

FARMACI INNOVATIVI
QUALITA' EFFICACIA APPROPRIATEZZA

"Farmaci a misura di paziente: L'esperienza del CRO di Aviano"

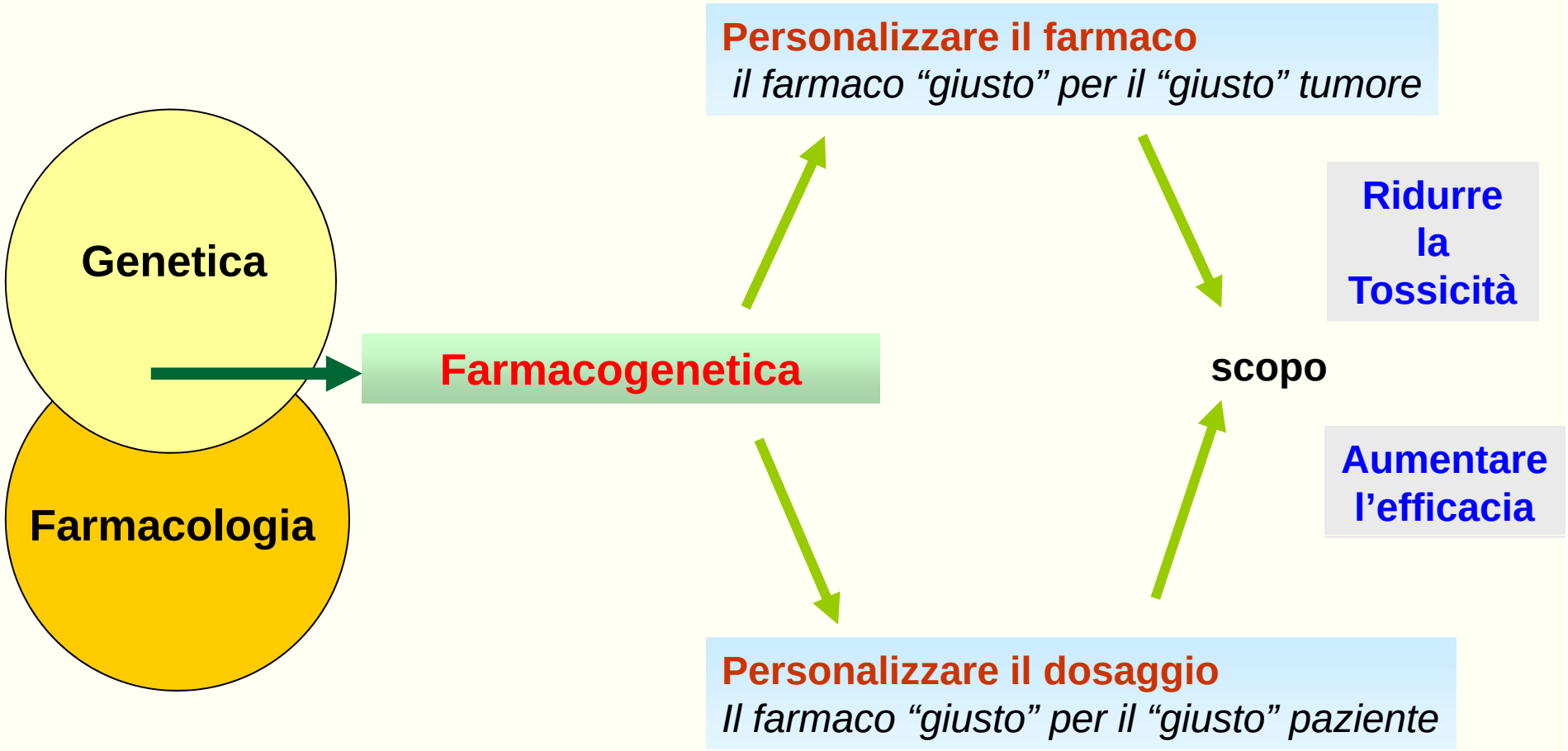
CAMERA DEI DEPUTATI
Palazzo Marini Sala delle Conferenze
Roma 25 ott. 2010

Giuseppe Toffoli, MD

Experimental and Clinical Pharmacology Unit

CRO- National Cancer Institute- AVIANO, PN , Italy

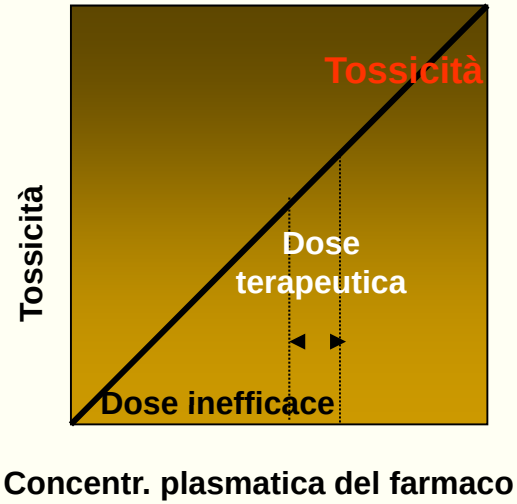
Farmacogenetica



Caratteristiche e dosaggio dei farmaci antitumorali tradizionali

-**La dose efficace è vicina alla dose tossica**

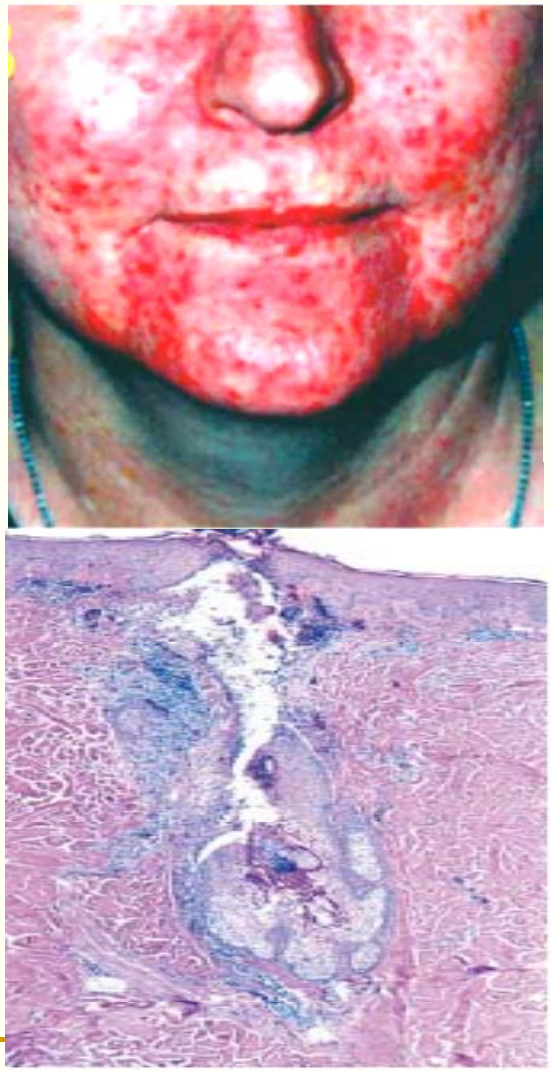
-**I chemioterapici sono impiegati a dosaggi prossimi alla loro massima dose tollerata (MTD)**

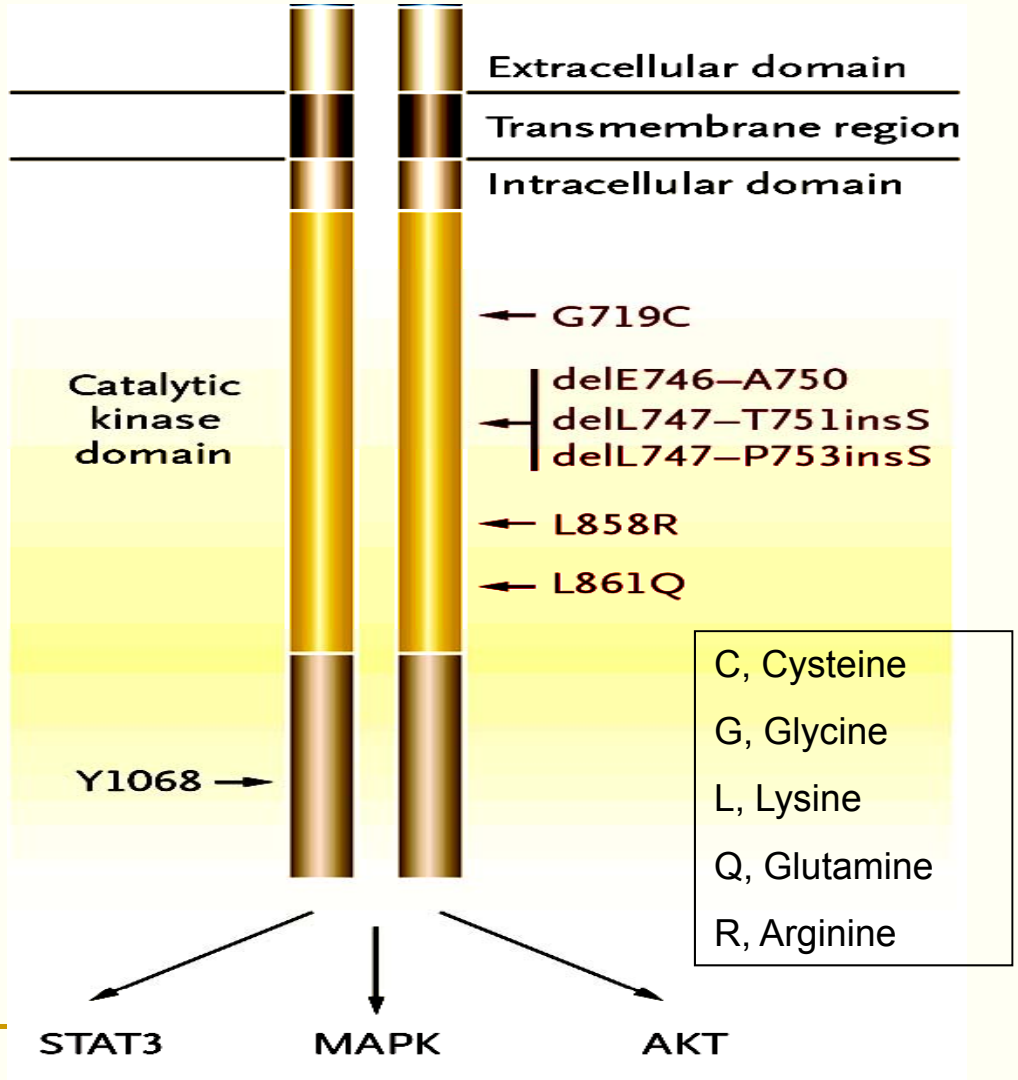


-***Il dosaggio dei chemioterapici è basato sulla superficie corporea del paziente***



EGFR mutations and response to gefitinib





Lynch T et al. N Engl J Med 2004

Mancata risposta

• Solo nel 30-60% dei pazienti i farmaci sono impiegati in modo ottimale

Reazioni gravi ai farmaci (*adverse drug reactions* -*ADRs):*

• 5-7% di tutte le ospedalizzazioni

• degenza prolungata di 2 giorni

•2,500 US dollari per paziente, USD 100 billioni per anno

•100,000 morti all'anno

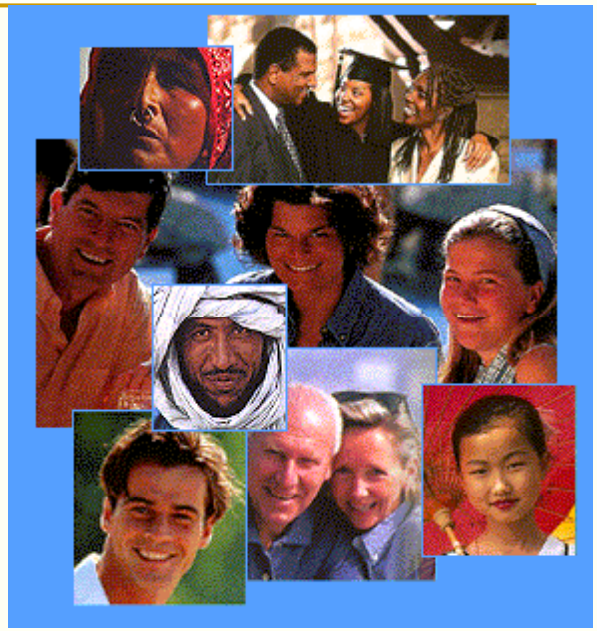
• I pazienti che presentano ADRs sono generalmente anziani, donne, che assumono molti farmaci. *

• Metà delle reazioni avverse ai farmaci possono essere "parzialmente"evitate

(Davies 2009. Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3695 Patient-Episodes. **PLos ONE 4(2): e4439. doi:10.1371/journal.pone.0004439)*

La Farmacogenetica può essere utile per evitare le reazioni avverse ai farmaci

IL GENOMA UMANO

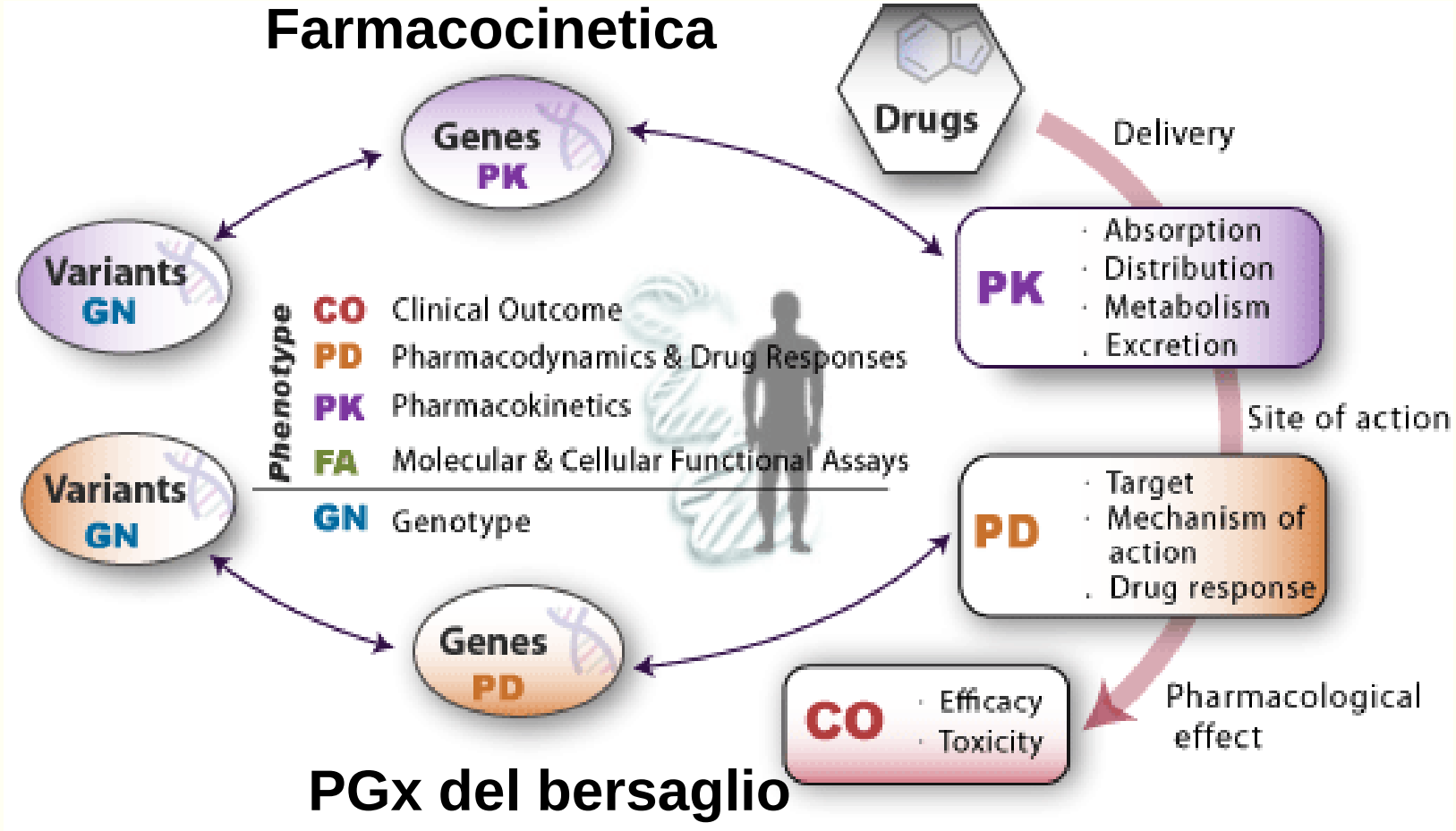


- 3.120.000.000 nucleotidi
- 25.000 geni
- > 100.000 trascritti (!)
- Fino a 100.000 aa diversi in due proteomi
- 100.000.000 SNPs (polimorfismo singolo nucleotide)

RIKEN consortium *Science* 2005

Informazioni sulla PGx

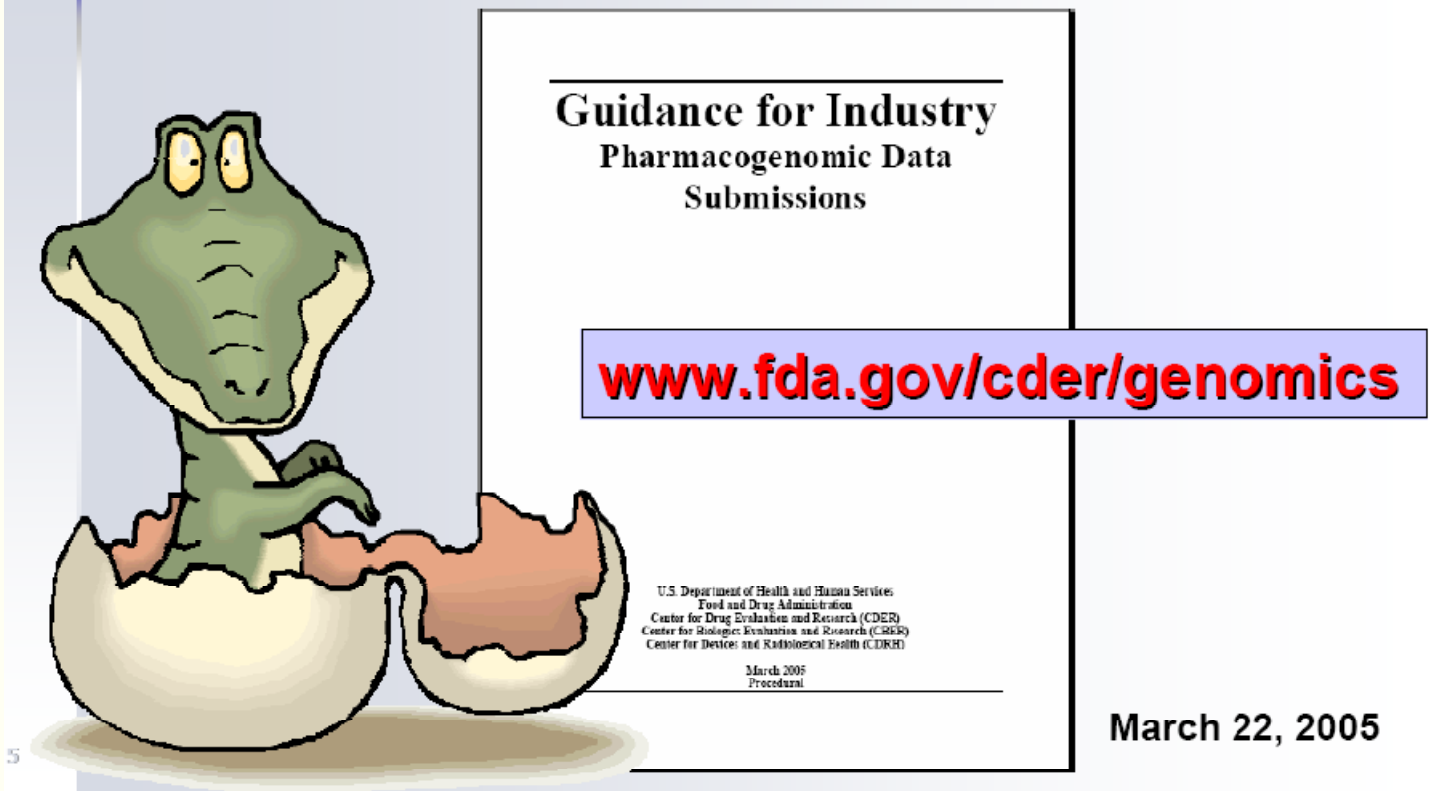
PGx della Farmacocinetica



PGx del bersaglio farmacologico



Guidance for Industry: Pharmacogenomic Data Submissions



www.fda.gov/cder/genomics

March 22, 2005

La Farmacogenetica nella pratica clinica

Validità Analitica

- Riproducibilità
- Sensibilità e specificità del test

Validità Clinica

- Genotipo e Farmacocinetica
- Genotipo e Farmacodinamica
- **Sensibilità clinica (associazioni positive PG/PD)**
- **Specificità clinica (associazioni negative (PG/PD)**

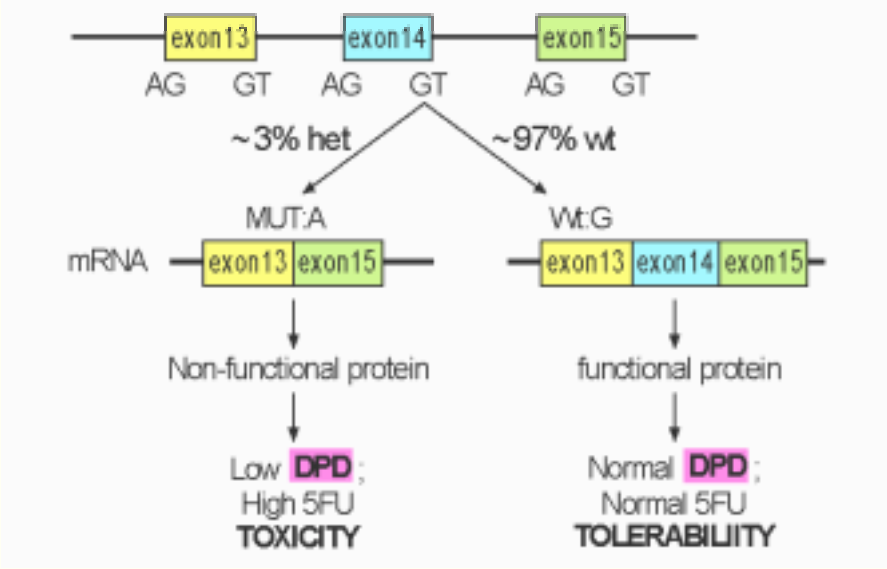
Utilità Clinica

- Quali opzioni per modificare la terapia?
  - Modifica del dosaggio
  - Modifica del farmaco
  - Prevenzione della tossicità (es. pretrattamento con fattori di crescita)

- **Effetto della modificazione della dose: comparazione della tossicità e dell'efficacia.**

Validità clinica: polimorfismi della diidropirimidina deidrogenasi *(DPD*2A - IVS 14+1G>A)*





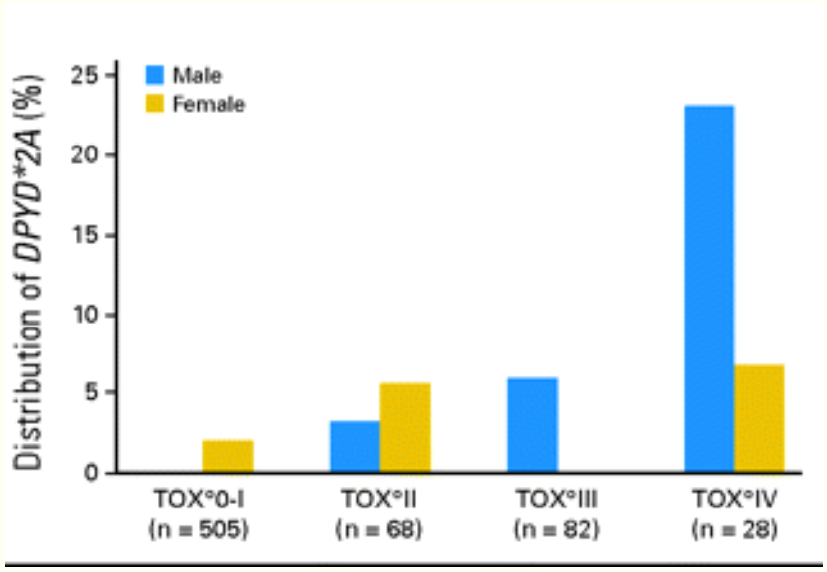
DPD (IVS 14+1G>A)

VOLUME 26 · NUMBER 13 · MAY 1 2008

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Role of Genetic and Nongenetic Factors for Fluorouracil Treatment-Related Severe Toxicity: A Prospective Clinical Trial by the German 5-FU Toxicity Study Group

Matthias Schwab, Ulrich M. Zanger, Claudia Marx, Elke Schaeffeler, Kathrin Klein, Jürgen Dippon, Reinhold Kerb, Julia Blievernicht, Joachim Fischer, Ute Hofmann, Carsten Bokemeyer, and Michel Eichelbaum



"…..in conclusion, our results demonstrate a limited impact of DPD, TYMS and MTHFR polymorphisms on the risk for developing FU related toxicity"

DPD*2A (IV14+1G>A)

Polimorfismo	N°paz.	Genotipo N (%)			Frequenza allelica (%)		Referenza
		GG	GA	AA	G	A	
IVS14+1G>A	1357	1333 (98.2%)	24 (1.8%)	0 (0%)	99.09%	0.91%	Van Kuilenburg ABP, Clin Cancer Res (2001)
IVS14+1G>A	574	567 (98.7%)	7 (1.2%)	0 (0%)	99.39%	0.61%	CRO-Aviano

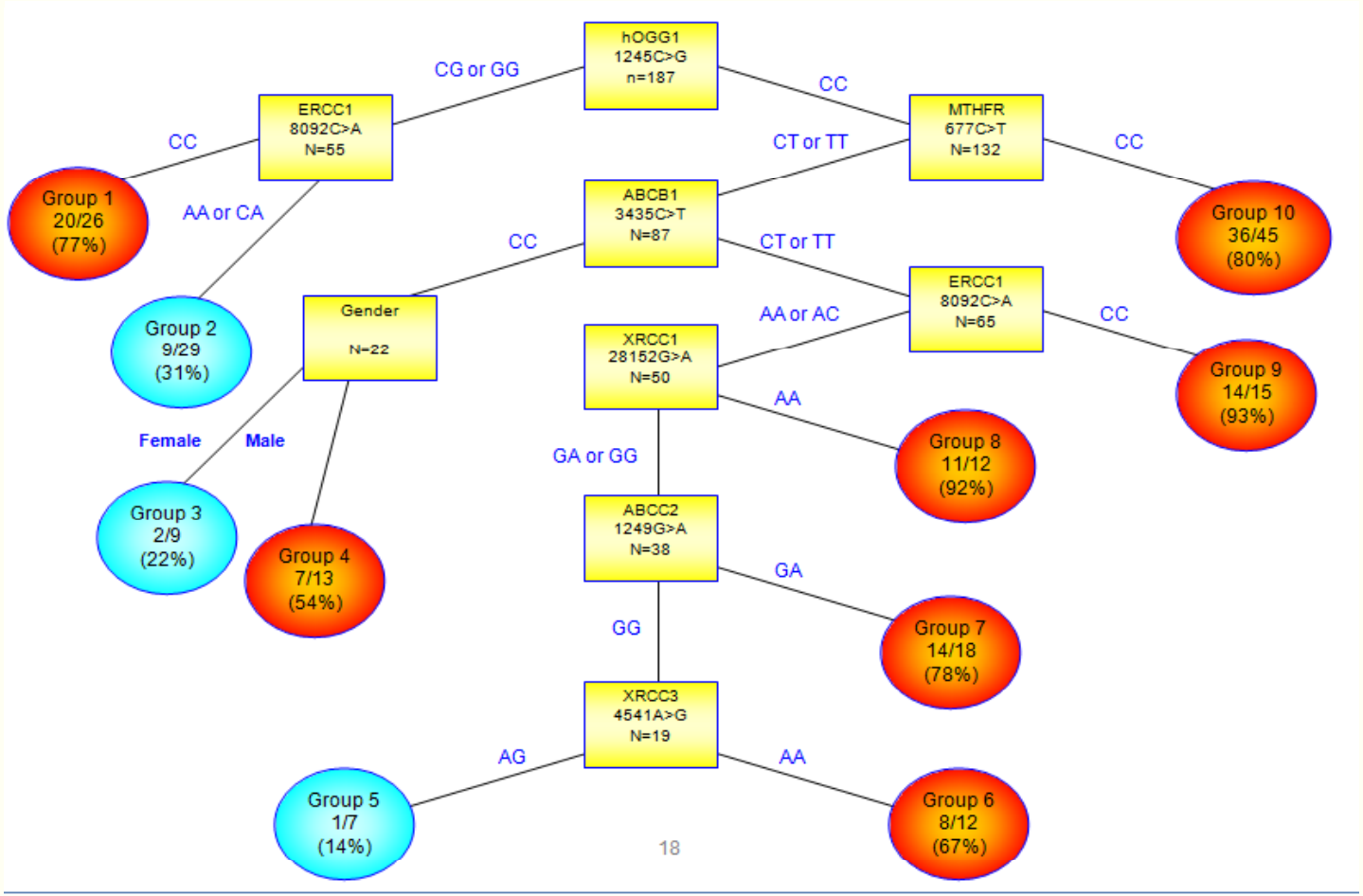
Tossicita'

Pts 1 (donna) 50 aa. Ca seno	CAPECITABINA Adiuvante	Gastrointestinale (mucosite, diarrrea), pancitopenia G5
Pts 2 (donna) 58 aa. Ca Colon	CAPECITABINA Adiuvante	Pancitopenia G4, sepsi, diarrrea G2, terapia intensiva di supporto
Pts 3 (donna) 16 aa Testa e Collo (T4N2N0)	TAXOTERE, CISPLATINO, 5-FU	Pancitopenia G4 – diarrrea G3, terapia intensiva di supporto
Pts 4 (maschio) 72 aa. Stomaco(T3N2M0)	FU+LV (De gramont) Adiuvante	Gastrointestinale (diarrea, mucosite), pancitopenia G5



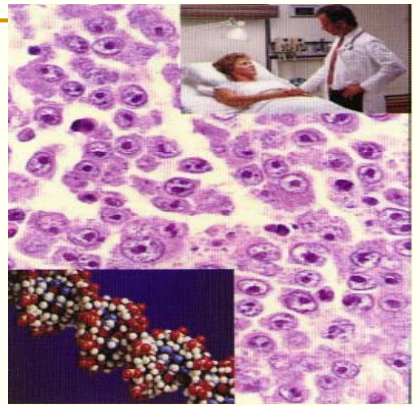
La farmacogenetica può cooperare con altri fattori?

The tumor response is predicted by the patient genetic profile in rectal cancer patients treated with neo-adjuvant chemo-radiotherapy.
Cecchin….and Toffoli Pharmacog. J. 2010



Patients were successfully stratified according to the probability to get a clinical benefit (TRG≤2) *by* ***Recursive Partitioning***

Utilità Clinica: La Farmacogenetica dell'irinotecano: un esempio paradigmatico



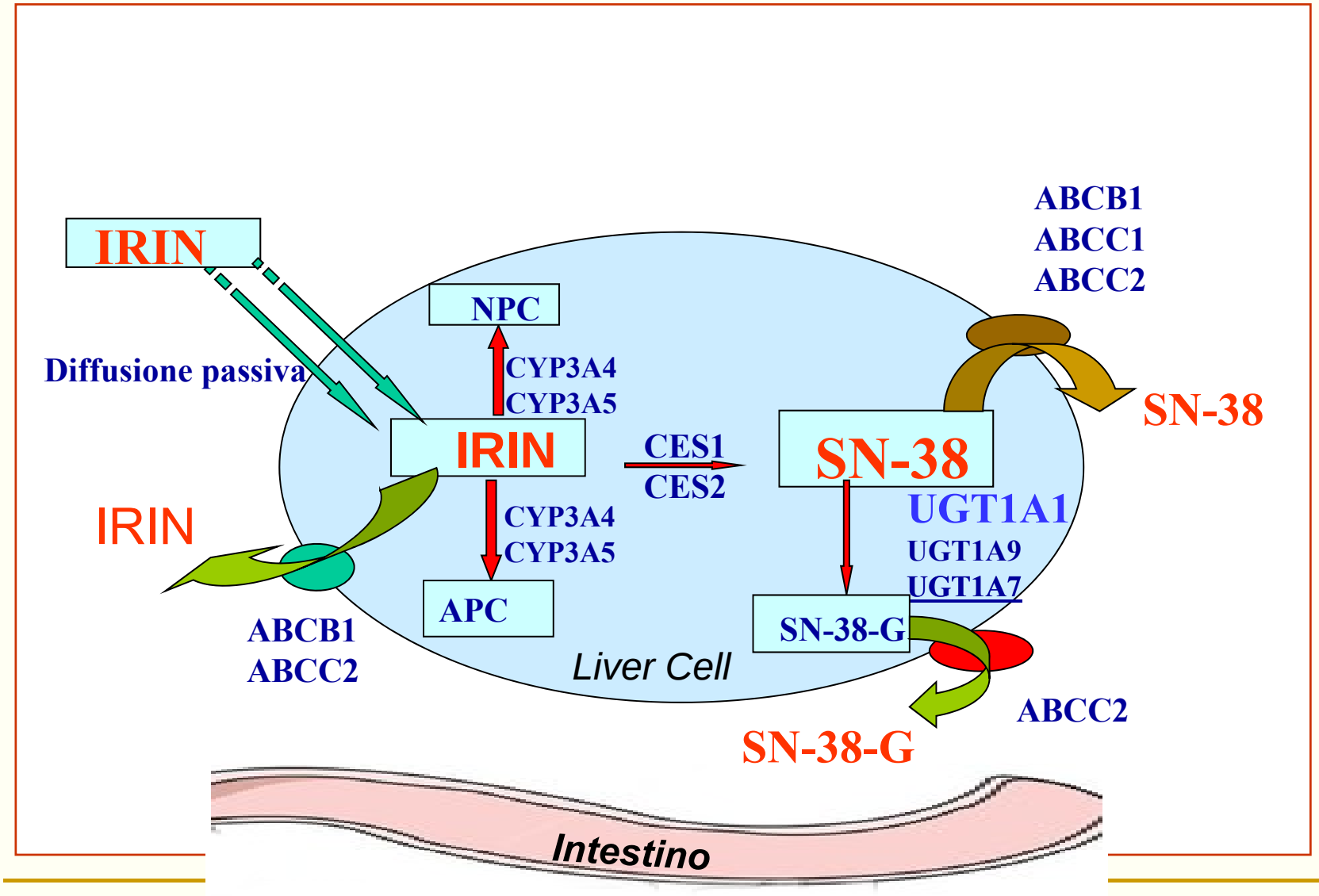
L'Irinotecano nel carcinoma colorettale

- Irin +5FU/LV (FOLFIRI - IFL)
- Irin+ Oxalipltino+5FU/LV(FOLFOXIRI)

- Irin + Bevacizumab +5FU/LV
- Irin + Cetuximab +5FU/LV
- Irin + Panitunumab+ 5FU/LV

"Cosa abbiamo imparato dalla farmacogentica dell'irinotecano?"

metabolismo e trasporto dell'irinotecano



Revisione della scheda tecnica del Camptosar®

Nel 2005 la FDA approva un test genetico per l'UGT1A1*28 e modifica la scheda tecnica del farmaco evidenziando l'associazione fra tossicità dell'irinotecano e allele UGT1A1*28.

Nel 2009 è approvato in Giappone il test genetico per UGT1A1*28 e per UGT1A1*6.

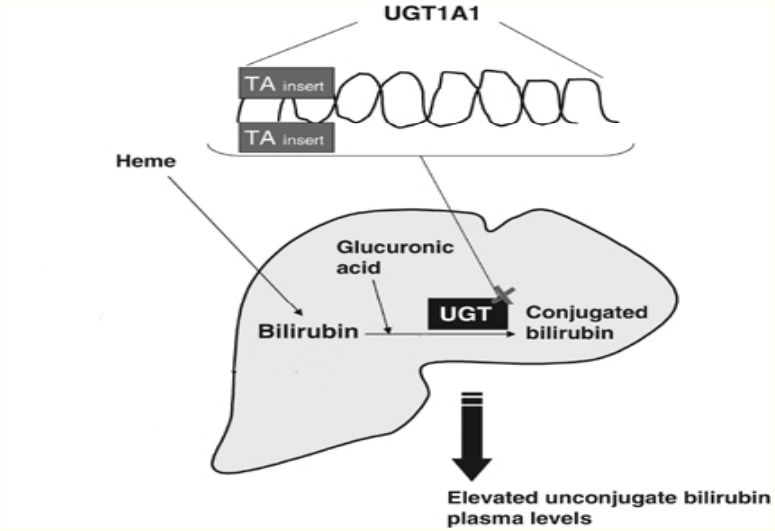
Tuttavia, rimane ancora da definire la dose ottimale di irinotecano basata sul genotipo.

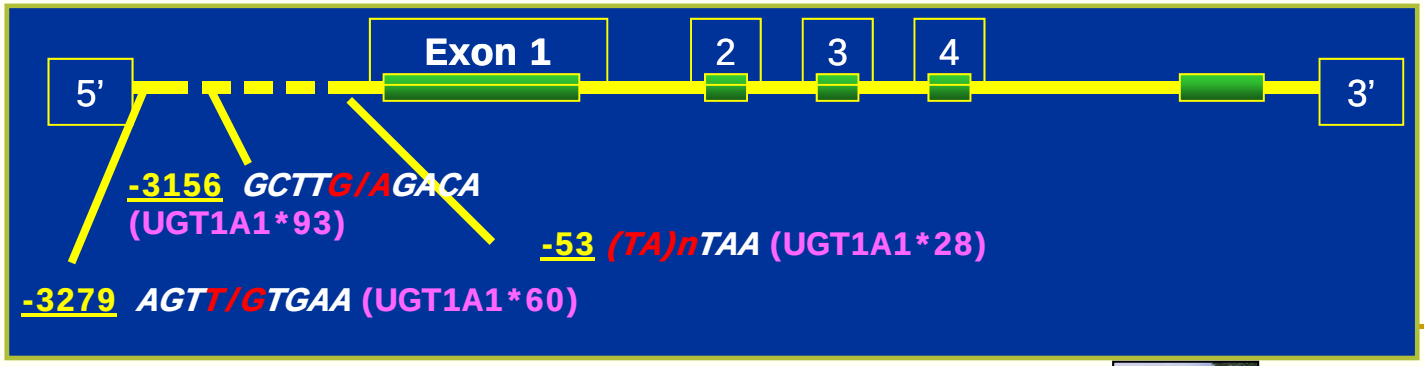
Polimorfismo UGT1A1*28



TATATATATATA=$(TA)_6$ = **WT**

TATATATATATATA=$(TA)_7$=*28







Pharmacogenetics into clinical practice

Revised Camptosar® label

*…….a reduction in the starting dose by at least one level of CAMPOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele……*

- **Clinical utility**
  - **Effect of dose modifications (comparing benefit and harms: toxicity and response)**

UGT1A variants and development of severe hematological toxicity

SNP	STUDY	PTS	TUMOR TYPE	POPULATION	IRINOTECAN DOSE	RISK RATIO	95% CI
NEUTROPENIA							
UGT1A1*28	Iyer et al. (2002)	20	Solid tumors	Caucasian	300 mg/m^2	10.00 *	0.58-171.20
	Innocenti et al. (2004)	65	Solid tumors or lymphoma	Caucasian (53), Black (10) and Asiatic (2)	350 mg/m^2	9.3	2.4-36.4
	Rouits et al. (2004)	75	CRC	Caucasian	85 mg/m^2 or 180 mg/m^2 + 5-FU + LV	5.90 *	1.69-20.66
	Rouits et al. (2008)	44	CRC	Caucasian	180 mg/m^2 + 5-FU + LV	5.00	1.13-22.18
	Toffoli et al. (2006)	250	CRC	Caucasian	180 mg/m^2 FOLFIRI	1.73 *	0.61-4.86
	Hoskins et al., (2007)	Meta-analysis (821pts)	Solid tumors, lymphoma	Mixed ethnicities	Low doses (<150 mg/m^2) Medium doses (150-250 mg/m^2) High doses (>250 mg/m^2)	1.80 3.22 27.8	0.37-8.84 (ns) 1.52-6.81 4-195
	Martinez-Balibrea et al. (2010)	149	CRC	Caucasian	80 mg/m^{2}or 180 mg/m^2 + 5FU	6.40	1.11-37.03
	Mc leod et al. (2010)	520	CRC	Mixed ethnicities	125 mg/m^2 + 5FU 85mg/m^2 + oxaliplatin	N.A. N.A.	N.A. N.A.

* $TA_{(7/7)}TAA$ repeats vs $TA_{(6/6)}TAA$ repeats
# 211AA versus 211GG
§ $T_{(9/9)}$ repeats vs $T_{(10/10)}$ repeats

Hematological toxicity and UGT1A1*28 polymorphism (250 pts)

1st cycle

UGT1A1*28 Genotype	Toxicity G 3+4	Toxicity G 0+1+2	*OR (95% CI)
$(TA)_6/(TA)_6$	2	112	1
$(TA)_6/(TA)_7$	7	107	3.47 (0.69-17.34)
$(TA)_7/(TA)_7$	3	19	8.63 (1.31-56.55)

All cycles

UGT1A1*28 Genotype	Toxicity G 3+4	Toxicity G 0+1+2	*OR (95% CI)
$(TA)_6/(TA)_6$	12	102	1
$(TA)_6/(TA)_7$	21	93	1.93 (0.89-4.23)
$(TA)_7/(TA)_7$	4	18	1.97 (0.56-6.99)

χ^2 for trend p =0.02

* Logistic regression model

Toffoli et al J Clin Oncol 2006



Response to chemotherapy (WHO) and UGT1A1*28 polymorphism (238 pts)

UGT1A1*28 Genotype	CR	PR	SD	PD	Risk for PD[1] *OR (95% CI)	Risk for PD+SD[2] *OR (95% CI)
$(TA)_6/(TA)_6$ n=109	10	34	29	36	1	1
$(TA)_6/(TA)_7$ n=108	5	40	32	31	0.77 (0.42-1.39)	0.92 (0.53-1.56)
$(TA)_7/(TA)_7$ n=21	3	11	5	2	0.19 (0.04-0.89)	0.32 (0.12-0.86)

[1] Responder= stable, partial and complete; non responder= progression
[2] Responder= partial and complete; non responder= stable and progression

*Logistic regression model including terms for age, gender, location of CRC (right colon, left colon and rectum) and adjuvant chemotherapy

Toffoli et al J Clin Oncol 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

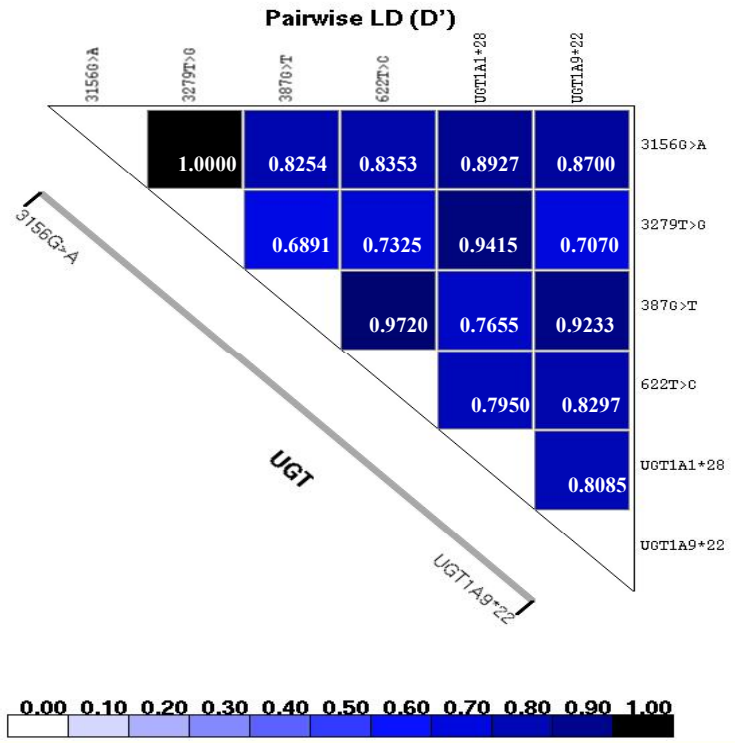
Predictive Role of the *UGT1A1*, *UGT1A7*, and *UGT1A9* Genetic Variants and Their Haplotypes on the Outcome of Metastatic Colorectal Cancer Patients Treated With Fluorouracil, Leucovorin, and Irinotecan

Erika Cecchin, Federico Innocenti, Mario D'Andrea, Giuseppe Corona, Elena De Mattia, Paola Biason, Angela Buonadonna, and Giuseppe Toffoli

JOURNAL OF CLINICAL ONCOLOGY EDITORIAL

UGT1A and Irinotecan Toxicity: Keeping It in the Family

Jarelle M. Hoskins, *Institute of Pharmacogenomics and Individualized Therapy; and Division of Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC*
Howard L. McLeod, *Institute of Pharmacogenomics and Individualized Therapy; Division of Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy; and Division of Hematology and Oncology, Lineberger Comprehensive Cancer Center, School of Medicine, University of North Carolina, Chapel Hill, NC*



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Predictive Role of the *UGT1A1*, *UGT1A7*, and *UGT1A9* Genetic Variants and Their Haplotypes on the Outcome of Metastatic Colorectal Cancer Patients Treated With Fluorouracil, Leucovorin, and Irinotecan

Erika Cecchin, Federico Innocenti, Mario D'Andrea, Giuseppe Corona, Elena De Mattia, Paola Biason, Angela Buonadonna, and Giuseppe Toffoli

	UGT1A HAPLOTYPES						
	UGT1A1			UGT1A7		UGT1A9	
	*93 3156G>A	*60 3279T>G	*28	*2 387 G>T	*4 622 T>C	*22 T9>10	Allelic frequency
I	*1	*1	*1	G	T	*22	34.2%
II	*93	*60	*28	T	C	*1	23.2%
III	*1	*1	*1	G	T	*1	14.4%
IV	*1	*60	*1	G	T	*1	4.6%
others							23.0%

Outcome	Risk genetic marker	§OR	95%CI	*P*
Response rate	UGT1A1*28/*28 (ref. *1/*1)	3.32	1.22-9.02	0.02
	Haplotype II/II (ref. 0 alleles)	**8.61**	**1.75-42.38**	**0.01**
Clinical benefit	UGT1A1*28/*28 (ref. *1/*1)	4.68	0.03-21.22	0.04
G3-4 hem tox (entire course)	**Haplotype I/I or I/- (ref. 0 alleles)**	**0.39**	**0.19-0.82**	**0.01**

§By logistic regression models includeing genetic variants and terms for age, gender, radical surgery, number of metastatic sites, tumor location and TNM stage



CRO AVIANO

* Significant by Fisher's Exact Test (P<0.05)

Clinical utility

UGT1A1*28
&
irinotecan

dose reduction ?

(TA_7/TA_7 patients)

Might individuals with the wild-type be underdosed?



"Several studies have demonstrated a dose–intensity relationship for irinotecan, and high doses (up to 600 mg/m^2 as monotherapy, 260 mg/m^2 in combination therapy) have been used with satisfactory safety and higher objective response rates but this concept is only based on phase I or II trials and must be validated by a randomized trial"

Hebbar M, Yehou M, Ducreux M J. Cancer Res Clin Oncol, 13:759, 2009

High-dose irinotecan monotherapy, Phase II study

Van Custem et al. Br J Cancer 2005

Ychou et al. Cancer Chemother Pharmacol, 2002

High-dose irinotecan in combination with 5-FU, Phase II Study

Ducreux et al. Oncology, 2008

Duffour et al. Cancer Chemother Pharmacol, 2007

Rivoire et al. Proc Am Soc Clin Oncol. J Clin Oncol absr 4075, 2008

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Genotype-Driven Phase I Study of Irinotecan Administered in Combination With Fluorouracil/Leucovorin in Patients With Metastatic Colorectal Cancer

Giuseppe Toffoli, Erika Cecchin, Giampiero Gasparini, Mario D'Andrea, Giuseppe Azzarello, Umberto Basso, Enrico Mini, Sergio Pessa, Elena De Mattia, Giovanni Lo Re, Angela Buonadonna, Stefania Nobili, Paolo De Paoli, and Federico Innocenti

Patient characteristics.

Number of assessable patients	
For safety	59
For efficacy	44
For pharmacokinetics	33
Age, years	
Median, range	64, 46-79
Sex	
Male	34 (57.6%)
Female	25 (42.4%)
Body-surface area (BSA), m^2	
Median, range	1.8 (1.4-2.4)
Adjuvant chemotherapy	
Yes	23 (39.0%)
No	36 (61.0%)
Performance status (ECOG)	
0	22 (37.3%)
1	37 (62.7%)
Primary site	
Colon	35 (59.3%)
Rectum*	24 (40.7%)
Number of metastatic sites**	
1	13 (22.0%)
≥2	42 (71.2%)
Radical surgery	
Yes	51 (86.5)
No	8 (13.5%)
Stage	
III	1 (1.7%)
IV	58 (98.3%)

Dose escalation and DLT of increased irinotecan doses

Irinotecan (mg/m^2)	*1/*1 patients (DLTs)	*1/*28 patients (DLTs)
215	**4 (0)**	**6 (1)** G3 nausea, diarrhea, anorexia
260	**12 (1)** G4 thrombocyt., G3 diarrhea	**4 (0)**
310	**6 (1)** G3 stomatitis, grade 4 pancytopenia*	**10 (0)**
370	**10 (0)**	**4 (2)** G4 neutropenia and leucopenia, G3 asthenia
420	**3 (2)** G3 anorexia, G4 asthenia, G3 diarrhea	**-**

*One toxic death (G5)

Toffoli et al. J Clin Oncol

Response rate: effect of irinotecan dose and UGT1A1*28 genotype

	Patients	CR+PR	SD+PD	Odds ratio, 95% CI
Overall	44	19 (43%) *7 CR + 12 PR*	25 (57%) *14 SD + 11 PD*	
[a]Doses <MTD	24	6 (25%) *2 CR + 4 PR*	18 (75%) *13 SD + 5 PD*	
[b]Doses ≥MTD	20	13 (65%) *5 CR + 8 PR*	7 (35%) *1 SD + 6 PD*	5.57, 1.51-20.51 *P*=0.014
***1/*1**	27	8 (30%) *2 CR + 6 PR*	19 (70%) *13 SD + 6 PD*	
***1/*28**	17	11 (65%) *5 CR + 6 PR*	6 (35%) *1 SD + 5 PD*	4.35, 1.20-15.87 *P*=0.031

a215, 260, 310 mg/m2 for the *1/*1 patients and 215, 260 mg/m2 for the *1/*28 patients
b370, 420 mg/m2 for the *1/*1 patients and 310, 370 mg/m2 for the *1/*28 patients

Domande?

- L'UGT1A1*28 ha un ruolo nella tossicità ematologica da irinotecano ? SI
- Il dosaggio dell'irinotecano nei pazienti UGT1A1*28 deve essere lo stesso dei pazienti UGT1A1*1? No
- Deve essere ridotta la dose di farmaco nei pazienti *28/*28, oppure deve essere aumentata nei pazienti *1/*1? Non c'è ancora risposta

Prospettive e potenzialità della Farmacogenetica

Analizzando il profilo genetico del paziente possiamo generare una terapia personalizzata individulaizzando il dosaggio più appropriato del farmaco

Sono tuttavia necessari studi di validazione per trasferire la farmacogenetica alla pratica clincia e per formulare regole prescrittive.

- **Studi clinici di fase I basati sulla farmacogenetica**
- **Studi clinici randomizzati per confrontare l'efficacia di un dosaggio del farmaco basato su parametri farmacogenetici rispetto ai sistemi tradizionali**
- **Favorire gli scambi fra ricerca di base e clinica per una ricerca "traslazionale" indipendente mirata alle effettive necessità dei pazienti**

Experimental and Clinical Pharmacology Unit

