Key Therapeutic Area: Hematologic Malignancies

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Presentation Outline

• Select pharmacogenomic effects in patients with hematologic malignancies
  – Mercaptopurine
    • Thiopurine S-methyltransferase (TPMT)
  – Methotrexate
    • Methylenetetrahydrofolate reductase (MTHFR)
    • Thymidylate synthase (TYMS)
  – Busulfan
    • Glutathione S-transferase (GST)
  – Nilotinib
    • Uridine diphosphate glucuronosyltransferase (UGT1A1)
  – Rasburicase
    • Glucose-6-phosphate dehydrogenase (G6PD)
  – FLT3 tyrosine kinase inhibitor (investigational)
    • FMS-like tyrosine kinase 3 (FLT3)

Learning Objectives

• Upon completion of this program, participants will be able to:
  – Identify specific drug therapies used 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
**Therapeutic Area Discussion**

- **Format**
  - Patient case
  - Gene/Allele of interest
  - Functional effect
  - Population prevalence
  - Clinical relevance (dosing/selection, efficacy, and toxicity)
  - Genomic test and testing recommendation
  - Patient case summary

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**Patient Case 1**

- A 5 year old female diagnosed with pre B cell acute lymphocytic leukemia (ALL) has completed induction therapy and has just started a 24-week course of consolidation.
  - Methotrexate 1g/m² IV q 3 weeks x 6 doses
  - Vincristine 1.5 mg/m² IV q 8 weeks x 2 doses
  - Dexamethasone 6 mg/m²/day PO x 7 days
  - Mercaptopurine 50 mg/m² PO daily
  - Methotrexate 12 mg IT q 8 weeks
- After 3 weeks of consolidation, the patient presents with pancytopenia.
  - Absolute neutrophil count (ANC) 0 /mm³, platelets 30,000/mm³, Hct 30%
  - Other lab values are normal.
- What is the most likely cause for her profound myelosuppression?

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**Mercaptopurine**

- **Gene/Allele:** thiopurine S-methyltransferase (TPMT) (TPMT*3A, TPMT*3C, TPMT*2)
- **Functional Effect:** Presence of one of these alleles causes deficiency of TPMT, leading to decreased clearance of the inactive methylated metabolites and greater toxicity including myelosuppression and hepatotoxicity (Evans et al 2001)
- 17 variant TPMT alleles have been identified, although 3 alleles account for ~95% of the clinically relevant alleles that results in enzyme deficiency (Krynetski et al 1995, Yates et al 1997)
Mercaptopurine Metabolism

Azathioprine

Xanthine Oxidase

6-TU (inactive metabolite)

TPMT

6-mercaptopurine (6-MP)

6-methylmercaptopurine (6-MeMP)

6-thioguanine nucleotides (6-TGN) (active metabolite that affects efficacy and toxicity)

Adapted from Weinshilboum 2001

Mercaptopurine: Clinical Relevance

• Population Prevalence:
  – 10% of Caucasians and African Americans are heterozygous resulting in intermediate TPMT activity
  – 0.3% are homozygous resulting in low or absent TPMT activity
  – TPMT*3A most common allele in Caucasians (Schaeffler et al 2004)
  – TPMT*3C most common allele in Asians and African-Americans (Xin et al 2009, Oliveira et al 2007)

Mercaptopurine: Clinical Applications

• Dosing/Selection: Patients who are homozygous, and thus possess 2 variant TPMT alleles, should have ~80-90% reduction of initial dose
• For patients who are heterozygous for a variant TPMT allele, dosing recommendations are less defined.

Efficacy: No loss of efficacy including incidence of relapse was observed if mercaptopurine was dose-reduced in patients with low or absent TPMT activity (Relling et al 2006)
• Toxicity: All patients who were homozygous for one of these alleles and were given standard doses developed severe hematologic toxicity (Evans et al 1991, Relling et al 2006)
Pharmacogenomic Test and Recommendations

- Genomic Test: Genotyping or phenotyping (red blood cell TPMT activity) Prometheus® TPMT Genetics (Prometheus® Therapeutic and Diagnostics 2010)
- Recommendations:
  - FDA and package insert recommends genotype or phenotype screening for: TPMT*3A, TPMT*3C, TPMT*2 prior to initiating therapy (Purinethol (mercaptopurine) package insert 2003, FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels 2010)
  - Patients homozygous for the affected alleles should have an initial dose reduction
  - Patients heterozygous for the affected alleles should be monitored closely for toxicities as they are still at risk for toxicities

Patient Case 1 Summary

- Patient had genotype testing for TPMT
  - Test positive for homozygous TPMT*3A/*3A
  - Concluded that severe myelosuppression occurred secondary to dose of mercaptopurine
  - Mercaptopurine was discontinued and myelosuppression slowly recovered over a several week period
  - Mercaptopurine reinitiated at a 90% dose reduction

Patient Case 2

- 57 year old male is admitted for a new diagnosis of primary central nervous system (CNS) lymphoma. He has no significant PMH.
- Labs
  - SCr: 0.8 mg/dl, T. bilirubin: 0.7 mg/dl, AST: 35 IU/L, ALT: 42 IU/L
  - He is ordered methotrexate 8 g/m² IV over 4 hours along with leucovorin rescue (25 mg/m² IV q 6 hours)
- The patient asks you to explain what kind of toxicities he would likely have.
- Are there any patient characteristics that would place him at higher risk for toxicities?
Methotrexate Metabolism

• Polymorphisms have been described for many of the pathways and enzymes for methotrexate
  – methylenetetrahydrofolate reductase (MTHFR)
  – thymidylate synthase (TYMS)
  – dihydrofolate reductase (DHFR)
  – SLC19A1 associated with cellular influx
  – ABCG2 associated with drug resistance from efflux
  – Many others

• Focus will be on the effects of polymorphisms for MTHFR and TYMS

Methotrexate

• Gene/Alleles: 2 variants, MTHFR 677C>T and MTHFR 1298A>C

• Functional Effect: Presence of variant allele decreases the MTHFR activity thereby increasing risk of methotrexate toxicities.
  – Relative decreases in MTHFR activity between these 2 variants are unknown, although more evidence is provided for MTHFR 677C>T

• Also associated with increased risk of relapse
### Methotrexate: Clinical Relevance

- **Dosing/Selection:** Dosing nor selection affected by pharmacogenomic testing
- **Efficacy:**
  - Reductions in efficacy leading to decreased response or increased relapses have been reported, but have not been confirmed in controlled trials.
  - Krajinovic and colleagues saw an association with combined *MTHFR 677C>T* and *1298C>A* genotypes and reductions in 5 year post-treatment event free survival. (Krajinovic et al 2004)

### Methotrexate: Clinical Relevance

- **Toxicity:**
  - *In vitro* correlation between the *MTHFR 677T* allele and methotrexate in lymphoblasts from ALL patients who had experienced methotrexate-related neurotoxicity or hepatotoxicity. Cells with the 2 copies of the *MTHFR 677T* allele showed greater sensitivity to methotrexate. (Taub et al 2002)
  - 61 adult patients with ALL and 2 copies of the *MTHFR 677T* allele demonstrated increased reactions to methotrexate. These patients had to discontinue or temporarily stop methotrexate. (Chiusolo et al 2002)
  - A study of 200 pediatric patients with ALL reported no correlation with 2 copies of the *MTHFR 677T* allele and toxicity. (Krajinovic et al 2004)
  - More complete studies are necessary since this data is conflicting.

### Pharmacogenomic Test and Recommendations

- **Genomic Testing:** Genotype testing not widely available
- **Recommendations:** Currently, data are conflicting. Routine testing for *MTHFR* polymorphisms are not recommended.

### Methotrexate

- **Gene/Alleles:** Thymidylate synthase (*TYMS*)
  - *3R* (3 repeats) in 28 base pair repeat sequence in enhancer element of 5’UTR (untranslated) gene region
  - G to C substitution of the 3R allele
  - In the 3’UTR region, there is a 6 base pair deletion
- **Functional Effect:** Presence of a triplet of the 28 base pair repeat is associated with higher levels of *TYMS* expression, thereby reducing the efficacy of methotrexate
Methotrexate: Clinical Relevance

- Population Prevalence
  - 3R: Eastern Asians 80%, Caucasian 50-60%, Southwest Asians 60%, (Marsh et al 1999)
  - 6 bp deletion: African American 52%, Caucasian 41%, Chinese 76%, Hispanic 26% (Mandola et al 2004)

Methotrexate: Clinical Relevance

- Dosing/Selection: Dosing nor selection affected by pharmacogenomic testing
- Efficacy: In 200 pediatric patients with ALL, those that were homozygous for the 3R allele had more disease events and shorter event free survival compared to patients without the genotype. (Krajinovic et al 2005)
- In 247 pediatric patients with ALL, the 3R/3R genotype in low risk patients was associated with central nervous system relapse. (Rocha et al 2005)
- Conflicting results in 80 pediatric patients have been presented. No association between the homozygous 3R variant and outcome was observed. (Lauten et al 2003.)

Methotrexate: Clinical Relevance

- Toxicity: Relling and colleagues demonstrated in 64 children with ALL, that patients with the genotype for decreased activity, TYMS 2R/2R genotype, would have a higher sensitivity to methotrexate.
- A higher incidence of hip osteonecrosis was observed. (Relling et al 2004)

Pharmacogenomic Test and Recommendations

- Genomic Testing: Genotype testing not widely available
- Recommendations: Currently, data are conflicting. Routine testing for the different TYMS polymorphisms are not recommended.
Methotrexate: Gene-Gene Interaction

- Variants of other genes may enhance or diminish the effect of a given gene
- Karjinovic and colleagues evaluated individuals with the MHTFR 667T allele in combination with TYMS 3R/3R genotype
- There was a greater decline in 5-year event free survival of the combination group compared to no event predisposing genotype together than either of the variants separately (Krajinovic et al 2004)

Patient Case 2 Summary

- Toxicities most commonly associated with high dose methotrexate include myelosuppression, mucositis, nausea and vomiting.
- If patients develop severe toxicity, transaminitis, hyperbilirubinemia, renal failure, and encephalopathy may occur.
- Patient characteristics that may place him at higher risk for toxicities include: renal dysfunction, hyperbilirubinemia, effusions, ascites, certain concomitant medications (e.g. trimethoprim-sulfamethoxazole), and possibly homozygous MTHFR 677C>T and homozygous TYMS 2R genotypes.
- Further studies may confirm the correlation of toxicity with different enzyme polymorphisms.

Busulfan

Patient Case 3

- AT is a 60 yo male with AML in first complete response. He presents for a myeloablative matched unrelated donor hematopoietic stem cell transplant (HSCT). His conditioning regimen includes busulfan 1 mg/kg/dose PO q6 hours days -6, -5, -4, -3 and cyclophosphamide 50 mg/kg IV q 24 hours on days -2, -1.
- Should pharmacogenomic testing be completed to optimize dosing and minimize toxicity of busulfan?
**Busulfan**

- Gene/Allele: Glutathione S-transferase
  - \( \text{GSTM1}^*0 \) (null) and \( \text{GSTA1}^*B \)
- Functional Effect: Presence of \( \text{GSTA1}^*B \) allele is associated with lower transcriptional activity. \( \text{GSTM1}^*0 \) allele confers no enzymatic functional activity. Presence of these variants may be associated with higher busulfan concentrations.
- Population Prevalence
  - \( \text{GSTM1}^*0 \), 50% homozygous deletion
    - Arabs 44.6-56.3%, Asians 47.6-56.2%, Blacks 17-46.7%, Caucasian 34-58.3%, Native Latin-American 0-43% (DiPetro et al 2010)
  - \( \text{GSTA1}^*B \)
    - Not clearly described

**Busulfan: Clinical Relevance**

- Dosing/Selection: Studies published thus far only show that \( \text{GSTA1}^*B \) and \( \text{GSTM1}^*0 \) genotype may contribute to busulfan pharmacokinetic variability. Selection of agents is not guided by pharmacogenomic evidence.
  - Neither \( \text{GSTA1} \) protein expression nor conjugation was affected by \( \text{GSTM1} \) status \( \text{in vitro} \) (Bredschneider et al 2002)

**Busulfan: Clinical Reference**

- IV Dosing
  - \( \text{GSTA1}^*B \) and \( \text{GSTM1}^*0 \) are reported with conflicting association to busulfan pharmacokinetic variability \( \text{in vivo} \)
    - In 29 pediatric patients, IV busulfan clearance was lower with \( \text{GSTA1}^*B \) variants thereby increasing busulfan concentrations. No difference in effect was seen with \( \text{GSTM1}^*0 \) polymorphisms. (Johnson et al 2008)
    - IV busulfan clearance was not correlated to any \( \text{GSTA1} \) or \( \text{GSTM1} \) polymorphisms in 77 pediatric patients receiving busulfan (Zwaveling et al 2008)
    - \( \text{GSTM1}^*0 \) genotype was the best predictor of first-dose pharmacokinetic variability along with age and drug dose in 28 pediatric patients (Ansari et al 2010)

- Efficacy: No literature related to \( \text{GSTA1}^*B \) or \( \text{GSTM1}^*0 \) impacting drug efficacy or outcomes
- Toxicity: Data are limited as to whether \( \text{GSTM1} \) status may predict side effects of busulfan
  - 114 pediatric patients undergoing transplant had a significantly increased incidence of hepatic veno-occlusive in patients with the \( \text{GSTM1}^*0 \) genotype (Srivastava et al 2004)
Pharmacogenomic Testing and Recommendations

- Genomic Test: Genotype test not commercially available
- Recommendations: Currently, data are conflicting. Routine testing for the GSTA1*B and GSTM1 null variants are not recommended.

Patient Case 3 Summary

- AT did not have any genotyping completed for his busulfan doses. He did have pharmacokinetics completed and AUC calculated to guide dosing
- Many factors influence the pharmacokinetics and subsequent dosing of oral and IV busulfan.
- Currently, there is insufficient evidence to support a recommendation for or against testing patients’ GST genotypes prior to initiating busulfan.

Patient Case 4

- A 48 year old female with imatinib-resistant CML in chronic phase presents to clinic for routine follow-up.
  - Labs: T. bilirubin 8.7mg/dl, Direct bilirubin 7.2mg/dl, AST 60 IU/L, ALT 85 IU/L
  - Medications: pantoprazole, ondansetron, nilotinib, ciprofloxacin
- What is the cause of her hyperbilirubinemia?
Nilotinib

- Gene/Allele: Uridine diphosphate glucuronyltransferase UGT1A1*28
- Functional Effect: Presence of UGT1A1*28/*28 has demonstrated increased risk of hyperbilirubinemia with nilotinib administration
- Results in decreased UGT1A1 transcription and enzyme (glucuronidation) activity (Hall et al. 1999)
- Population Prevalence:
  - African 42-56%
  - Asian 9-16%
  - Caucasian 26-31%

Nilotinib: Clinical Relevance

- Dosing/Selection: Dosing nor selection are affected by pharmacogenomic testing
- Efficacy: No literature related to pharmacogenomics impacting drug efficacy
- Toxicity: Concurrent pharmacogenetic study in 212 patients in Phase 1 and 2 trials, showed significant increases in relative risks of hyperbilirubinemia in patients with homozygous UGT1A1*28 compared to heterozygous UGT1A1*28 and wild type UGT1A1*1 (Singer et al. 2007)
  - No events of Grade 4 toxicity (T. bilirubin > 10 X ULN) were observed
  - Nilotinib discontinued in 2 patients

Pharmacogenomic Test and Recommendations

- Genomic Test: UGT1A1 genotype - Third Wave
- Recommendations: None currently recommended
- Currently, practical implications of this toxicity are not defined
- Patients should not be prohibited from receiving nilotinib on the basis of their UGT1A1 genotype
- Review of concomitant medications that are metabolized or are substrates for UGT1A1 should be completed

Patient Case 4 Summary

- Patient had genotype testing for UGT1A1
- Test positive for homozygous UGT1A1*28/*28
- Nilotinib was continued in this patient with subsequent resolution of T. bilirubin to 1.2 mg/dl 3 months after initiating the agent
- Genotype testing in this patient’s case did not affect the selection of the drug, the dose, nor course of therapy
Patient Case 5

- A 34-year old male presents with night sweats, weight loss, and shortness of breath. CT reveals a 12 cm mediastinal mass and wide spread lymphadenopathy.
- Labs: WBC 30,000 cells/mm$^3$, ANC 1200 cells/mm$^3$, potassium 4.7 mEq/L, SCr 2.1 mg/dl, phosphate 6.8 mg/dL, uric acid 15.3 mg/dl, and LDH 2250 IU/L.
- Diagnosis from a bone marrow biopsy reveals acute lymphoblastic lymphoma and immediate treatment with induction chemotherapy is initiated.
- What agent may be given for hyperuricemia resulting from tumor lysis syndrome?

Rasburicase

- Gene/Allele: Glucose-6-phosphate dehydrogenase (G6PD) A-variant and Mediterranean variant
- Functional Effect: Excessive hydrogen peroxide is produced as rasburicase converts uric acid to more soluble allantoin
- Excess hydrogen peroxide places patient at risk for hemolytic anemia and methemoglobinemia

Rasburicase: Clinical Relevance

- Population Prevalence: 400 million individuals worldwide
  - Hundreds of different mutations
    - Result in mild to severe enzyme deficiency
    - Highest frequencies in Africa, Mediterranean, Middle East, and Asia
  - Most common: G6PD A- variant (Val68Met + Asn128Asp mutation)
    - Seen in individuals with an African ancestry
  - G6PD Mediterranean variant
    - G6PD Mediterranean variant (Ser188Phe) (Vives-Corrons et al 1990)
Rasburicase: Clinical Application

• Dosing/Selection: Dosing not affected by pharmacogenomic testing but drug selection may be affected. Patients with known $G6PD$ deficiency should not receive rasburicase.
• Efficacy: No literature related to pharmacogenomics impacting drug efficacy

Rasburicase: Clinical Application

• Toxicity: Rasburicase contraindicated in patients with $G6PD$ deficiency
• Black box warning to not administer in patient with known $G6PD$ deficiency and to screen patients at higher risk for $G6PD$ deficiency
• Overall incidence of hemolysis and methemoglobinemia < 1% in 703 patients in initial clinical trials for efficacy and safety
• Reactions occur 2-4 days from first administration of agent

Pharmacogenomic Test and Recommendations

• Genomic Testing: Phenotype blood test
  – Multiple sources of tests both commercial and institutional
  – The FDA and the rasburicase package insert recommends screening prior to initiating therapy
  (Elitek™ (Rasburicase) package insert. 2010, FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels, 2010)
• Recommendations:
  – Screening for $G6PD$ deficiency prior to prescribing rasburicase is not widely completed given the emergent need for use
  – If sufficient time is available prior to initiation of chemotherapy, screening may be helpful in patients at higher risk for having $G6PD$ deficiency (patients of African or Mediterranean descent)

Patient Case 5 Summary

• This patient was Caucasian and needed treatment of his hyperuricemia emergently.
• The medical team decided to forego $G6PD$ testing since the patient was not at highest risk for this enzyme deficiency.
• The patient received rasburicase 3 mg IV x 1 dose, allopurinol 300 mg PO daily, and began NS 200 ml/hr.
**Patient Case 6**

- 48 year old African American female
  - Symptoms: SOB, fatigue, fevers, sore throat
  - Labs
    - WBC: 120,000/mm³, Blasts: 90%, Hct: 25%, Platelets: 22,000/mm³
    - Bone marrow biopsy confirms AML
    - Normal cytogenetics: 46XX (46 is normal number of human chromosomes and XX represents a female)
    - FLT3 PCR amplification test: positive for FLT3-ITD (internal tandem duplication)
  - What are her treatment options?
  - What is her prognosis?

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**FLT3 (fms-like tyrosine kinase 3) in AML**

- The FLT3 gene encodes a class III tyrosine kinase receptor that regulates hematopoiesis
  - Receptor is composed of an extracellular domain, a transmembrane domain, a juxtamembrane domain, and a kinase domain (Sanz et al. 2009)

- The FLT3 receptor is activated by binding of the FLT3 ligand to the extracellular domain
  - Subsequently, downstream pathways involved in apoptosis, proliferation, and differentiation of hematopoietic cells in bone marrow are activated (Sanz et al. 2009)

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**FLT3 Structure**

- 2 distinct mutations in the juxtamembrane and kinase domains of the *FLT3* gene (Meshinchi et al 2009)
  - Internal tandem duplication (ITD)
  - Missense point mutation in the activation loop domain (D835Y)
FLT3 Mutations in AML

- Gene/Allele: FLT3 on chromosome 13q12
- Functional Effect: The presence of the FLT3-ITD (internal tandem duplication) mutation confers a poor prognosis in AML
- Population Prevalence: 25-45% of all AML patients carry a mutation (including both ITD and point mutations)
  - Prevalence of FLT3 ITD ~25-35% of all AML
    - Increases with age: Rare in infants; 5-10 years old (5-10%); young adults (20%); >55 years old (>35%)
  - Other diseases
    - Chronic myeloid leukemia (CML) 5-10%;
    - Myelodysplastic syndrome (MDS) 5-10%
  - Prevalence of FLT3 point mutation ~ 7% of AML patients
    - Consistent across all age ranges

Clinical Relevance

- Dose/Selection: Dosing may be affected by pharmacogenomic testing
  - Several FLT3 inhibitors are in Phase 3 clinical studies.
  - Lestaurinib Phase 2 study demonstrated that a cytotoxic effect of this agent required a 80% inhibition of FLT3 autophosphorylation
    - The dose required to achieve this inhibition varied between patients (Knapper et al 2006)

Clinical Relevance

- Dose/Selection: Selection of therapies may be affected by pharmacogenomic testing
  - FLT3-ITD patients should be evaluated for allogeneic hematopoietic stem cell transplant (HSCT) in their first complete remission (CR)
  - In a study of FLT3-ITD + patients, HSCT versus standard chemotherapy had a lower relapse risk (22% vs 49%) (Gale et al 2005)
  - Several other studies have confirmed that allogeneic transplant in first CR has improved overall survival (Meshinchi et al 2006)
  - FLT3 inhibitors may be an option in these patients in the future pending clinical trial outcomes and FDA approvals
Clinical Relevance

- Efficacy: Patients with FLT3-ITD + AML have similar complete remission rates after induction chemotherapy, but have shorter duration of responses and higher relapse rates.
- Overall response rates with FLT3 inhibitor monotherapy are 20-30%.
- Combination chemotherapy with FLT3 inhibitors have shown responses. Trials are ongoing.
- Toxicity: No literature related to pharmacogenomics.

Pharmacogenomic Testing Recommendations

- Genomic Test: PCR amplification
  - Multiple sources of tests both commercial and institutional (example: LabPMM FLT3 PCR)
- Recommendations:
  - Routine testing for FLT3 mutation at diagnosis is evolving as a standard practice for evaluating prognosis and determining treatment strategies.
  - Patients with FLT3-ITD + mutation who have relapsed may be considered for a clinical trial.

Patient Case 6 Summary

- FLT3-ITD confers an overall poor prognosis.
- She may start standard induction chemotherapy with cytarabine and daunorubicin.
  - Another option would be to start a clinical trial that includes a targeted agent of FLT3 (e.g., FLT3 inhibitor).
- After her first complete remission, she should be evaluated for possible hematopoietic stem cell transplant (Acute Myeloid Leukemia, NCCN Practice Guidelines in Oncology, 2010.)

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**References**


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**References**


Knapper S, et al. The effects of lestaurinib (CEP701) and PKC412 on primary AML blasts: the induction of cytotoxicity varies with dependence of FLT3 signaling in both FLT3-mutated and wild-type cases. Blood. 2006; 108; 3477-83.


References


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