Key Therapeutic Area: Hematologic Malignancies

Last Updated: 10 August 2010

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Presentation Outline

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

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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

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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

Mercaptopurine

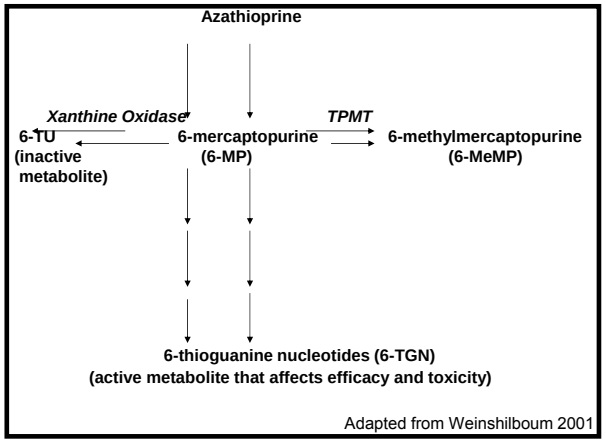
Patient Case 1

- 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/m^2 IV q 3 weeks x 6 doses
  - Vincristine 1.5 mg/m^2 IV q 8 weeks x 2 doses
  - Dexamethasone 6 mg/m^2/day PO x 7days
  - Mercaptopurine 50 mg/m^2 PO daily
  - Methotrexate 12 mg IT q 8 weeks
- After 3 weeks of consolidation, the patient presents with pancytopenia.
  - Absolute neutrophil count (ANC) 0 /mm^3, platelets 30,000/mm^3, Hct 30%
  - Other lab values are normal.
- What is the most likely cause for her profound myelosuppression?

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



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 Relevance

- 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.

Mercaptopurine: Clinical Applications

- 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

Methotrexate

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/m^2 IV over 4 hours along with leucovorin rescue (25 mg/m^2 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
  - methyltetrahydrofolate 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*

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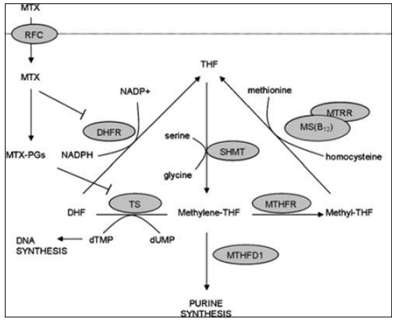
Methotrexate Metabolism



Simplified scheme illustrating folate metabolism. DHF, dihydrofolate; DHFR, dihydrofolate reductase; dTMP, deoxythymidine-50-monophosphate; dUMP, deoxyurindine-50-monophosphate; MTHFR, methylenetetrahydrofolate reductase; MS, methionine synthase; MTRR, methionine synthase reductase; MTX, methotrexate; MTX-PGs, methotrexate polyglutamates; RFC, reduced folate carrier; SHMT, serine hydroxymethyl transferase; THF, tetrahydrofolate; TS, thymidylate synthase

Reprinted by permission from Macmillan Publishers Ltd: [Leukemia Journal] (Huang L et al. Polymorphisms in folate-related genes: association with side effects of high-dose methotrexate in childhood acute lymphoblastic leukemia. Leukemia. 2008; 1798-1800), copyright (2008).

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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

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Methotrexate

- Population Prevalence: Varies greatly in different parts of the world.
  - Overall, *MTHFR 677C>T* 10% of the population is homozygous and 40% are heterozygous (Molloy et al 1997)

***MTHFR* Allele**	**Caucasians**	**Africans**	**Eastern Asians**
677C>T	34%	8%	42%
1298C>A	34%	9%	21%

(Rosenberg et al 2002)

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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
  - *GSTM1*0* (null) and *GSTA1*B*
- Functional Effect: Presence of *GSTA1*B* allele is associated with lower transcriptional activity. *GSTM1*0* allele confers no enzymatic functional activity. Presence of these variants may be associated with higher busulfan concentrations.
- Population Prevalence
  - *GSTM1*0*, 50% homozygous deletion
    - Arabs 44-56.3%, Asians 47.6-56.2%, Blacks 17-46.7%, Caucasian 34-58.3%, Native Latin-American 0-43% (DiPetro et al 2010)
  - *GSTA1*B*
    - Not clearly described

Busulfan: Clinical Relevance

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

Busulfan: Clinical Relevance

- IV Dosing
  - *GSTA1*B* and *GSTM1*0* are reported with conflicting association to busulfan pharmacokinetic variability *in vivo*
    - In 29 pediatric patients, IV busulfan clearance was lower with *GSTA1*B* variants thereby increasing busulfan concentrations. No difference in effect was seen with *GSTM1* polymorphisms. (Johnson et al 2008)
    - IV busulfan clearance was not correlated to any *GSTA1* or *GSTM1* polymorphisms in 77 pediatric patients receiving busulfan (Zwaveling et al 2008)
    - *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)

Busulfan: Clinical Reference

- Efficacy: No literature related to *GSTA1*B* or *GSTM1*0* impacting drug efficacy or outcomes
- Toxicity: Data are limited as to whether *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 *GSTM1*0* genotype (Srivastava et al 2004)

Pharmacogenomic Testing and Recommendations

- Genomic Test: Genotype test not commerically 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.

Nilotinib

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

Rasburicase

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* (*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 commerical 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.

FLT3 (fms-like tyrosine kinase 3) in AML

Patient Case 6

- 48 year old African American female
  - Symptoms: SOB, fatigue, fevers, sore throat
  - Labs
    - WBC: 120,000/mm^3, Blasts: 90%, Hct: 25%, Platelets: 22,000/mm^3
  - 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?

FLT3 Structure

- 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)

FLT3

- 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

- Prognosis: No difference in complete response rates after induction chemotherapy have been associated with *FLT3-ITD* mutations
- Higher relapse rates and worse overall survival have been associated with *FLT3-ITD* mutations
- *FLT3-ITD* is an independent prognostic factor for relapse and poor outcome in AML (Thiede et al 2002, Schnittger et al 2002)
  - Overall survival *FLT3 ITD* + 20-30% vs *FLT3 ITD* -, 50%
- Appears that the *FLT3* point mutation is not associated with an adverse outcome (Choudhary et al 2004)

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

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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

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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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Acknowledgements

- **Author**

  Amy Hatfield Seung, PharmD, BCOP
  Clinical Specialist, Hematologic Malignancies
  The Johns Hopkins Hospital
- **Reviewers and Editorial Staff**

  Primary Reviewer and Editor
  - Joseph D. Ma, PharmD

  Reviewers and Associate Editors
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  - Kelly C. Lee, PharmD, BCPP

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- **Project Coordinator**
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The program is 100% funded by the CDC
(*Grant Number IU38GD000070*)

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