Contents

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Welcome

On behalf of The Leukemia & Lymphoma Society (LLS), thank you for joining us for **Administration & Management of Current Therapies for Hematologic Malignancies**, a continuing education activity originally presented in Washington, DC.

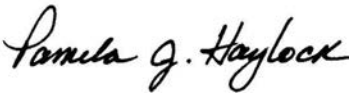
We also thank our esteemed speakers for sharing their time and expertise. Through this activity, they will discuss new drugs/new applications of drugs, methods of administration for new drugs, the importance of monitoring side effects and treatment adherence, management of potential treatment side effects, and communication touchpoints on side effects management and treatment adherence for nurses and patients.

This workbook includes the presenters' slides to help guide you through the activity. If you would like to receive 1.5 continuing education contact hours, please complete the online learning assessment and evaluation.

We hope this activity is informative and rewarding for you.

Sincerely,

Lauren Berger, MPH
Senior Director, Patient Services Programs
The Leukemia & Lymphoma Society



Pamela J. Haylock, PhD, RN, FAAN
Chair, Patient Services Committee
The Leukemia & Lymphoma Society

Agenda

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Welcome & Introductions
Pamela J. Haylock, PhD, RN, FAAN
Lauren Berger, MPH
The Leukemia & Lymphoma Society

Administration & Management of Current Therapies for Hematologic Malignancies

Monoclonal Antibodies in Hematologic Malignancies
Amy Goodrich, ACNP-BC

New Treatments for CML: The Nurse's Role in Side Effects Management and Therapy Adherence
Kevin Brigle, PhD, ANP

New Treatments for Myeloma: The Nurse's Role for Administration, Side Effects Management and Patient Education
Sylvia K. Wood, DNP, ANP-BC

Symposium Overview

TARGET AUDIENCE

This activity has been designed to meet the education needs of nurses, social workers and other healthcare professionals involved in the care of patients living with hematologic cancers.

PROGRAM GOAL AND OVERVIEW

Oncology nursing management includes thorough knowledge of drug administration and awareness of adverse effects, including those that may cause serious and life-threatening issues. Nurses must be not only knowledgeable about administering medicines and managing possible reactions, it is also important for nurses to initiate and foster ongoing communication about side effects management and treatment adherence with both other treatment team members and with patients.

With a number of new hematologic cancer drug approvals, as well as new indications, or newly approved methods of administration for approved drugs, continuing nursing education is essential.

Through discussion of case studies, this activity will provide the opportunity for nurses to build their knowledge about administering some of the current therapies used to treat hematologic malignancies. Monitoring and managing possible serious reactions, including infection, and communications among nurses, other treatment team members, and patients will be discussed.

EDUCATION OBJECTIVES

At the conclusion of this program, participants should be able to:

- List three new drugs/new applications of drugs to treat patients with blood cancer
- Explain methods of administration for two new drugs to treat patients with blood cancer
- Describe the importance of monitoring side effects and treatment adherence
- Identify management of two potential treatment side effects
- Identify two communication touchpoints on side effects management and treatment adherence for nurses and patients

CE Information & Disclosures

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NURSES AND SOCIAL WORKERS

Approval for nurses has been obtained by the national office of The Leukemia & Lymphoma Society under provider number CEP 5832 to award 1.5 continuing education contact hours through the California Board of Registered Nursing.

The Leukemia & Lymphoma Society (LLS), provider number 1105, is approved as a provider for social work continuing education by the Association of Social Work Boards (ASWB) www.aswb.org Approved Continuing Education Program (ACE). Approval Period: December 2011 - December 2014. LLS maintains responsibility for the program. Social workers should contact their regulatory board to determine course approval. Social workers will receive 1.5 CE clinical clock hours.

SUPPORT STATEMENT

This program is supported by grants from Millennium: The Takeda Oncology Company and Spectrum Pharmaceuticals.

FEE INFORMATION

There is no fee for this education activity.

FACULTY DISCLOSURES

All faculty participating in continuing education activities by The Leukemia & Lymphoma Society are expected to disclose to the activity participants any significant financial interest or other relationships with the manufacturer(s) of any commercial product(s) discussed in their presentations. Faculty also are expected to disclose any unlabeled or investigational uses of products discussed in their presentations.

- **Kevin Brigle, PhD, ANP**, has affiliations with Celgene, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals and Seattle Genetics *(Speakers Bureau)*.
- **Amy Goodrich, ACNP-BC**, has no affiliations with commercial interests to disclose.
- **Sylvia K. Wood, DNP, ANP-BC**, has an affiliation with Onyx Pharmaceuticals *(Speakers Bureau)*.

Faculty Biography

Amy Goodrich, ACNP-BC

Nurse Practitioner
Johns Hopkins Kimmel Cancer Center
Baltimore, MD

Amy Goodrich, ACNP-BC, is a nurse practitioner in the hematologic malignancies program and research nursing manager at the Johns Hopkins Kimmel Cancer Center in Baltimore, Maryland. Ms. Goodrich manages patients with various types of hematologic malignancies, concentrating on the lymphomas. She also manages the cancer center's research nurses and is extremely involved in research operations.

Ms. Goodrich earned her master's degree in 2000 as an acute care nurse practitioner from the Johns Hopkins University and her undergraduate nursing degree from the University of Pittsburgh. She has published and presented extensively on various research topics, hematologic malignancies, new agents, symptom management, and other topics important to research and clinical professionals.

Faculty Biography

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Kevin Brigle, PhD, ANP

Oncology Nurse Practitioner
Massey Cancer Center
Virginia Commonwealth University Health System
Richmond, VA

Kevin Brigle, PhD, ANP, is an oncology nurse practitioner in the hematological malignancies clinic at the NCI-designated Massey Cancer Center in the Virginia Commonwealth University Health System. He earned his bachelor's degree in biology from the University of Dayton in Dayton, Ohio followed by a PhD in molecular microbiology from Virginia Tech in Blacksburg, Virginia. Following completion of his dissertation, he took a position as a post-doctoral fellow and later as a laboratory director in the division of hematology and oncology at Virginia Commonwealth University in Richmond, Virginia.

While consulting on an NIH-funded grant in the School of Nursing at Virginia Commonwealth University, Dr. Brigle enrolled in the nurse practitioner program and graduated in 1998. Following one year of practice as an acute care nurse practitioner in the department of internal medicine, he came to his current position as an oncology nurse practitioner.

Faculty Biography

Sylvia K. Wood, DNP, ANP-BC

Adult Nurse Practitioner
Associate Director, BMT Clinical Research Program
Hematologic Malignancy Stem Cell Transplant Program
Stony Brook University Medical Center
Stony Brook, NY

Sylvia K. Wood, DNP, ANP-BC, is a nurse practitioner, associate director of the bone marrow transplant clinical research program, and clinical instructor in the department of medicine at Stony Brook University Medical Center, also serving as adjunct instructor and assistant professor at Long Island University. Dr. Wood received her bachelor of science degree in nursing at Roberts Wesleyan College in Rochester, New York and her master of science in the adult nurse practitioner and doctorate of nursing practice program at Stony Brook University.

Dr. Wood has lectured extensively and is the lead author for articles on treatment-related side effects of cancer published in peer-reviewed journals. In addition she serves as the co-investigator on multiple clinical trials evaluating novel agents in hematologic malignancies.

Presentations

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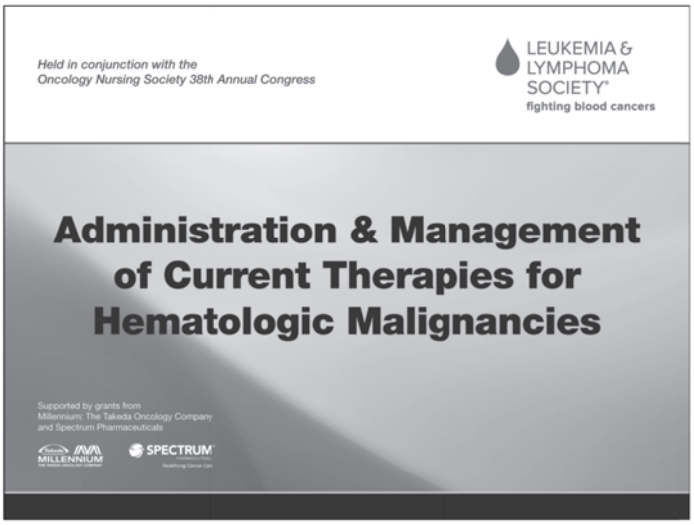

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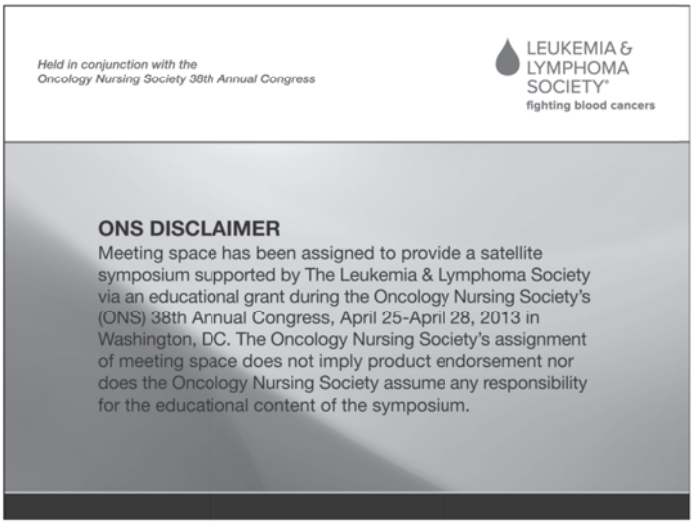

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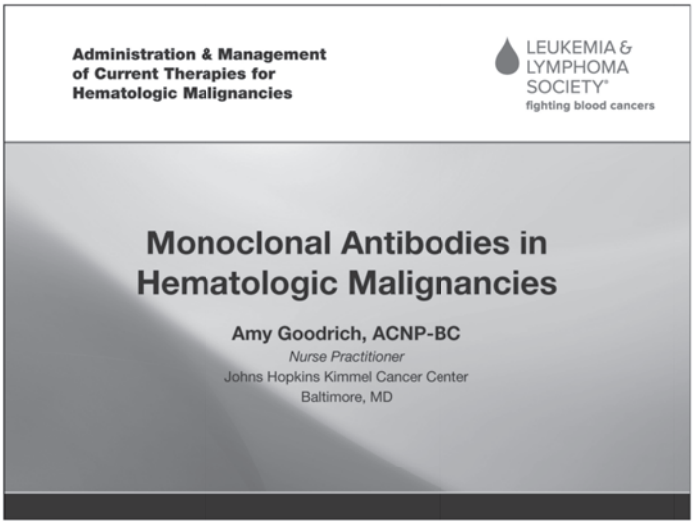
Presentations



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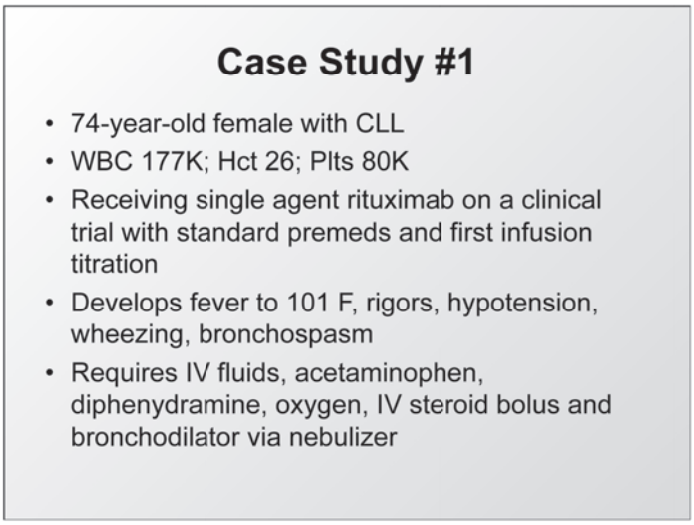

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Case Study #1

- Stabilized, rituximab stopped, watched for several hours
- Instructed to take running acetaminophen and diphenhydramine at home
- No problems overnight
- Completes remaining dose on Day 2 without incident
- Patient goes on to receive all subsequent doses of rituximab without problem

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Question #1

- Did this patient experience an infusion-related reaction or an allergic reaction?
- A. Infusion-related reaction
- B. Allergic reaction

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Presentations

Case Study #2

- 65-year-old man with relapsed follicular lymphoma, receiving CHOP and rituximab as third-line therapy
- All prior regimens included rituximab

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Case Study #2

Cycle	Premeds	Reaction
1	Acetaminophen 650 mg and diphenhydramine 25 mg po	- Mild hives responsive to diphenhydramine
2	Acetaminophen 650 mg and diphenhydramine 50 mg po	- Stabbing low back pain responsive to holding infusion, oxycodone, additional diphenhydramine and 100 mg IV solucortef. Completed infusion. - Developed fever, chills, vomiting - admitted for 2 days, symptoms resolved
3	DAYS 1 and 2 - Acetaminophen 650 mg, diphenhydramine mg IV, hydrocortisone 100mg IV, ranitidine 50 mg IV, lorazepam 0.5 mg IV	- Initial infusion rate used DAY 1 - Stabbing low back pain responsive to stopping infusion and 2 mg morphine IV. Infusion left at 75 mg/hr and received 50% of dose. Given 20 mg prednisone to take at bedtime and to receive 50% on Day 2 DAY 2 - Titrated to 75 mg/hr max - Rash mid-way through, responsive to diphenhydramine; Tylenol repeated. - Rash at end of infusion, responsive to diphenhydramine. Instructed to take OTC benadryl q 4-6 hours RTC x 24 hours
4	DAY 1 - Acetaminophen 650 mg, diphenhydramine mg IV, hydrocortisone 100mg IV, ranitidine 50 mg IV, loratadine 20 mg, lorazepam 0.5 mg IV	2-day infusion planned with 75 mg/hr max - Chest tightness, infusion stopped, EKG normal, resolved - Restarted at 50 mg/hr - Hives with pruritis responsive to infusion stop and diphenhydramine - Throat tightness responsive to stopping infusion - Rituximab abandoned

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Question #2

- Did this patient experience an infusion-related reaction or an allergic reaction?
- A. Infusion-related reaction
- B. Allergic reaction

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History of FDA-Approved Monoclonal Antibodies in Hematologic Malignancies

- 1997- Rituximab (Rituxan®)
- 2000 - Gemtuzumab ozogamicin (Mylotarg®)
- 2001- Alemtuzumab (Campath®)
- 2002 - Ibritumomab tiuxetan (Zevalin®)
- 2003 - Tositumomab (Bexxar®)
- 2009 - Ofatumumab (Arzerra®)
- 2011- Brentuximab vedotin (Adcetris®)

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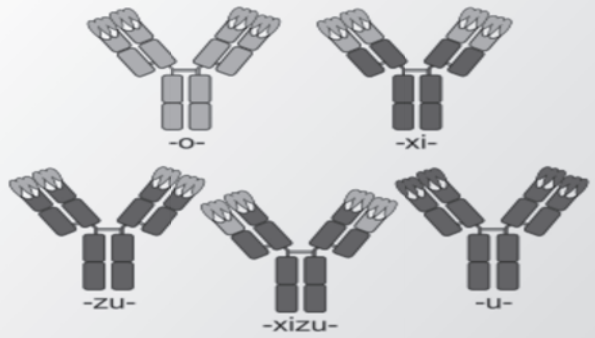
Presentations

Types of Monoclonal Antibodies



http://commons.wikimedia.org/wiki/File:Chimeric_and_humanized_antibodies_with_CDRs.svg

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How Antibodies Work

- 4 main mechanisms of action
  - Apoptosis
  - Neutralization
  - Antibody-Dependent Cellular Cytotoxicity
  - Complement-Dependent Cytotoxicity

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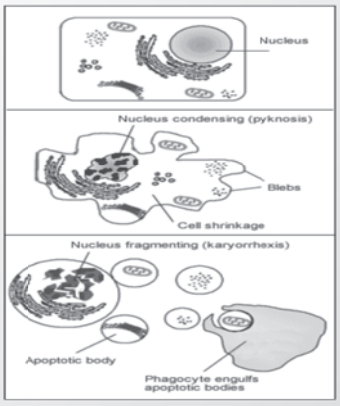
Apoptosis



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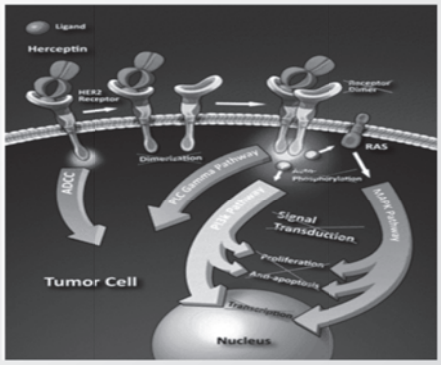
Neutralization



AJNR. 2011;32:1373-1374.

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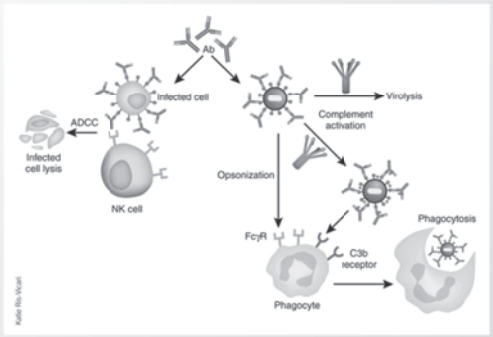
Presentations

Antibody-Dependent Cellular Cytotoxicity and Complement-Dependent Cytotoxicity



Marasco WA, Sui J. *Nature Biotechnology*. Dec 7, 2007.

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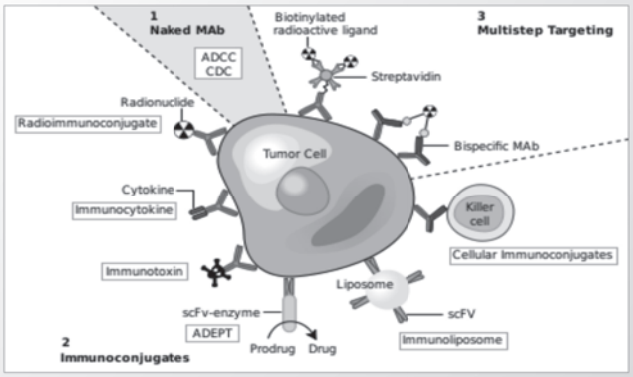
Conjugated vs Unconjugated



MD Becker Partners (www.mdbpartners.com).

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Infusion Reactions During Monoclonal Antibody Therapy

- Cytokines are proteins produced by most cells and include:
  - Interleukins
  - Interferons
  - Tumor necrosis factor
  - Colony stimulating factors
- Act as chemical messengers
  - Promote or inhibit cell growth
  - Activate lymphocytes and other immune effector cells
  - Mediate destruction of cells targeted by MoAb
  - Mediate inflammatory response
- When the cell is destroyed, cytokines and recruited cells are released into circulation (cytokine-release syndrome)

MoAb = monoclonal antibody

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Cytokine Release Syndrome/ Infusion Reaction

- Most common in first infusions when the highest number of targeted cells are being cleared
- Generally occurs in the first 2 hours of infusion
- Severity commonly mild to moderate
- Less reactions and reduced severity with subsequent infusions

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Presentations

Cytokine Release Syndrome/ Infusion Reaction (cont.) Severe and Allergic Reactions

- Severe and fatal infusion reactions possible
- Severe infusion reactions typically occur within minutes of infusion and include:
  - High fever
  - Dyspnea
  - Rigors
  - Bronchospasm
  - Hypoxemia
  - Acute respiratory distress syndrome
  - Pulmonary infiltrates and edema
  - Severe hypotension
  - Loss of consciousness
  - Cardiac and/or respiratory arrest
- True allergic reactions are characterized by increasing severity of signs and symptoms, despite maximizing premedications and other supportive care with each subsequent infusion
- Accounts for a VERY small number of reactions in patients receiving monoclonal antibodies
- When true allergy is suspected, patients are not typically not re-challenged at any time
- May be fatal

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Signs and Symptoms of Anaphylaxis

- Serious upper airway (laryngeal edema) or lower airway edema (asthma) may develop
  - Stridor, wheezing
  - Rhinitis
- Cardiovascular collapse
  - Vasodilation produces hypovolemia
  - Increased capillary permeability produces intravascular volume loss
  - Patient may be agitated or anxious, flushed, or pale
  - Cardiac dysfunction may occur from disease or ischemia from epinephrine
- Gastrointestinal signs and symptoms
  - Abdominal pain, vomiting, and diarrhea

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Grading of Infusion-Related Reaction

Grade	Description
1	Mild transient reaction; no infusion change indicated; no intervention
2	Infusion interrupted and responds promptly to symptom-directed treatment; prevention medication indicated for no more than 24 hours
3	Prolonged reaction not rapidly responsive to symptom-directed treatment and/or interruption of infusion; recurrent symptoms after initial improvement; hospitalization indicated
4	Life-threatening; urgent intervention required
5	Death

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Grading of Anaphylaxis

Grade	Description
3	Bronchospasm; parenteral intervention required; edema or angioedema; hypotension
4	Life-threatening; urgent intervention required
5	Death

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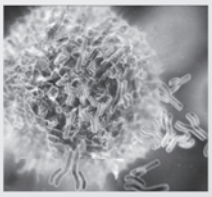
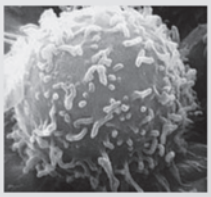
Presentations

Rituximab

- IgG antibody to CD20
- Activates complement cascade, ADCC, apoptosis
- Depletes B-cells from peripheral blood, lymph nodes, and bone marrow
  - Does not affect stem cells
- Broad indication in NHL
  - 375 mg/m^2 IV by a variety of schedules
  - 250 mg/m^2 IV as part of Zevalin therapy





ADCC = antibody-dependent cellular cytotoxicity

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Administration Schedule for Rapid Rituximab Infusion

- Eligibility for Rapid Infusion
  - Second or subsequent dose of rituximab
  - No severe reaction to previous dose of rituximab
  - Lymphocyte count ≤50,000/mm3
  - Previous dose of rituximab was less than 4 months prior to this dose
- Premedications
  - Diphenhydramine 50 mg PO
  - Acetaminophen 650-1000 mg PO
  - Daily prednisone dose according to chemotherapy protocol
- Cycle 1
  Rituximab 375 mg/m^2 IV infused according to product monograph
- Cycles 2-8
  Rituximab 375 mg/m^2 IV in 250 mL
  - 20% of dose infused over 30 minutes
  - Remaining 80% of dose infused over 60 minutes
  - Total infusion time of 90 minutes

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Alemtuzumab

- Humanized anti-CD52 monoclonal antibody
- Indicated for the treatment of CLL
- Mechanism of action: ADCC
- CD52 is expressed on
  - Mature B and T lymphocytes
  - Monocytes and macrophages
  - Dendritic cells
  - NK cells
  - Granulocytes
  - Bone marrow stem cells
  - Male genital trace
  - Mature sperm cells

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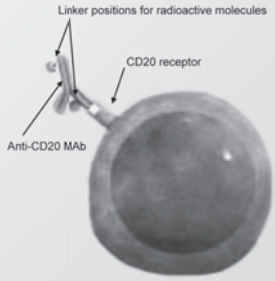
Radioimmunotherapy

- Indicated in low-grade NHL
- Anti-CD20 MAb linked with radioactive molecule
  - Combines irradiation damage with antibody-associated cytotoxicity
- Two-phase treatment regimen
  - Phase 1: dosimetry / biodistribution
  - Phase 2: therapy



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Presentations

Radioimmunotherapy Side Effects

Toxicity	*Incidence*	*Intervention*
Infusion reactions	~26%, including bronchospasm, chills, dyspnea, fever, hypotersion, nausea, rigors, diaphoresis	▪ Prophylaxis: antihistamine and acetaminophen before and q4 h during administration; withhold antihypertensives 12 h before infusion; screen for HAMA ▪ Symptomatic treatment for mild reactions, aggressive treatment for severe reactions ▪ Antihistamines, corticosteroids, epinephrine
Prolonged severe cytopenias	Grade 3-4 thrombocytopenia, neutropenia common (up to 86%) Nadir: 7-9 weeks Duration: 22-35 + days	▪ Do not administer to patients with 25% marrow involvement and/or impaired marrow reserve ▪ Monitor counts closely, and delay dosing until counts recover ▪ Hematopoietic growth factor support
GI toxicity	~50%; abdominal pain, diarrhea, nausea	▪ Antiemetic prophylaxis ▪ Bulk-forming laxatives such as Metamucil® ▪ Loperamide ▪ Adequate fluid intake
Asthenia	43%-47%; grade 3-4 <5%	▪ Adequate hydration, nutrition, rest ▪ Exercise as capable

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Ofatumumab

- Humanized anti-CD20 monoclonal antibody
- Indicated for the treatment of CLL
- As with rituximab, CD20 expressed on mature B-cells
- No CD20 expression on bone marrow stem cells
- Mechanisms of action
  - ADCC
  - CDC

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Brentuximab-Vedotin

- Anti-CD30 chimeric monoclonal antibody conjugated to monomethyl auristatin E (MMAE), a synthetic antitublin agent
- Mechanisms of Action: ADCC and apoptosis
- CD30 found on:
  - Small numbers of activated B and T lymphocytes
  - Small portion of eosinophils
  - A number of malignant lymphomas
    - Hodgkin lymphoma
    - Anaplastic large cell lymphoma
    - Some cases of mediastinal large cell lymphoma
    - Primary effusion lymphoma
    - Multiple myeloma
    - Embryonal carcinomas

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Minimizing Infusion Reactions

- Comprehensive allergy history
- Know:
  - The target
  - The tumor burden
  - The patient's risk factors
- Premedication
- Desensitization
- Diligent monitoring
- Prompt intervention
  - Alteration of infusion rates
  - Supportive care (pharmacologic and non-pharmacologic)

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Presentations

Premedications and Black Box Warnings for Monoclonal Antibodies

Agent	Black Box Warning for IRR	Type of Monoclonal Antibody	Premedication
Ibritumomab tiuxetan	Yes	Murine	Acetaminophen and diphenhydramine
Tositumomab	Yes	Murine	Acetaminophen and diphenhydramine
Rituximab	Yes	Chimeric	Acetaminophen and diphenhydramine
Brentuximab vedotin	No	Chimeric, conjugated with a drug	None required
Gemtuzumab ozogamicin Not currently available on the US market	Yes	Humanized, conjugated with an antitumor antibiotic	Diphenhydramine and acetaminophen initially, then 2 more doses of acetaminophen
Ofatumumab	Yes	Humanized	Acetaminophen, antihistamine and IV corticosteroid

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Patient Education

- Antibody education
- Expected side effects
- Prophylaxis plan
- How side effects will be managed
- What to expect and report after returning home
- Medication instructions after infusion

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Case Study #1

- Elderly female with CLL receiving rituximab with significant reaction with initial dose but no issues with subsequent doses

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Question #1

- Did this patient experience an infusion-related reaction or an allergic reaction?
- A. Infusion-related reaction
- B. Allergic reaction

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Presentations

Case Study #2

- 65-year-old man with follicular lymphoma on third-line therapy with worsening infusion related reactions despite increasing prophylaxis and supportive care

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Question #2

- Did this patient experience an infusion-related reaction or an allergic reaction?
- A. Infusion related reaction
- B. Allergic reaction

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Administration & Management of Current Therapies for Hematologic Malignancies
LEUKEMIA & LYMPHOMA SOCIETY®
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New Treatments for CML: The Nurse's Role in Side Effects Management and Therapy Adherence
Kevin Brigle, PhD, ANP
Oncology Nurse Practitioner
Massey Cancer Center
Virginia Commonwealth University Health System
Richmond, VA

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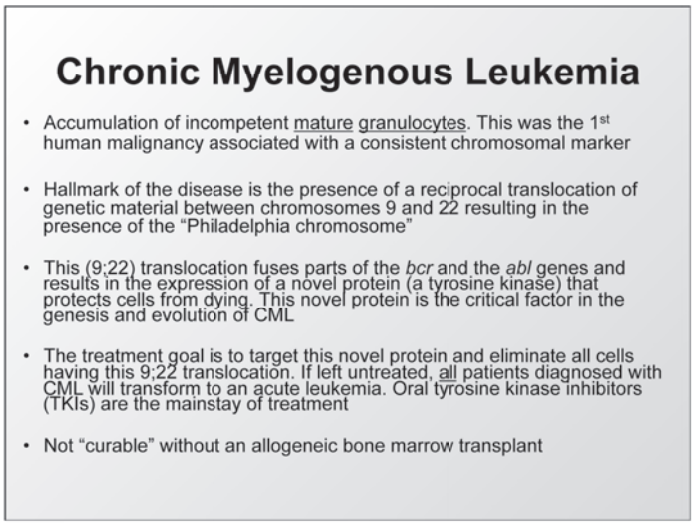
Chronic Myelogenous Leukemia
• Accumulation of incompetent mature granulocytes. This was the 1st human malignancy associated with a consistent chromosomal marker
• Hallmark of the disease is the presence of a reciprocal translocation of genetic material between chromosomes 9 and 22 resulting in the presence of the "Philadelphia chromosome"
• This (9;22) translocation fuses parts of the bcr and the abl genes and results in the expression of a novel protein (a tyrosine kinase) that protects cells from dying. This novel protein is the critical factor in the genesis and evolution of CML
• The treatment goal is to target this novel protein and eliminate all cells having this 9;22 translocation. If left untreated, all patients diagnosed with CML will transform to an acute leukemia. Oral tyrosine kinase inhibitors (TKIs) are the mainstay of treatment
• Not "curable" without an allogeneic bone marrow transplant

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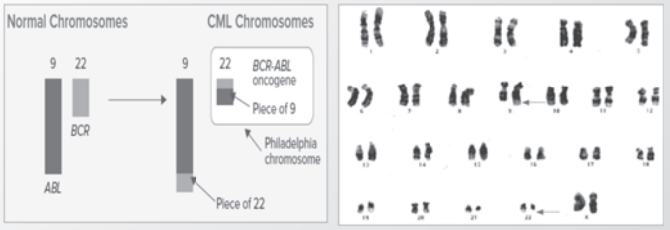
Presentations

The Philadelphia Chromosome



The Philadelphia chromosome

http://www.lls.org/#/resourcecenter/freeeducationmaterials/leukemia/cml

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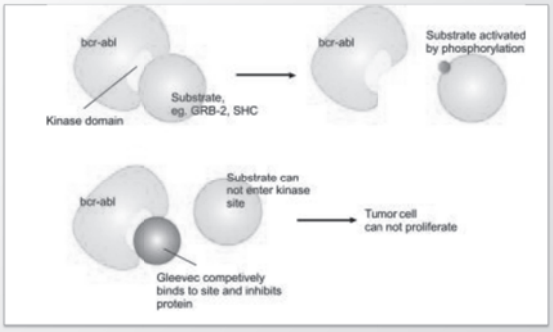
Gleevec®: The Proof of Principle Drug
A Tyrosine Kinase Inhibitor (TKI)



www.chemistrydaily.com/chemistry/Image:Mechanism_imatinib.jpg

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Definitions of Response in Chronic Phase CML

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- **Hematologic responses:** Based on peripheral blood counts and the differential
- **Cytogenetic responses:** Based on identifying the presence of 9;22 positive cells by cytogenetic analysis (1:20 cells) or by FISH analysis (1:500 cells)
- **Molecular responses:** Based on identifying the presence of 9;22 positive cells by PCR analysis (1:100,000 cells)

	Hematological Response (HR)	Cytogenetic Response (CyR)	Molecular Response (MR)*
Response Definitions	**Complete (CHR):** Platelets <450 x 10^9/L; WBC count <10 x 10^9/L; differential without immature granulocytes and <5% basophils; nonpalpable spleen	**Complete (CCyR):** Ph+ 0% **Partial (PCyR):** Ph+ 1%-35% **Minor:** Ph+ 36%-65% **Minimal:** Ph+ 66%-95% **None:** Ph+ >95% **Major:** PCyR + CCyR	**Complete:** Transcripts non-quantifiable and undetectable **Major:** 0.1%†
Monitoring Frequency	▪ **Every 2 weeks** until a complete response has been achieved and confirmed ▪ **Every 3 months** unless otherwise required	▪ **Every 6 months** until a complete response has been achieved and confirmed ▪ **Then every 12 months**	▪ **Every 3 months**

*FISH = Fluorescent In-Situ Hybridization; PCR = Polymerase Chain Reaction

Monitoring Response: Assay Sensitivity

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- The monitoring assays need to become more sensitive as the CML disease burden decreases as treatment continues
- **Cytogenetics:** Can identify a 1-2 log reduction in the number of Philadelphia chromosome positive cells
- **Fluorescent In-Situ Hybridization (FISH):** Can identify a 1-3 log reduction in the number of Philadelphia chromosome positive cells
- **Reverse-Transcribed Polymerase Chain Reaction (RT-PCR):** Can identify a 5-6 log reduction in the number of Philadelphia chromosome positive cells

*FISH = Fluorescent In-Situ Hybridization; RT-PCR = Reverse Transcriptase-Polymerase Chain Reaction

Presentations

Expected Response *versus* Time in Chronic Phase CML

Time frame	Optimal	Suboptimal	Failure
Baseline	NA	NA	NA
3 months	CHR and minor CyR (≤65% Ph⁺)	No CyR (>95% Ph⁺)	No CHR
6 months	PCyR (≤35% Ph⁺)	Less than a PCyR (35%-95%Ph⁺)	No CyR (>95% Ph⁺)
12 months	CCyR (no Ph⁺)	PCyR (≤35% Ph⁺)	Less than a PCyR
18 months	MMR (<0.1% QPCR transcripts)	No MMR	Less than CCyR
Anytime during treatment	Stable or improving MMR	Loss of MMR, development of mutations	Loss of CHR or CCyR, development of new mutations or chromosome abnormalities

•CHR = Complete Hematologic Response; CyR = Cytogenetic Response; PCyR = Partial Cytogenetic Response; CCyR = Complete Cytogenetic Response; MMR = Major Molecular Response; QPCR = Quantitative Polymerase Chain Reaction
•All from European Leukemia Net (ELN)

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Question #1

What symptom is common to all of the oral tyrosine kinase inhibitors?

A. Constipation
B. Headache
C. Fluid retention
D. Prolongation of QTc interval

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Case Study

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- JR is a 33-year-old male diagnosed with chronic phase CML. He was started on imatinib 400 mg daily and experienced Grade 3/4 diarrhea that did not respond to treatment
- After one month he was switched to a second generation TKI (dasatinib). Each of the TKIs has their own unique side effects that can help determine which drug will be used

Drug	Dose	Side Effects
Imatinib (Gleevec®)	400-800 mg PO daily with food	Neutropenia and thrombocytopenia, fluid retention, edema, diarrhea, nausea, muscle cramps, and rash
Dasatinib (Sprycel®)	100 mg PO daily with or without food	Neutropenia and thrombocytopenia, fluid retention, pleural/pericardial effusion, nausea, diarrhea, headache, fatigue, dyspnea, and rash
Nilotinib (Tasigna®)	300 mg PO twice daily (1st line) and 400 mg PO twice daily (2nd line) on an empty stomach	Neutropenia and thrombocytopenia, prolongation of QT interval (black box warning), elevated levels of amylase, lipase, bilirubin and transaminases, decreased electrolytes, fluid retention, nausea, diarrhea, headache, rash, and peripheral arterial occlusive disease

Intolerance to Therapy

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- Life-threatening Grade 4 non-hematologic toxicity
- Grade 3/4 non-hematologic toxicity that has recurred despite dose reduction and optimal symptom management
- Grade 2 non-hematologic toxicity persisting >1 month or recurring >3 times despite dose reduction and optimal symptom management–i.e., adversely impacts function and quality of life
- Grade 3/4 hematologic toxicity that is unresponsive to optimal management and would require dose reductions below the accepted minimal effective dose

Presentations

Symptom Management

Adverse Event	Management
Nausea/vomiting	Antiemetics; Take imatinib with food
Diarrhea	Loperamide or diphenoxylate and atropine
Peripheral edema	Diuretics and monitor electrolytes
Periorbital edema	Steroid-containing cream
Rash	Topical or systemic steroids
Cramps	Calcium supplement, tonic water
Arthralgia/bone pain	NSAIDs
Pleural effusion	Diuretics; Short course of corticosteroids; Thoracentesis if symptomatic
↑ Lipase/amylase	Evaluate for signs/symptoms of pancreatitis
↑ Transaminases	Monitor until Grade 3
↑ Bilirubin	Monitor until Grade 3
QTc prolongation	Assess prior to starting therapy; Correct electrolytes; Avoid co-administration of other agents that prolong QTc

- For all symptoms, consider dose reduction, treatment interruption, or switch to a different TKI
- Inadequate symptom management is a significant factor in nonadherence to treatment

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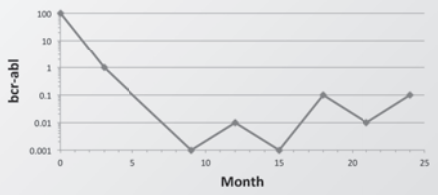
Case Study

- After starting dasatinib, JR achieved a rapid reduction in *bcr-abl* levels by 3 months and *bcr-abl* became undetectable by 9 months. However, he began to experience serial increases and declines over the next 12 months.
  - Fluctuating levels of *bcr-abl* by orders of magnitude rarely occurs in acquired resistance, i.e., the development of mutations
  - This pattern is more commonly seen as a result of nonadherence to a medication regimen



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Adherence to Therapy

- Medication Adherence: "Extent of conformity to the recommended treatment plan by the provider with respect to dose, timing and frequency."

***Blood*. 2009;113(22):5401-5411.**
- 33% of patients nonadherent to Gleevec
- Only 14% patients completely adherent

***Journal of Oncology Practice*. 2013;9:5s-13s.**
- ASCO/ONS chemo administration safety standards update
- Nine new standards: majority specific to oral cancer agents including monitoring adherence

- The World Health Organization attributes nonadherence to five interrelated factors
  - Health system factors
  - Social/economic factors
  - Condition-related factors
  - Therapy-related factors
  - Patient-related factors

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Question #2

Costs for patient education concerning oral medications are increasingly being covered by insurance companies.

A. True
B. False

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Presentations

Factors Affecting Adherence

Social/Economic Factors	Language proficiency, family/social support, living conditions, access to health care/pharmacy services, lack of insurance, cultural beliefs
Health Care System Factors	Provider-patient relationship and communication skills, ineffective patient education, lack of positive reinforcement, high drug costs, long wait times, poor continuity of care
Condition-Related Factors	Lack or severity of symptoms, chronicity of problem, depression/ psychiatric disorders
Therapy-Related Factors	Complexity of regimen, duration of therapy, actual or perceived side effects, interference with life-style, stigma attached to therapy
Patient-Related Factors	Visual, hearing or cognitive impairment, impaired mobility or swallowing, understanding of disease and medication, stigma of disease, motivation, fear of side effects versus perceived benefit, confidence to follow the regimen, frustration with health care system, alcohol or substance abuse, stress or anger

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Oral Medications

- Approximately 25% of oncology drugs are oral formulations
  - Shifts burden of adherence to the patient and their family
- Adherence was long ignored with oncology drugs
  - Assumed oncology patients "will do what was good for them"
  - Assumed oncology patients knew the dire consequences of missing doses
- As cancer becomes a "chronic" disease, oral drugs become long term
  - Diabetes and hypertension medications have 50% complete adherence rates
  - Missing doses does not make patients feel bad
  - Along with medications taken for other chronic conditions, the sheer number of pills creates issues
  - Patients have increased opportunities for interactions (side effects) with newly prescribed drugs for other chronic conditions
- Nonadherence can be unintentional
  - Patients may think they are taking it correctly
  - Patients may not report side effects such as diarrhea which impacts absorption
  - Patients occasionally just "forget" or the timing does not fit into their plans

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Improving Adherence

- "Oral chemotherapy" nurse
  - One-on-one education sessions–discuss barriers to the treatment plan and find solutions
  - Costs for patient education are not covered by insurance
- Manage Side Effects
  - Physical and emotional/self image
- Insurance companies
  - Adherence programs
- Dispensing pharmacy
  - Follow up phone calls and counseling
- Reminder phone calls/texts/emails
- Online calendar automatically linked to email (Google calendar)
- Reminder apps –smartphone or device
  - Pillboxie (iOS), RxmindMe (iOS), and MedCoach (Android/iOS)
  - www.CMLTrackerLLS.org
  - Beware patients may suffer "Alert Fatigue"
- "Low tech" written calendars, or pill diaries or alarm clocks
  - Track daily side effects
- Beware of the "Hawthorne effect"
  - Patients over-report adherence because of desire to please providers

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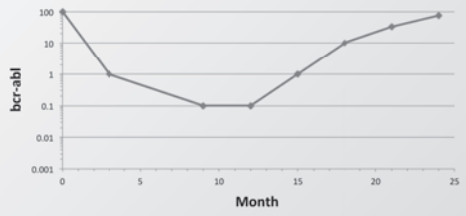
Case Study

- After starting dasatinib JR achieved a partial cytogenetic response by 9 months but never achieved a major reduction in *bcr-abl* levels. He then experienced a rapid increase in *bcr-abl* levels over the next 12 months. Mutation analysis showed the presence of the T315I mutation.
  - A rapid rise in *bcr-abl* transcripts often indicates loss of kinase inhibition and the emergence of mutations which are resistant to a specific TKI



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Presentations

Question #3

Which oral drug is effective against the T315I mutation?

A. Gleevec
B. Nilotinib
C. Bosutinib
D. Ponatinib
E. Omacetaxine mepesuccinate

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Treatment Options Based on *bcr-abl* Kinase Domain Mutation Status

- Mutation analysis should be performed if the patient shows:
  - Inadequate initial response
  - Loss of response
  - Disease progression to accelerated or blast phase

Mutation	Treatment Options
T315I*	Ponatinib (preferred) or omacetaxine, HSCT or clinical trial
V299L	Consider ponatinib, nilotinib or omacetaxine
T315A	Consider ponatinib, nilotinib, imatinib, bosutinib or omacetaxine
F317L/V/I/C	Consider ponatinib, nilotinib, bosutinib or omacetaxine
Y253H, E255K/V, F359V/C/I	Consider ponatinib, dasatinib, bosutinib or omacetaxine
Any other mutation	Consider ponatinib, high-dose imatinib, dasatinib, nilotinib, bosutinib or omacetaxine

•HSCT – Hematopoetic Stem Cell Transplant

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Protein Translation Inhibitor

- JR was switched to omacetaxine mepesuccinate. This is the only approved agent that is not a protein kinase inhibitor and which is effective against the T315I mutation. Within two months he had complete hematologic response but did not like being "tied to injections" every 12 hours. He began to miss scheduled injections and asked for another treatment option as "inconvenience" was becoming his main side effect

Drug	Dose	Side Effects
Omacetaxine mepesuccinate (Synribo™) **•Effective for T135I mutation** **•Approved October 2012**	1.25 mg/m^2 subcut x 14 days every 28 days until CHR. Then subcut x 7 days every 28 days	Neutropenia and thrombocytopenia, hyperglycemia, and diarrhea

- Reconstitute vial with 1 ml normal saline. The resulting solution will contain 3.5 mg/ml of drug. Protect reconstituted solution from light. Use within 12 hours if stored at room temperature and within 24 hours if refrigerated.

CHR = Complete Hematologic Response

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Case Study

- As such, JR was switched to ponatinib, the only approved kinase inhibitor that is effective against the T315I mutation. Bosutinib, also approved in 2012, is not effective against this mutation
- Due to his young age, he was also sent to be evaluated for a potential allogeneic bone marrow transplant should this drug fail to control his disease

Drug	Dose	Side Effects
Bosutinib (Bosulif®) **Approved October 2012**	500 mg PO daily with food. May increase to 600 mg	Neutropenia and thrombocytopenia, fluid retention, diarrhea, nausea, vomiting, abdominal pain, rash, hepatic toxicity, and fever
Ponatinib (Iclusig™) **•Effective for T135I mutation** **•Approved December 2012**	45 mg PO daily with or without food.	Neutropenia and thrombocytopenia, arterial thrombosis (black box warring), hepatotoxicity (black box warring), pancreatitis, fluid retention, rash, constipation, nausea, and headache

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Presentations

Case Study

- Prior to starting ponatinib, JR participated in a nurse-led one-on-one education session
- A "pill reminder app" was loaded onto his smartphone. He was shown how to use it and how to transmit the medication log to the clinic nurse
- In addition, a clinic nurse made periodic follow-up phone calls to JR to discuss side effects. Later, they agreed to simply text each other on a regular basis
- JR achieved a complete molecular remission within 9 months and, to date, he has avoided the need for an allogeneic bone marrow transplant. He continues to text his clinic nurse

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Question #1

What symptom is common to all of the oral tyrosine kinase inhibitors?

A. Constipation
B. Headache
C. Fluid retention
D. Prolongation of QTc interval

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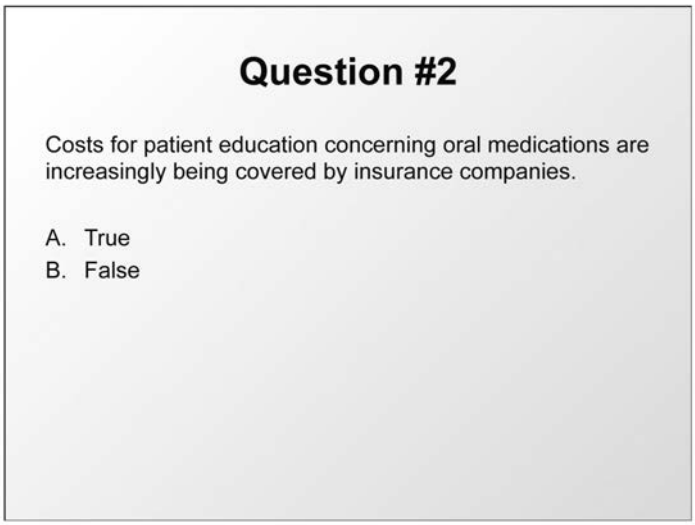
Question #2
Costs for patient education concerning oral medications are increasingly being covered by insurance companies.
A. True
B. False

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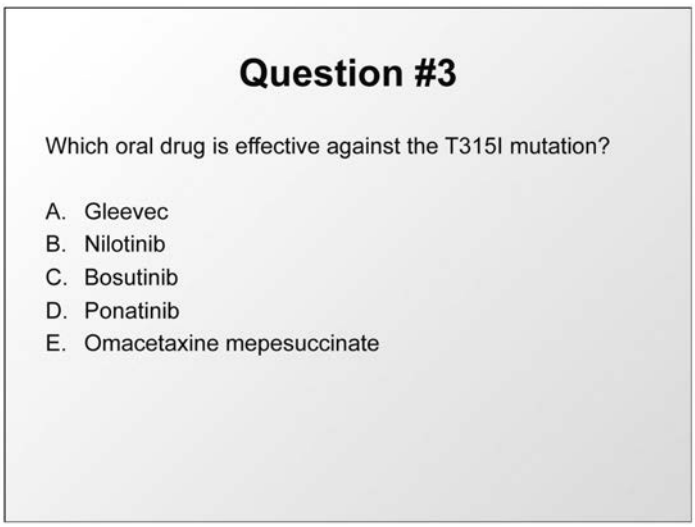
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A. Gleevec
B. Nilotinib
C. Bosutinib
D. Ponatinib
E. Omacetaxine mepesuccinate

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Presentations

Administration & Management of Current Therapies for Hematologic Malignancies

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New Treatments for Myeloma: The Nurse's Role for Administration, Side Effects Management and Patient Education

Sylvia K. Wood, DNP, ANP-BC
Adult Nurse Practitioner
Associate Director, BMT Clinical Research Program
Hematologic Malignancy Stem Cell Transplant Program
Stony Brook University Medical Center
Stony Brook, NY

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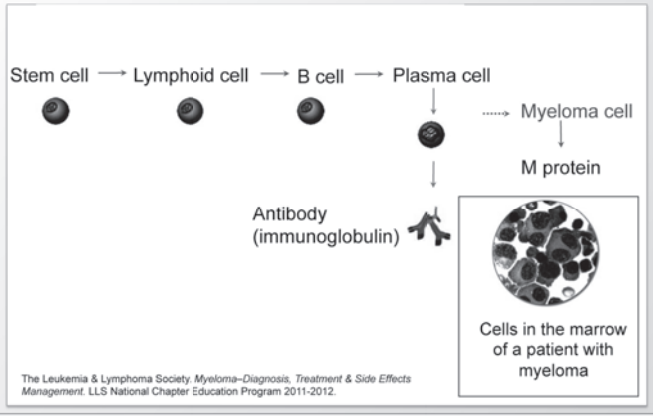
Development of a Myeloma Cell



The Leukemia & Lymphoma Society. *Myeloma–Diagnosis, Treatment & Side Effects Management.* LLS National Chapter Education Program 2011-2012.

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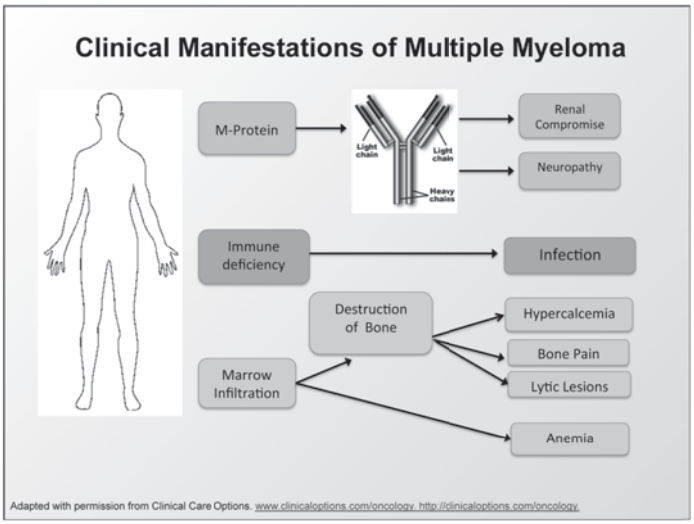

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Question #1

Which statements are true regarding carfilzomib?

A. Carfilzomib is an irreversible proteosome inhibitor
B. Carfilzomib exacerbates peripheral neuropathy
C. Carfilzomib is not indicated for patients who have previously received either bortezomib or lenalidomide
D. Primarily inhibits trypsin and caspase-like proteases

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Presentations

Case Study MG

- MG is a 61-year-old male
- Multiple myeloma (IgG Kappa heavy and light chain)
  - CRAB: normal calcium, renal function, hgb 11.5g/dL, solitary lytic lesion L ischium 2 cm
  - International Staging System: Stage 1 (Beta 2 microglobulin 2.9; serum albumin 4.0 g/dL)
  - FISH t (4;14)
  - Paraproteins: Serum IgG 3400; SFKLC 210
- PMH:
  - Type II Diabetes-diet controlled
  - HTN
  - Peripheral Vascular Disease
  - CAD hx MI
  - Medications: Norvasc, Toprol, ASA

Durie, et al for the International Myeloma Working Group. *Leukemia*. 2006:1-7. http://myeloma.crg/.

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Case Study MG Treatment History

- Initial Rx: 4 cycles bortezomib (IV), lenalidomide, dexamethasone with "very good partial response"
  - Auto PBSCT – achieved complete remission (BM <5%)
- Thalidomide maintenance for 8 months stopped 2^0 peripheral neuropathy
- Relapsed 8 months later….now with renal insufficiency 2^0 multiple myeloma
- Symptoms: anemia, new generalized bony aches - worse in thoracic spine, increasing fatigue, chronic peripheral neuropathy since thalidomide
- W/U: New lytic lesion with compression of T 9 vertebra, scattered lytic lesions ribs, calvarium increased activity in L ischium on PET/CT
- Treated with XRT T 9 vertebrae
- Treated with PAD (bortezomib (IV) 1.3 mg/m2 d 1,4,8,11; adriamycin 9 mg/m2 d 1-4; and dexamethasone 40 mg po d 1-4 (C 2 dexamethasone dose)
- Achieved significant reduction in serum IgG and SFKLC, reduced bone pain improved renal function, increased PN after 4 cycles treatment.

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Case Study MG Treatment History

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- 2nd auto PBSCT
- 100 days post transplant started lenalidomide maintenance
- After 5 months on lenalidomide maintenance rising paraproteins
- Increased sx fatigue, worsening anemia, elevated creatinine
- BM >60% involvement
- Started treatment
  - Carfilzomib C1 **20** mg/m2 with dexamethasone 10 mg IV on d 1,2,8,9,15,16 (q 28d)
  - Carfilzomib C2 **27** mg.m2 with dexamethasone 10 mg IV on d 1,2,8,9,15,16 (q 28 d)

Carfilzomib

A second generation irreversible proteasome inhibitor
Highly selective for chymotrypsin like active site within the proteosome

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- PX-171-003-A1
- 266 pts≥2 regimens for relapsed MM
  - 95% refractory to prior Rx
  - 5 prior lines of Rx including bortezomib, lenalidomide thalidomide
  - 99% prior bortezomib
  - 100% prior IMiD
  - Plt ≥50k, ANC≥1.0, Hgb≥8.0
  - ORR 23.7%, MDR 7.8 months
  - Median OS: 15.6 months
- FDA approval based on response rate for relapsed refractory multiple myeloma
  - Pts who have received at least 2 prior therapies including bortezomib and an immunomodulatory agent (thalidomide or lenalidomide)
  - Disease progression on or within 60 days of completion of the last therapy

Siegel D, et al. *Blood*. 2012;120:2817-2825.

Presentations

Carfilzomib

- C1 20 mg/m2 given IV over 2-10 minutes D1,2,8,9,15,16 q 28 d
  if tolerated increase C2 dose to 27 mg/m2 D 1,2,8,9,15,16 q 28 d
  - IV Fluid pre/post
  - Dexamethasone pre med
    prior to all Cycle 1 doses, during the first cycle of dose escalation, and if infusion reaction symptoms develop or reappear
  - Allopurinol if indicated

Common AE of all pt on study
All grades
- Fatigue 49%
- Anemia 46%
- Nausea 45%
- Thrombocytopenia 39%
- 12.4% Peripheral neuropathy gr 1/2

- All grades carfilzomib related
  - Fatigue 37%
  - Anemia 22%
  - Nausea 34%
  - Thrombocytopenia 29%
  - Dyspnea 17%
  - Pyrexia 15%
  - Diarrhea 24%
  - Vomiting 16.5%
  - Peripheral neuropathy 8.3%
  - URI 5.6%
  - Headache 17%

Siegel D, et al. *Blood*. 2012;120:2817-2825.
Kortuem, Stewart. *Blood*. 2013;121:893-897.

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Carfilzomib
Case Study MG

- Some treatment related issues of MG on carfilzomib
  - Schedule
  - Blood sugar
  - Renal function
  - Pancytopenia
  - Infection
  - Patient education; symptom recognition, instruction, intervention…..
- Key points for nurse management:
  - Baseline cbc, renal, hepatic, cardiac, pulmonary function
  - Patient risk factors for potential side effects
  - Administration, pre-medications and tolerability of infusion
  - Infusion reactions, potential tumor lysis syndrome
  - Dose modifications if needed with treatment
  - Concomitant medications
  - Tolerability of chemo schedule
  - Supportive, preventive & prophylactic strategies i.e.: infection, growth factors, transfusions, physical therapy

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Question #1

Which statements are true regarding carfilzomib?

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D. Primarily inhibits trypsin and caspase-like proteases

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Case Study
MG Treatment History

- Relapse after 7 months of carfilzomib
- Renal function actually improved while on carfilzomib and was stable at time of relapse
- Symptoms of fatigue, asthenia worsening low back pain and development of sciatica
- Started pomalidomide 4 mg po D 1-21 with dexamethasone 40 mg po weekly
- Start of C1 baseline cbc:
  - ANC 1.9, Hgb 9.0, Plt ct 55K
- Developed profound fatigue after first 2 weeks of treatment
  - Swelling of RLE
- Significant reduction in paraproteins noted after C1
- Hospitalized with pneumonia and neutropenic fever after C2

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Presentations

Question #2

Which statements are true regarding pomalidomide?

A. Pomalidomide is indicated for newly diagnosed patients with multiple myeloma
B. Pomalidomide's mechanism of action is both immunomodulatory and non-immunomodulatory
C. Pomalidomide unlike thalidomide is not a known teratogen
D. Risk for DVT with pomalidomide is much higher than with either thalidomide or lenalidomide

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IMiDs

- Thalidomide
  - 100-200 mg/d
    - Neuropathy
    - Constipation
    - Sedation
    - DVT
- Lenalidomide
  - 15-25 mg/d
    - Myelosuppression
    - Skin rash
    - DVT
- Pomalidomide
  - 2-4 mg/d
    - Neutropenia
    - Fatigue

Structurally similar
Functionally different both qualitatively and quantitatively

Lacy MQ. *Blood*. 2013;121(11)1926-1927.

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Pomalidomide

An orally bioavailable derivative of thalidomide

- Accelerated approval based on CC-4047-MM-002
- 221 pt relapsed and refractory MM prior lenalidomide and bortezomib refractory to last myeloma therapy
- Pomalidomide single agent vs Pom +LoDex
- Updated Phase 2 results ASH 2012 n=113 pts
  - ORR 34% in Pom + LoDex
  - Overall MDR 8.3 mo
- Indicated for patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and bortezomib
- Demonstrated disease progression on or within 60 days of completion of the last therapy
- Dose 4 mg po D 1-21 q 28 days with dexamethasone 40 mg po weekly

Jagannath S, et al. ASH 2012;Abstract 450.
http://www.cancer.gov/.

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IMiDs

Immunomodulatory Effects

- Co-stimulation of T cells
- Inhibition of regulatory T cells
- Suppressor effects on the host immune system
- Enhancement of NK and NKT cell function
- Enhancement of NK and NKT cell proliferation

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Presentations

IMiDs

Non-Immunomodulatory Effects

- Anti-angiogenic activity
- Inhibition of cell growth
- Enhancement of MM cell apoptosis
- Inhibition of osteoclasts activity
- Reduction of myeloma cells/stromal cells interaction

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Pomalidomide
MG Case Study

- Some treatment related issues of MG on Pomalidomide/LoDex…
  - Drug access
  - Fatigue
  - Infection
  - Neutropenia
  - Anemia
  - DVT RLE; sciatica; mobility

    *Thromboembolic events on pomalidomide were 2%
- Key points for nurse management
  - Baseline cbc, renal, hepatic, cardiac, pulmonary function
  - Patient risk factors for potential side effects
  - Oral administration at home-compliance issues
  - Concomitant medications
  - Patient and or caregiver teaching medications/sx recognition
  - Timely clinic follow-up
  - Dose modifications if needed with treatment
  - Supportive, preventive & prophylactic strategies i.e.: infection, growth factors, transfusions, physical therapy

*Jagannath S, et al. ASH 2012;Abstract 450.

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D. Risk for DVT with pomalidomide is much higher than with either thalidomide or lenalidomide

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Key nursing considerations for timely interventions to achieve successful response to therapy…….

- Current state of general health?
- What are disease related symptoms?
- What are treatment related symptoms?
- What is the patient's understanding of his disease/treatment?
- What is the patient's current quality of life?
  - Symptoms-controlled or not
  - Eating, sleeping, energy levels, functional mobility, mental acuity
  - Treatment and disease effect on productivity issues/work/recreation/relationships
  - Caregiver support
  - Does treatment regimen fit in lifestyle
  - Current issues regarding health maintenance
  - Insurance/Financial burden
  - Transportation issues/frequency of clinic visits

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Presentations

Nursing Guidelines for Enhanced Patient Care

The IMF Nurse Leadership Board is made up of nurses from leading centers treating myeloma patients in the US

Their mission is to develop broad recommendations for nursing care for myeloma patients

Top 5 side effects of novel therapies for myeloma

- Steroid toxicities
- Peripheral neuropathy
- Gastrointestinal side effects
- Thromboembolic events
- Myelosuppression

http://myeloma.org/

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Nurses key role:

- Knowledge of pathophysiology of multiple myeloma to fully understand etiology of disease and related sx/complications
- Understand novel therapies, indications, unique mechanism of action, potential toxicities, side effects, prevention of serious adverse events, pre-emptive interventions and prophylactic strategies
- Identify individual pt risk factors for potential complications related to PMH, current health maintenance, side effects of current novel treatment
- Education/support of patient and caregiver for successful treatment
  - Proper medication administration
  - Patient teaching for sx recognition and potential side effects
  - Unique patient issues with compliance and schedule for treatment
  - Post treatment care needs and f/u
- Referrals, support networks

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