experimental**
    - **1*/28*** 260 mg/m²
    - **1*/1*** 300 mg/m²
  - **Control**
    - **1*/28*** 180 mg/m²
    - **1*/1*** 180 mg/m²

patients treated with HD-FOLFIRI was significantly higher than in patients treated with FOLFIR

	Overall population N=79	HD-FOLFIRI group N=40	Control group N=39
CR + PR (%)	45 (57)	27 (67.5)	17 (43.6)
SD (%)	19 (24)	3 (7.5)	17 (43.6)
PD (%)	15 (19)	10 (25)	5 (12.8)
mPFS (months) [IC 95%]	8.6 [8 -9.2]	8.6 [7.9 -9.4]	8.2 [6.8 – 9.6]
mOS (months) [IC 95%]	26 [15 -37]	26 [16.7 – 35.2]	29 [12.2 – 45.8]



Estamos infra-tratando a los pacientes WT



¿Qué hace el farmacéutico?

TODO

menos prescribir

Indicación genotipado
Petición/toma muestra
Desarrollado y Genotipado
Interpretación de los resultados
Informe de recomendación farmacoterapéutica

3 años

n = 276

Ideal realizar un estudio controlado: *Ajuste FG vs. No ajuste FG*

Pero sin querer…

1A

***14 = 6 pacientes**
***2A = 1 paciente**

Logística ✔ — ***14 = 3 pacientes**

0% de toxicidad grado III/IV
0% de ingresos tras primer ciclo

p = 0,008

Logística ✗ — ***14 y 2A = 4 pacientes**

100% de toxicidad grado III/IV
50% de ingresos tras primer ciclo

Ahora tenemos 484 pacientes

Una potencial reducción de 2 ingresos/año en la UVI

Una potencial reducción de 5 ingresos/año

0-1 fallecimientos anuales

A pesar de no ser coste/eficaz…

GRACIAS

A pesar de no ser coste/eficaz…