Oncology I: Solid Tumors

Last updated: August 2010

Learning Objectives

- Upon completion of this program, participants will be able to:
  - Identify specific drug therapies used in cardiology in which pharmacogenomic testing can be applied in the clinical setting
  - Summarize evidence-based recommendations for pharmacogenomic testing
  - Using patient case scenarios, formulate a plan for pharmacogenomics testing based upon available scientific evidence

Presentation Outline

- Irinotecan and *UGT1A1*
  - Role in *UGT1A1* in metabolism of irinotecan
  - Association of *UGT1A1* genotype and irinotecan toxicity
  - Practice recommendations
- EGFR Therapy and KRAS
  - Overview of EGFR pharmacology and role of KRAS
  - Impact of *KRAS* on response to EFGR therapy
  - Practice recommendations
- Tamoxifen and *CYP2D6*
  - Role of *CYP2D6* in metabolism of tamoxifen
  - Overview of clinical data evaluating the impact of *CYP2D6* on tamoxifen clinical outcomes
  - Practice recommendations

Irinotecan and *UGT1A1*

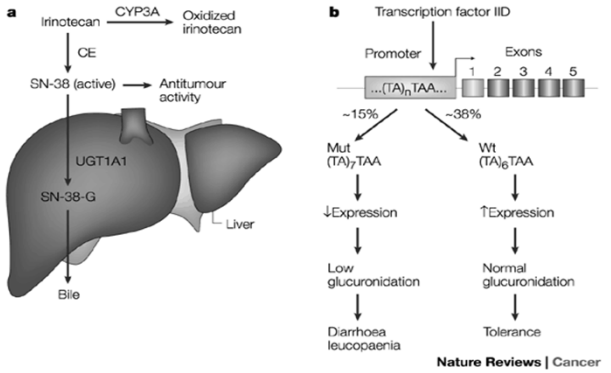
Case Study #1

- SK is a 55-year-old male with newly diagnosed stage IV colorectal cancer
- His oncologist orders a *UGT1A1* genotype and finds the SK is homozygous for the *UGT1A1*28* polymorphism
- How would this information change your recommendation for irinotecan dosing?

Irinotecan (Camptosar®)

- Camptothecin class of topoisomerase inhibitors
- Activity against a variety of malignancies
  - Colorectal cancer
  - Small cell lung cancer
- Significant side effects including diarrhea, neutropenia, and vascular syndromes

Irinotecan Metabolism & *UGT1A1* polymorphism



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UGT1A1 Polymorphism and Functional Effect

- Gene/Allele of interest: *UGT1A1*28*
  - Result of 7 TA repeats in the promoter region instead of 6 repeats
- Functional effect: reduced *UGT1A1* transcription & enzyme (or glucuronidation) activity
- Associated with reduced clearance of SN-38 (active and toxic metabolite)
- Associated with hyperbilirubinemia (Gilbert's Syndrome)

Hahn et al 2006

Population Prevalence of *UGT1A1* Genotype

Race	*UGT1A1* Genotype		
	**1/*1*	**1/*28*	**28/*28*
Caucasian	46%	39%	13%
Asian	76%	20%	5%
African American	26%	37%	19%

Liu et al 2007; Beutler et al 1998

Clinical Relevance: Toxicity & Efficacy

Rates by *UGT 1A1* Genotype (%) (95% CI)			
Outcome	***1/*1**	***1/*28**	***28/*28**
Severe Neutropenia	9.8 (6.8-14)	18 (14-23)	38 (22-57)
Severe Diarrhea	18 (11-28)	27 (20-36)	27 (12-48)
Tumor Response	41 (33-40)	45 (33-63)	70 (40-84)

Adapted from: EGAPP Working Group 2009

Clinical Relevance: Dosing

In July 2005, product labeling change to include initial dose reduction by one dosing level for patients homozygous for *UGT1A1*28* polymorphism

DOSAGE AND ADMINISTRATION
Dosage in Patients with Reduced UGT1A1 Activity
When administered in combination with other agents, or as a single-agent, 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 (see CLINICAL PHARMACOLOGY and WARNINGS). 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 (see Tables 10-13).

Camptosar Product Information 2008

Pharmacogenomic Test

- Invader *UGT1A1* Molecular Assay Manufactured by Third Wave Molecular Diagnostics
- FDA approval August 2005
- 100% accuracy compared to DNA sequencing
- Processing time of 4-5 hours
- Several commercial tests are available

UGT1A1 Genotyping Debate

- Pro
  - Strong association with dose limiting toxicities
  - Commercially available assay
  - Common polymorphism in general population
  - FDA recommendation included in PI
- Con
  - Only 30-40% of *UGT1A1*28* homozygous patients suffer severe toxicities
  - Dose reduction may result in decrease efficacy
  - 20% dose reduction not prospectively studied
  - Current common dose used (100-125mg/m^2) is lower than in previous studies (200-350mg/m^2)

EGAPP Working Group 2009; Hoskins et al 2007

Testing Recommendations

- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group
  - "Evidence is currently insufficient to recommend for or against the routine use of *UGT1A1* genotyping in patients with metastatic colorectal cancer who are to be treated with irinotecan."
  - "Found no intervention trials showing that targeted dosing of irinotecan based on *UGT1A1* genotyping could reduce the rates of two specific adverse drug events, severe (Grade 3–4) neutropenia or diarrhea."

EGAPP Working Group 2009

Could the *UGT1A1*28* polymorphism impact dose finding studies?

- Standard dose of irinotecan in FOLFIRI determined to be 180mg/m^2
- Presumption that early dose finding studies included patients with *UGT1A1*28* polymorphism
- If *UGT1A1*28* homozygous patients excluded from previous dose finding studies, would maximum tolerated dose (MTD) differ?

UGT1A1 and MTD

- Patients screened for genotype and excluded all *UGT1A1*28* homozygous patients
- Starting dose of irinotecan 215mg/m^2 with FOLFIRI regimen
- MTD for *UGT1A1*1/*1*: 370mg/m^2
- MTD for *UGT1A1*1/*28*: 310mg/m^2
- Currently recommended dose of 180mg/m2 considerably lower than tolerated dose when *UGT1A1*28* homozygous patients excluded

Toffoli et al 2010

*UGT1A1*28* Summary

- *UGT1A1* genotype associated with irinotecan toxicities
- Prospective genotype-guided dosing trials with irinotecan are needed to confirm or deny the benefit of *UGT1A1* genotyping

Case #1 Summary

- SK was homozygous for the *UGT1A1*28* polymorphism
- This puts SK at significantly higher risk of severe neutropenia and possibly higher risk of diarrhea
- Although empiric dose reductions may reduce this risk, it may also compromise the efficacy of therapy

EGFR Inhibitors and KRAS

Case Study #2

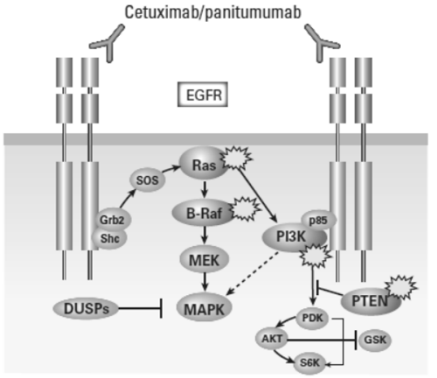
- KG is a 58 year-old female with a recent diagnosis of metastatic colorectal cancer (mCRC)
- She is told that her tumor will be tested for KRAS to help determine the best chemotherapy regimen for her
- The results return that she has a KRAS mutation in codon 12
- How should this influence the selection of therapy for this patient?

EGFR Inhibitors

- Two monoclonal antibodies currently approved to treat mCRC
  - Cetuximab
  - Panitumumab
- Bind to extracellular EGFR domain leading to inhibition of downstream signaling
- Only 10-20% of patients with mCRC benefit from anti-EGFR therapy
- EGFR expression does not correlate with clinical benefit

Bardelli et al 2010

EGFR Mechanism of Action



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KRAS

- Gene of interest: KRAS
  - Kirsen (K) RAS is a downstream effector of EGFR
  - KRAS belongs to the gene family of oncogenes encoding guanocine di-/triphosphate-binding proteins
  - The KRAS signaling pathway is thought to control cell growth, differentiation, and apoptosis

Bardelli et al 2010

KRAS

- Functional effect: Activating mutations in KRAS result in activation of downstream signaling pathways and confers resistance to inhibition of cell surface receptor tyrosine kinases such as EGFR
- Population Prevalence: The prevalence of mutated KRAS ranges between 27-43% in tumor samples collected from colorectal cancer patients across 7 trials

Siddiqui et al 2010

Clinical Relevance: Efficacy

- Tumors from 30 mCRC patients evaluated for KRAS
- KRAS mutation found in 43% of all mCRC tumor samples
- 37% (11 of 30) of patients responded to cetuximab
- No responders had KRAS mutation (0 of 11)
- 68% of non-responders had KRAS mutation (13 of 19)

Lievre et al 2006

Clinical Relevance: Efficacy of anti-EGFR monotherapy

Trial	# Patients	Intervention	Outcomes in KRAS-mutated patients
2002048	469	BSC ± Panitumumab	No difference in PFS, OS, ORR
NCIC-017	572	BSC ± Cetuximab	No difference in PFS, OS, ORR

BSC-Best supportive care; PFS-Progression free survival; OS-Overall survival; ORR-Overall response rate

Adapted from Bardelli et al 2010

Efficacy of Combination Chemotherapy with anti-EGFR

Trial	# Patients	Intervention	Primary endpoint in KRAS-mutated patients
PRIME	1,183	FOLFOX4 + Panitumumab	Worse PFS
CRYSTAL	1,198	FOLFIRI + Cetuximab	No difference PFS
OPUS	337	FOLFOX4 + Cetuximab	Worse ORR
PACCE	1,053	Chemo + Bev + Panitumumab	Worse PFS
CAIRO2	736	CapOx + Bev + Cetuximab	Worse PFS
EPIC	1,298	Irinotecan + cetuximab	Worse OS
181 Trial	1,186	FOLFIRI + panitumumab	No difference PFS, OS

Adapted from Bardelli et al 2010

Clinical Relevance

- Efficacy*:* In summary, colorectal cancer patients whose tumor has a mutated KRAS , have a low likelihood of responding to anti-EGFR monoclonal antibody therapy
- Toxicity: No literature related to KRAS mutational status impacting anti-EGFR toxicity
- Dosing: No literature related to KRAS mutational status impacting anti-EGFR dosing

Pharmacogenomic Test

- FDA updated prescribing information to recommend against use of EGFR inhibitors in KRAS mutated tumors
- Tumor DNA extracted from tissue sample
- Multiple commercials KRAS test kits available

Testing Recommendations

- American Society of Clinical Oncology (ASCO) Provisional Clinical Opinion
  - "All patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for KRAS mutations."
  - "If KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment."

Allegra et al 2009

KRAS Summary

- Only 10-20% of patients with mCRC respond to anti-EGFR therapy
- KRAS mutational status predicts responsiveness and clinical benefit with anti-EGFR monoclonal antibodies in mCRC
- Mutations for KRAS should be evaluated for all mCRC patients considered for anti-EGFR monoclonal antibody therapy

Case #2 Summary

- KG's tumor is positive for a KRAS mutation
- She is unlikely to benefit from EGFR therapy and possibly may do worse if an EGFR inhibitor is used
- KG should not receive therapy which contains cetuximab or panitumumab

Tamoxifen and *CYP2D6*

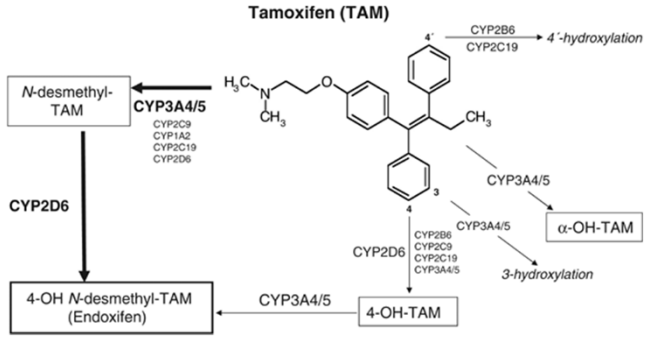
Case Study #3

- JB is a 45 year-old female with breast cancer who has recently completed adjuvant chemotherapy and is scheduled to begin tamoxifen
- She has recently read that her genetics could help identify if she would respond to tamoxifen
- Upon asking her pharmacist, he states that this has not been proven yet
- Could this patients genetics predict the efficacy of tamoxifen for breast cancer?

Tamoxifen

- Tamoxifen is considered the gold standard endocrine therapy for patients with estrogen receptor positive (ER+) or progesterone receptor positive (PR+) breast cancer
- Considered a selective estrogen receptor modulator
- Approved for a variety of indications including metastatic and adjuvant therapy as well as breast cancer risk reduction

Tamoxifen Biotransformation



Chemical structure of tamoxifen and major biotransformation pathways.

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CYP2D6 and Endoxifen

- Endoxifen is the metabolite most responsible for the in vivo pharmacologic activity of tamoxifen
- The formation of endoxifen is dependent on the hepatic *CYP2D6* pathway
- The *CYP2D6* enzyme is highly polymorphic

Hoskins et al 2009

CYP2D6 Polymorphisms

- Gene of interest: *CYP2D6*
  - At least 74 *CYP2D6* allele variants have been identified
    - Different polymorphisms exist based on the allele subtype
- Functional effect: (Broly et al 1993, Zhou et al 2010)
  - Wild type allele (normal enzyme activity): *CYP2D6*1*
  - Alleles associated with decreased enzyme activity: *CYP2D6 *10, *17*, and **41*
  - Alleles associated with a loss (null) of enzyme activity: *CYP2D6 *3, *4, *5, and *6*
  - Alleles associated with increased enzyme activity: *CYP2D6 *17x2* and **41x2*
  - Polymorphisms in *CYP2D6* can have as much as a 200-fold effect on drug metabolism

CYP2D6 Phenotype-Genotype Association

- Phenotype classification
  - Definition of phenotype: The clinical presentation of an individual with a particular genotype.
  - In general:
    - Extensive metabolizers (EM) will possess 2 wild type alleles (e.g., *CYP2D6 *1/*1*)
    - Intermediate metabolizers (IM) will have 1 wild type allele and 1 variant allele (e.g., *CYP2D6*1/*4*)
    - Poor metabolizers (PM) will have 2 variant alleles (e.g., *CYP2D6*4/*4*)

Population Prevalence of Common *CYP2D6* Variant Alleles

Race	*CYP2D6* Variant Allele		
	**4*	**10*	**17*
Caucasian	20-25%	2-5%	<1%
Asian	1%	35-55%	2-5%
African American	6-7%	2-5%	10-43%

Zhou 2010, Bradford et al 1998, Wang et al 1993, Leathart et al 1998

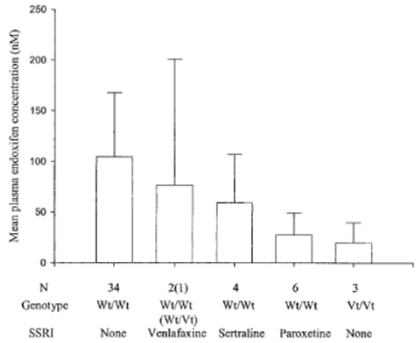
Impact of *CYP2D6* Genotype on Endoxifen Concentrations

***CYP2D6* Genotype**	**# Patients**	**Mean Endoxifen Concentration nM (95% CI)**
**1/*1*	48	78.0 (65.9 to 90.1)
**1* plus 1 variant allele	29	43.1 (33.3 to 52.9)
2 variant alleles	3	20.0 (11.1 to 28.9)

P<0.001

Jin et al 2005

Impact of Drug Interactions and *CYP2D6* on Endoxifen Concentrations



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Clinical Relevance: Efficacy

	Extensive Metabolizer	Intermediate Metabolizer	Poor Metabolizer
Overall Recurrence Rate	12.4%	17.7%	24.1%
Event-free survival event	22.2	27.6	32.9
All-Cause Mortality	16.7%	18.0%	22.8%

Schroth et al 2009

Supportive Clinical Trial Data

Author	Setting	Data Collection	TAM Dose	CYP2D6 Variants	Outcome
Goetz 2005	Adjuvant n = 256	Retro	20mg QD x 5y	*4	*4/*4 DFS HR 1.85
Goetz 2007	Adjuvant n = 190	Retro	20mg QD x 5y	*4	*4/*4 TTR HR 1.91
Schroth 2007	Adjuvant n = 206	Retro	Not provided	*4, *5, *10	PMs RFS HR 2.24
Lim 2007	Adjuvant / Metastatic n = 232	Prospective	20mg QD x 8wk PK Trial	*5, *10	*10/*10 ↓ Endoxifen P < 0.0001
Xu 2008	Adjuvant n = 152	Retro	20mg QD	*10	*10/*10 DFS HR 4.7
Kiyotani 2008	Adjuvant n = 67	Retro	20mg QD x 5y	*4, *5, *6, *10, *21, *41	*10/*10 Recur OR 16.6
Newman 2008	Adjuvant n = 115	Retro	20mg QD x 4y	*4, *5, *41	CYP2D6 Activity RFS HR 1.9
Bonnani 2006	Prevention n = 47	Retro	20mg QD x 5y	32 alleles	PMs ↑ breast cancer, p = 0.4

DFS = disease free survival, HR = hazard ratio, TTR = time to relapse, RFS = relapse free survival, OR = odds ratio

Contradictory Results

Author	Setting	Data Collection	TAM Dose	CYP2D6 Variants	Outcome
Wegmen 2005	Adjuvant n = 226	Retro	40mg QD x 2y	*4	*4 carrier: ↓ recurrence risk (RR 0.28, p = 0.009)
Wegmen 2007	Adjuvant n = 677	Retro	20-40mg QD x 2-5y	*4	*4/*4 vs *1/*1 ↑DFS (p = 0.05)
Nowell 2005	Adjuvant n = 162	Retro	Not included	*4	HR+, *4 carrier: HR 0.77 (95% CI 0.32-1.81)

DFS = disease free survival, HR = hazard ratio

Tamoxifen: Clinical Relevance

- Efficacy
  - *Overall Survival*
    - No effect or association of *CYP2D6*4* with overall survival (Goetz et al 2005, Schroth et al 2007, Nowell, et al 2005)
  - *Disease recurrence (measured as either relapsed free time or relapsed free survival)*
    - Increased risk (Goetz et al 2005, Schroth et al 2007, Goetz et al 2007)
    - Decreased risk (Wegman et al 2005)
    - No risk associated (Wegman et al 2007)
  - *Disease Free Survival*
    - Decreased disease free survival (Goetz et al. 2007, Schroth et al 2007)

Tamoxifen: Clinical Relevance

- Toxicity
  - Incidence of hot flashes
    - Decreased incidence in *CYP2D6*4/*4* patients (Goetz et al 2005)
    - Variable incidence reported elsewhere in *CYP2D6*4/*4* patients (Bonanni et al 2006)

Pharmacogenomic Test & Testing Recommendations

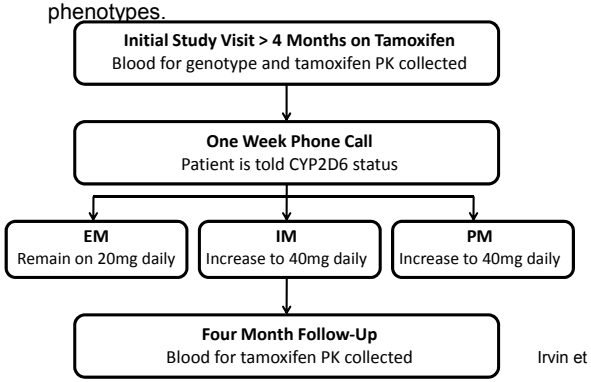
- Genomic Test
  - Genotyping should include *CYP2D6*3, *4, *5, *6, *9, *10, *17, *41*
- Pharmacogenomic Test Recommendations
  - No formal recommendation (FDA, PI)
  - FDA Advisory Committee recommended label update to reflect increased risk; no formal consensus on genetic testing (10/18/06)

What are the therapeutic alternatives to tamoxifen?

- Post-Menopausal women
  - Could switch to aromatase inhibitor
  - Possible dose increase but unproven benefit
- Pre-Menopausal women
  - No proven alternatives to tamoxifen
  - Possible dose increase

Study LCCC 0801: Dosage Increase in IM/PM

- Objective: Evaluate changes in endoxifen concentration following tamoxifen dose increase in patients with IM and PM phenotypes.



Irvin et al 2009

Study LCCC 0801: Results

- Endoxifen Concentrations *Within* Phenotypes (ng/mL)

Phenotype	N (%)	Baseline	4-Month	P-value
EM	29 (33%)	34.33	29.23	0.42
IM	51 (57%)	18.45	21.84	0.0008
PM	9 (10%)	4.18	12.89	0.0195

- Endoxifen Concentrations *Between* Phenotypes (ng/mL)

	Baseline (p-value)	4-Month (p-value)
EM vs. IM	34.33 vs. 18.45 (0.005)	29.23 vs. 21.84 (0.84)
EM vs. PM	34.33 vs. 4.18 (<0.0001))	29.23 vs. 12.89 (0.02)
IM vs. PM	18.45 vs. 4.18 (0.0006)	21.84 vs. 12.89 (0.02)

Irvin et al 2009

Case #3 Summary

- JB inquired if her genetics could predict response to tamoxifen
- Several trials have demonstrated a correlation between *CYP2D6* genotype and outcomes with tamoxifen
- No trials have demonstrated clinical benefit to screening *CYP2D6* in breast cancer patients taking tamoxifen

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