Optimizing Irinotecan Safety/Efficacy Profile with UGT1A1 Genotypes

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Case Study:

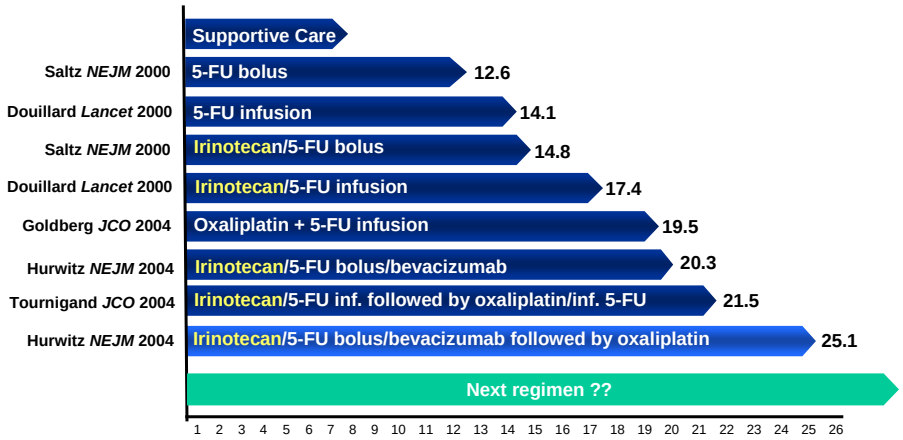
Data becomes available associating a genomic biomarker with the safety of a drug that provides substantial clinical benefit

- What is the current clinical practice?
- How was the evidence reviewed?
- How was the information captured, communicated and translated to specific, actionable recommendations?
- Conclusions and key lessons

Current Clinical Practice for Metastatic Colorectal Cancer

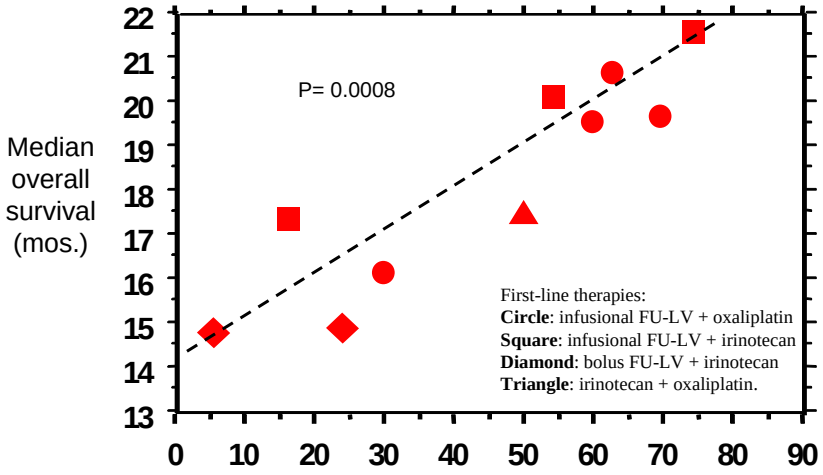
Increasing survival benefit while managing toxicities

Increasing Survival Benefit for mCRC



Median overall survival (months)

Survival Correlates with Use of All 3 Cytotoxics: 5 FU, irinotecan, oxaliplatin



Grothey, Goldberg, Sargent, Schmoll et al., JCO 2004

Toxicity Concerns With 1st line mCRC Combination Regimens

	FOLFOX 4[1]	FOLFOX 6[2]	FOLFIRI [2]	IFL [1]	IFL + BEV[3]	IROX [1]
	5 FU + oxaliplatin	5 FU + oxaliplatin	5 FU Inf + irinotecan	5 FU bolus + irinotecan	5 FU bolus + irinotecan + bevacuzimab	oxaliplatin + irinotecan
Neutropenia %	**50**	**44**	**26**	**40**	**37**	**36**
Parasthesias %	**18**	**34**	**0**	**3**	**NR**	**7**
Diarrhea %	**12**	**11**	**14**	**28**	**32**	**24**
Febrile neutropenia %	**4**	**0**	**7**	**15**	**NR**	**11**
Vomiting %	**3**	**3**	**10**	**14**	**NR**	**22**
Mucositis %	**NR**	**3**	**10**	**14**	**NR**	**22**
Hypertension %	**NR**	**NR**	**NR**	**NR**	**11**	**NR**

Adapted from El Khoueyri, A. Hendifar, H.j. Lenz Oncology Special edition, Volume 8 2005
1. Goldberg et al JCO 2004, 2. Tournigand et al JCO 2004 Hurwitz et al NEJM 2004

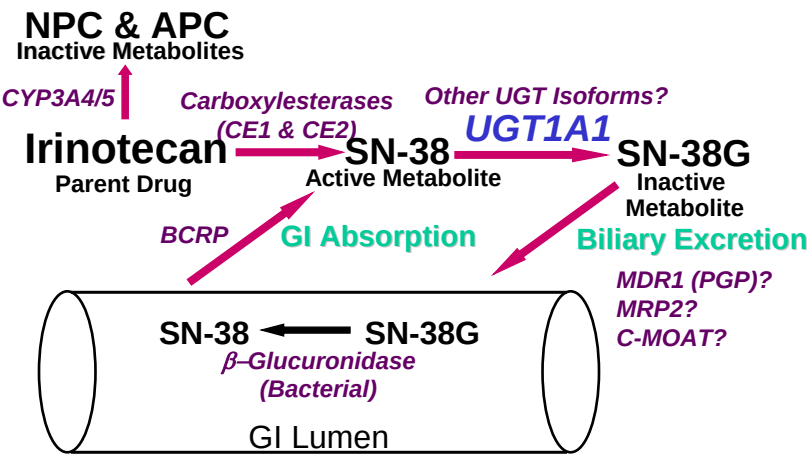
Gene expression, polymorphisms and metabolic pathways: Influence on response and toxicity of drug therapy in CRC

5 FU	Oxaliplatin	Irinotecan
• Thymidilate Synthase • Dihydropyrimidine Hydrogenase • Thymidine Phosphorilase	• GST-P1 • XPD gene • Excision repair enzymes XRCC1, ERCC2 • GSH dependent enzyme	• UGT1A1 • P450 3A4 • ATP Binding Cassette transporters • Carboxylesterase

Review of Evidence

Can genotyping help us better manage neutropenia?

Irinotecan Disposition & Metabolism



Key Publications Correlating UGT1A1 7/7 Genotype and Neutropenia

Author, Year	N	Tumor Type	Irinotecan Dose (mg/m^2), Schedule, & Combo
Innocenti, 2004	66	Lung 29%, GE 21%, **CRC 15%,** other 35%	**350 q-3-wk, single agent**
Marcuello, 2004	95	**CRC 100%**	**350 q-3-wk, single agent** 350 q-3-wk + raltitrexed 80 wkly + FU 180 biwkly + FU/LV
Routs, 2004	75	**CRC 100%**	85 wkly + FU/LV 180 biwkly + FU/LV
Ando, 2000	118	SCLC 18%, NSCLC 55%, **CRC 18%,** other 9%	Various

Severe (Gr 3+) Diarrhea Risk: 7/7 vs 6/6 + 6/7 Genotypes

Unadjusted Odds Ratio

	n/N (%)		Est. Odds Ratio	95% CI
	7/7	6/6 + 6/7		
Innocenti	1/6 (17%)	2/53 (4%)	5.1	0.4 - 66.6
Marcuello[a]	7/10 (70%)	22/85 (26%)	6.7	1.6 - 28.1
Rouits	2/7 (29%)	11/66 (17%)	8.4	0.3 - 11.7
Ando[b]	4/7 (57%)	22/111 (20%)	5.4	1.1 - 25.9
Font	1/7 (14%)	11/40 (27%)	0.4	0.05 - 4.1

[a]Gr 3+ diarrhea; [b]Gr 4 leukopenia and/or Gr 3+ diarrhea.

- **No clear association between 7/7 and severe diarrhea**
  - 2 of 5 studies show statistical significance
  - 2 studies don't show statistical significance
  - 1 study shows a trend in the opposite direction

Severe Neutropenia Risk: 7/7 vs 6/6 + 6/7 Genotypes

Unadjusted Odds Ratio

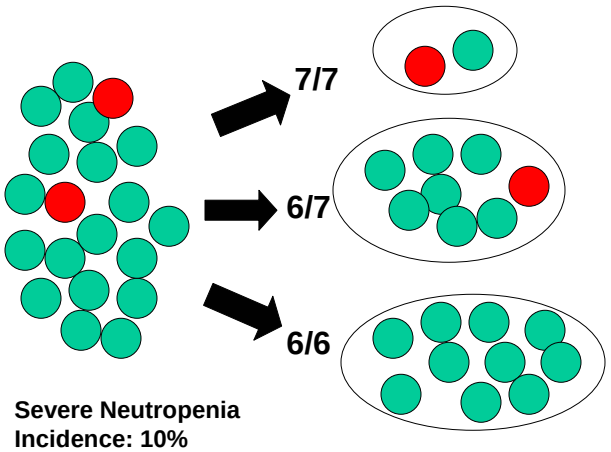
Author	n/N (%)		Est. Odds Ratio	95% CI
	7/7	6/6 + 6/7		
Innocenti	3/6 (50%)	3/53 (6%)	16.7	2.3 - 120.6
Marcuello[a]	4/10 (40%)	18/85 (21%)	2.5	0.6 - 9.7
Rouits	4/7 (57%)	10/66 (15%)	7.5	1.4 - 38.5
Ando[b]	4/7 (57%)	22/111 (20%)	5.4	1.1 - 25.9

[a]Gr 3+ neutropenia. [b]Gr 4 leukopenia and/or Gr 3+ diarrhea.

3 of 4 studies show statistically significant association between 7/7 and severe neutropenia

- Potential causes for inter-study variation include: small sample sizes, different schedules/dose intensity, populations and cancer types treated, different know risk factors (bilirubin, age, performance status, pelvic radiation)

Innocenti (2004) study population (N=66), Campto single agent (350mg/m²)



- **7/7 Frequency : 10%**
- **Severe Neutropenia: 50%**

- **6/7 Frequency : 40%**
- **Severe Neutropenia: 12.5%**

- **6/6 Frequency : 50%**
- **Severe Neutropenia: 0%**

Predictive Value of 7/7 Genotype for Grade 4 Neutropenia

Assumptions:

- Genotyping assay is 100% accurate for detection of 7/7 alleles
- Innocenti study population (N=66), campto single agent (350mg/msq)

	Sensitivity	Specificity	
UGT1A1	**0.5**	**0.94**	**Innocenti, 2004**
PSA	**.75**	**0.74**	**Bangma et al, 1997***

- **Sensitivity:** 50% of patients who will have grade 4 neutropenia are identified through UGT 1A1 7/7 allele test
- **Specificity:** 94% of patients who will not have grade 4 neutropenia are not 7/7
- **Positive Predictive Value**: 50% of patients who test 7/7 will develop grade 4 neutropenia
- **Negative Predictive Value**: 94% of patients who did not test 7/7 will not develop grade 4 neutropenia

Bangma et al British Journal of Urology, 1997

From Data to Practice

- Including genotype information in the label
- Availability of a diagnostic test

Revised Campto(-sar) Label

Clinical Pharmacology section, **Pharmacokinetics** subsection*:*

- *UGT1A1*28 leads to reduced enzyme activity*
- *Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele*
- *Patients who are homozygous for UGT1A1*28 have a higher exposure to SN-38*

Warnings section**, *Patients with Reduced UGT1A1 Activity:***

- *Individuals homozygous for the UGT1A1*28 allele are at increased risk for neutropenia*
- *A reduced initial dose should be considered for patients homozygous for the UGT1A1*28 allele*
- *Heterozygous patients unclear*

Dosage and Administration section, **Dosage in Patients with Reduced UGT1A1 Activity**

- *A reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele*
- *However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment*

Questions from Clinicians

- What efficacy risk do I take by reducing the initial dose in 7/7 patients?
- Are these predictive values of neutropenia valid for other regimens than Campto single agent (350 mg/msq)?
- With which other markers could/should UGT1A1 be combined to optimize safety/efficacy of mCRC treatment?

Although a test is available, clinicians are expecting specific, actionable and straightforward recommendations

Irinotecan Ongoing PGx Studies

- **NCCTG N9741**
  - Efficacy and toxicity end points associated with several genetic markers in IFL, FOLFOX and IROX in 1st line mCRC
- **Italian Eastern Coop Group study**
  - Role of UGT1A1*28 in PK/PD in patients treated with FOLFIRI
- **BICC-C CPTAIV-0020-366**
  - Predictive value of baseline bilirubin and UGT1A1 for severe neutropenia in patients treated with FOLFIRI, IFL or CAPIRI
- **PETACC 3**

What do we want to learn from these studies?

- **Better define magnitude and strength of the association between UGT1A1*28 and safety**
- **Identify other potential covariates of severe neutropenia & dose limiting toxicities**
  - Other markers and/or gene profile
- **Provide information & guidance to health care practitioners to aid in their treatment decisions**
  - Dose adaptation by sub-population
  - Dose adaptation for other regimens
  - Clinical utility and validity in other settings

Questions Associated with the Experience from This Case Study

- ***What should be the process for establishing consensus on the validity of clinical biomarkers?***
  -

Questions Associated with the Experience from This Case Study

- ***How do you identify a genomic biomarker as a risk factor?***

Questions Associated with the Experience from This Case Study

- ***What steps are required to improve therapy with these markers?***

Questions Associated with the Experience from This Case Study

- ***What additional factors need to be considered to identify better predictive markers?***

Questions Associated with the Experience from This Case Study

- ***What information is needed about the association between markers and effect to derive more specific warning and directions?***

Questions Associated with the Experience from This Case Study

- ***How can we establish intensive cooperation between pharmaceutical companies, diagnostics developers and regulatory agencies?***

Questions Associated with the Experience from This Case Study

- ***How can we optimize alignment between Dx and Tx labels?***

Thank You