Primary Care Updates 2008
Blood Cancers

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Disclosures

- Cephalon Oncology
  - Clinical research support, consultant
- Celgene Corp.
  - Clinical research support
- Markey Cancer Center Foundation
  - Clinical and translational research support

Objectives

- Understand the increasing need for collaboration between PCP and hematologist/oncologist
- Understand the potential toxicities of targeted therapies for hematologic malignancies
- Understand the importance of diagnosing the etiology of anemia in the elderly
- Understand the role of personalized medicine in hematologic malignancies

Collaborative relationship

- More than just a trendy phrase
- Closes the loop on information transfer between multiple physicians providing care
- Maximizes patient benefit while reducing waste
  - Patient's resources, physician's resources
- Inspires patient confidence for all associated physicians
- Increases physician satisfaction

Our Patients Grade Our Collaboration

posted 02-11-2008 07:25 PM

Hello - i am almost 4 years out from hodgkin's lymphoma, and am having major health issues - well major in my world as i have a 4yo and a 2yo and i have been sick for the past month. first i had the flu B, then bronchitis and a sinus infection, and i couldn't breathe, and they just looked at me like i was nuts and said there was nothing they could do for me. i am wondering what other people's experiences with your regular daily doctors is - every time i go to the dr's, i explain that i had a tumor in my chest and radiation in my chest and throat…

i am just wondering if this is the normal or if i need to find a new doctor's office.

Leukemia Lymphoma Society Blog

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Our Patients Grade Our Collaboration

posted 02-12-2008 06:07 PM

Unfortunately doctor's are human too, and I have found that you have to shop around for a doctor that is willing to at least "find out" about the long terms issues that arise due to treatment.

Take care - your paying them to take care of you and they clearly are not - so find snother internest who will try to understand.

Good luck and best wishes.

Hope you feel better soon.

Leukemia Lymphoma Society Blog

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posted 03-05-2008 11:17 PM

I agree, this is not normal. I still see my oncologist regularly as I am only 8 months post transplant. Still they don't treat everything and just the other day I needed to see my PCP for a couple of things. He knows everything that I have gone through over the last year or so, and was great at answering some questions for me. Some tests came back and he felt like I needed some medications for these, but he wasn't sure about mixing them with my immunesupressent meds, and so he called my oncologist while I was still there and found out. I have been seeing my PCP since I was 15 and totally love and trust him and when he retires I don't know what I will do. I think you might try finding another doctor.

Leukemia Lymphoma Society Blog

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Long-term Follow Up Guidelines

- Hodgkins
  - Most cohesively developed
- Adult survivors of ALL
  - Increasing understanding of long-term risk may help to refine strategies

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Follow Up of Pediatric ALL

- ALL is most common childhood cancer
  - 25% of pediatric malignancies
- 1960's cure rate < 30%
- Today >85 %

- However, long-term complications of treatment are common
  - Many are evaluated and treated by PCP

Disabling Toxicities Are Common

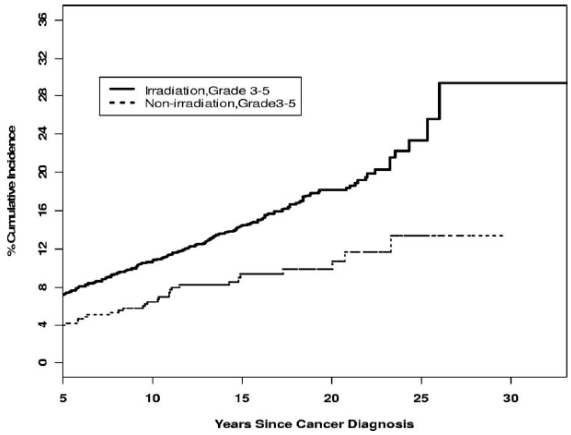

Figure 3. Cumulative incidence of severe chronic medical conditions in ALL survivors with and without history of irradiation.

Mody R, Li S, Dover D, et. al. Twenty-five year follow up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood*. 2008; 111:5515-5523.

Multiple Chronic Conditions

Outcome	Siblings, n (%)	All ALL survivors, n (%)	OR for all ALL survivors vs siblings (95% CI) †	P
Number in each group	3083	2599		
Chronic medical conditions				
Hearing	12 (0.4)	27 (1.0)	3.0 (1.5-6.8)	<.001
Vision	21 (0.7)	30 (1.2)	1.6 (0.9-3.1)	.19
Endocrine	56 (1.8)	114 (4.4)	3.1 (2.3-4.5)	<.001
Pulmonary	37 (1.2)	78 (3.0)	4.2 (2.8-6.6)	<.001
Cardiac	21 (0.7)	82 (3.2)	6.9 (4.212.9)	<.001
Gastrointestinal	14 (0.5)	18 (0.7)	2.2 (1.0-5.0)	.04
Renal	5 (0.2)	21 (0.8)	4.8 (2.118.9)	<.001
Musculoskeletal	3 (0.1)	14 (0.5)	7.7 (2.821.3)	<.001
Neurologic	13 (0.4)	62 (2.4)	5.3 (3.111.4)	<.001
Grade 3 to 4	179 (5.8)	382 (14.7)	3.7 (3.0-4.5)	<.001
2 or more in grades 1 to 4	433 (14.0)	667 (25.7)	2.8 (2.4-3.2)	<.001
Adverse health status				
General health	157 (5.1)	230 (8.9)	2.1 (1.6-2.7)	<.001
Mental health	302 (9.8)	389 (15.0)	1.7 (1.4-2.0)	<.001
Activity limitation	178 (5.8)	230 (8.9)	1.8 (1.5-2.3)	<.001
Functional impairment	79 (2.6)	227 (8.7)	4.1 (3.1-5.6)	<.001

Mody R, Li S, Dover D, et. al. Twenty-five year follow up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood*. 2008; 111:5515-5523.

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Social and Economic Consequences

	Female ALL survivors	Sibling	p value
Marital status			<.001
Never married	42.1%	23.0%	
Married	48.4%	67.4%	
Education			<.001
Didn't graduate	5.0%	2.6%	
High School	51.6%	41.5%	
College	43.3%	55.9%	

Mody R, Li S, Dover D, et. al. Twenty-five year follow up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood*. 2008; 111:5515-5523.

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Hope for the Future

- A Pilot Study Of The Correlation Of Cytokines And Oxidative Stress Markers To Cognitive Function After Administration Of Anti-neoplastic Chemotherapy
- A Study Evaluating Limited Target Volume Boost Irradiation and Reduced Dose Craniospinal Radiotherapy (18.00 Gy) and Chemotherapy in Children with Newly Diagnosed Standard Risk Medulloblastoma: A Phase III Double Randomized Trial
- A Phase III Study of Reduced Therapy in the Treatment of Children with Low and Intermediate Risk Germ Cell Tumors

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Long-term hodgkin guidelines are formalized and accepted as “best practice” by expert lymphoma consensus panels

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Long-term Follow Up of Hodgkin's

- After 5 years
  - Annual BP and aggressive management
  - Consider stress echo @ 10 years post XRT
  - Pneumococcal vaccine if splenectomy or splenic XRT q 5-7 years
  - Annual flu vaccine
  - Annual CBC-D, CMP, TSH, Lipids
  - Annual chest x-ray if XRT given

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Long-term Follow Up Hodgkin's

- Increased breast cancer risk
  - At 8-10 years post XRT or age 40 (whichever first)
    - Self exam
    - Mammography annually
    - Breast MRI annually

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PCP Should Expect

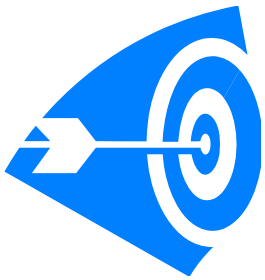
- Initial counseling regarding long-term risk provided by oncologist
- To anticipate that early cardiovascular disease and breast cancer is a risk of XRT
- Patients will need to have long term evaluations life-long
  - If oncologist provides clear guidance, these screenings may be incorporated into routine health maintenance with PCP

Objective #2

- Understand the potential toxicities of targeted therapies for hematologic malignancies

Targeted Therapy

- Molecular target identified first
- Philadelphia chromosome
  - t (9;22)
  - Imatinib, dasatinib, nilotinib
  - CML
- Immune modulators
  - Thalidomide, lenalidomide
  - Multiple myeloma, MDS



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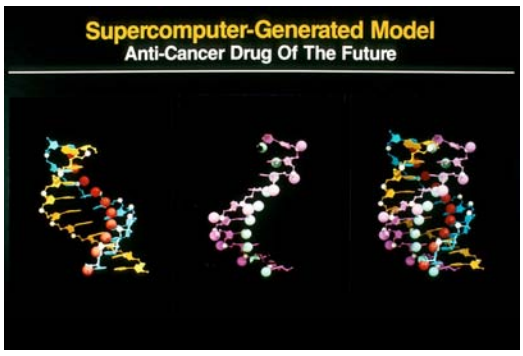
Targeted Therapy Realized

- 1960 t(9;22) characterized
- Multi-tyrosine kinase inhibitor
- Potent inhibitor of Bcr/Abl
- Now CML dx requires t(9;22)



NCI visualsonline

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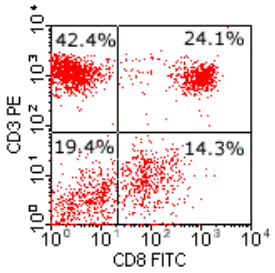
Three Tools Have Lead the Way

- Flow cytometry
- Fluorescent-labeled antibodies are added to cells
- High speed detector measures presence of protein on cell
- Can correlate numerous proteins to determine origin and clonality of cells



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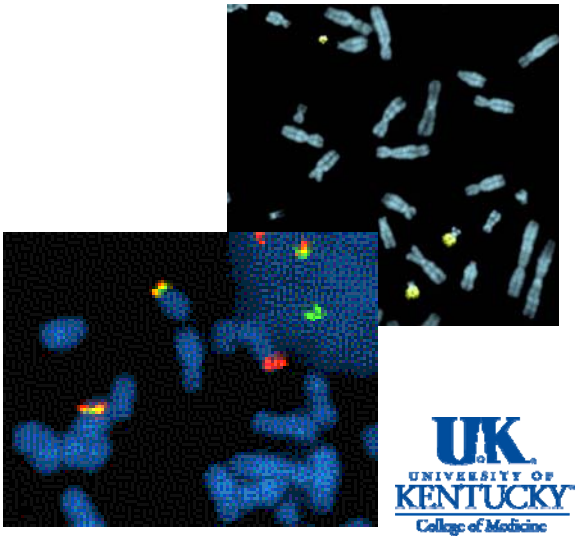
FISH

- Fluorescence In Situ Hybridization
- Traditional karyotyping requires actively dividing cells
- Fluorescent probe



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Polymerase Chain Reaction

- PCR
- Can measure presence of DNA or RNA
- 1 cell/many thousands
  - Sensitivity blessing and curse
  - Must be interpreted in proper context

Imatinib has Great Results

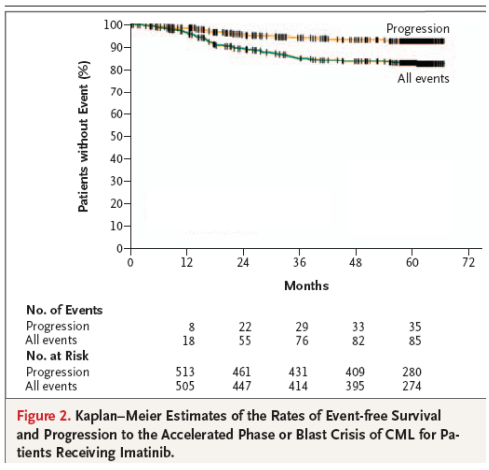


Figure 2. Kaplan–Meier Estimates of the Rates of Event-free Survival and Progression to the Accelerated Phase or Blast Crisis of CML for Patients Receiving Imatinib.

Druker BJ, Guilhot F, O'Brien SG, et. al. Five-year follow-up of patients receiving imatinib for Chronic Myeloid Leukemia. *New England Journal of Medicine*, 2006; 355:2408-4217.

Typical CML follow up

- Pt. diagnosed
- Treatment often initiated as an outpatient
- Follow up frequently initially
- After a 3-6 months, may return q1-3 months
- Thereafter, may see oncologist 4 times yearly

Drug Interactions

- Strong CYP 3A4 inducers may reduce imatinib levels by > 50%
  - Phenytoin, carbamazepine, rifampin, phenyobarb
- Most anti-HTN meds, diabetic meds, statins OK
- Most other new medications should be specifically checked

Other Imatinib Potential Toxicities

Fluid Retention	5%
Severe CHF	1%
Hepatotoxicity	Rare
Naussea/Diarrhea	Common, GI perforation is rare
Hypothyroidism	Unknown incidence May affect thyroid replacement levels
Renal disease	Unknown incidence Long term effects suggested in animals
Cytopenias	Typically in first few months

*New or unexpected deteriorations of health should be brought to attention of hematologist/oncologist

Imatinib package insert

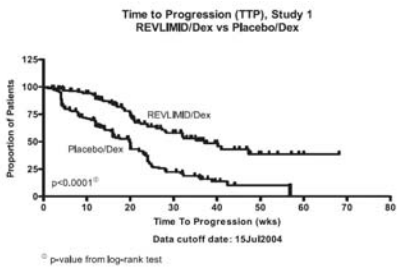
IMID's

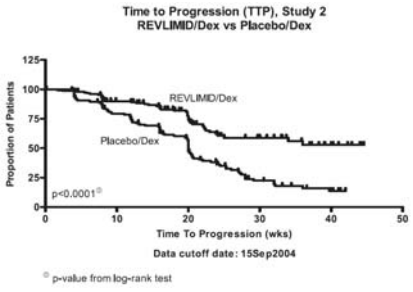
- Thalidomide, lenalidomide
- Mechanism of action not completely clear
  - Immunomodulatory
  - Anti-angiogenic
  - Inhibits multiple myeloma cell growth
  - Inhibits expression of COX-2

IMID's

- Indicated for treatment of myeloma
- Lenalidomide indicated for 5q- MDS
- May be used for extended period of time

Lenalidomide Prolongs Response





Lenalidomide package insert

Lenalidomide Toxicities

Potential for severe birth defects	Counseled by oncologist
DVT	Prophylaxis prescribed by oncologist
Cytopenias	Usually identified during first 8 weeks
Pruritis	40%
Rash	33%
Diarrhea/Constipation	50%/20%
Cough	20%
Fatigue	30%
Edema	20%
Dizziness	20%
Hypothyroidism	7%

Lenalidomide package insert

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Objective #3

- Understanding etiology of anemia in elderly
- Diagnosis and treatment of MDS

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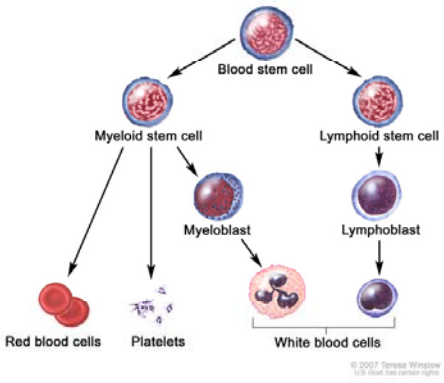
Elderly Anemia: Not Just Old Marrow

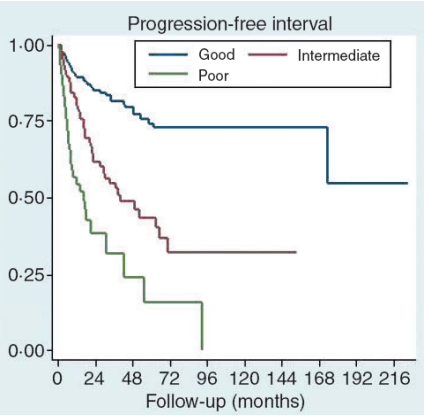
- Not a simple evaluation
  - Iron deficiency
  - B12, Folate
  - Hypothyroid
  - Multiple Myeloma
  - Renal Insufficiency
  - Myelofibrosis
  - MDS
  - Multiple co-morbids and drugs

MDS

- "Pre-leukemia"
- Clonal stem cell defect
- May variably progress to further marrow failure or acute leukemia
- Now with 3 FDA approved treatments



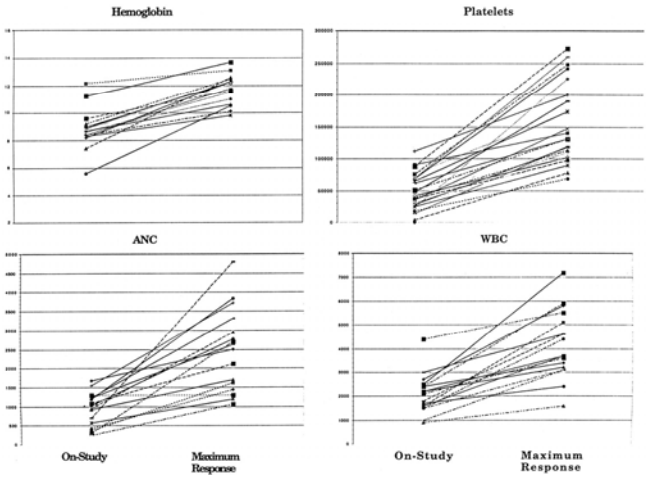
IPSS Predicts Progression



- Most good risk patients may be observed unless requiring transfusion support
- Calculating risk requires bone marrow biopsy

Bernasconi P, Klersy C, Boni M, et. al. World Health Organization classification in combination with cytogenetic markers improves the prognostic stratification of patients with *de novo* primary myelodysplastic syndromes. *British Journal Haematology*. 2006; 137:193-205.

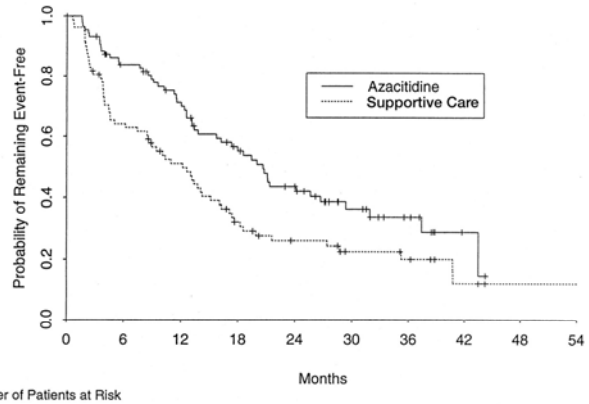
MDS Treatment Improves Counts



Silverman, L. R. et al. J Clin Oncol; 20:2429-2440 2002

JOURNAL OF CLINICAL ONCOLOGY

MDS Treatment Improves Survival



Number of Patients at Risk

Azacitidine	89	69	55	39	28	16	9	2	0	0
Observation	82	51	38	22	15	10	8	3	1	1

Silverman, L. R. et al. J Clin Oncol; 20:2429-2440 2002

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MDS with 5q- is Unique

Table 2. Erythroid Response to Lenalidomide.

Variable	Continuous Daily Dosing (N=102)*	21-Day Dosing (N=46)*	All Patients (N=148)
Erythroid response — no. (%)			
Transfusion independence	71 (70)	28 (61)	99 (67)
95% CI			59–74
≥50% decrease in no. of transfusions	8 (8)	5 (11)	13 (9)
95% CI			5–15
Total transfusion response	79 (77)	33 (72)	112 (76)
95% CI			68–82
Time to response — wk			
Median	4.7	4.3	4.6
Range	1–34	1–49	1–49
Hemoglobin — g/dl			
Baseline†			
Median	7.7	8.0	7.8
Range	5.3–10.4	5.6–10.3	5.3–10.4
Response‡			
Median	13.4	13.5	13.4
Range	9.2–18.6	9.3–16.9	9.2–18.6
Increase			
Median	5.4	5.4	5.4
Range	2.2–11.4	1.1–9.1	1.1–11.4

- 5q- MDS has a unique clinical history
- Complete cytogenetic responses may occur

List A, Dewald G, Bennett J, et. al. Lenalidomide in the Myelodysplastic Syndrome with chromosome 5q deletion. *New England Journal of Medicine.* 2006; 355: 1456-1465.

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Objective #4

- Current personalization is driven primarily by tumor genetic changes and protein expressions
- The level of specialized knowledge is straining the ability and resources of oncologists
  - Time spent interpreting literature
  - Time spent developing system to ensure acquisition of info and calculation of risk scores
  - Staffing
  - No additional reimbursement

Personalized Medicine is the Norm

- Before
- Age
- Disease
- Experience based
- Physician judgment emphasized

- Now
- Co-morbidites
- Cytogenetics
- Protein Expression
- Pathway activation
- Evidence-based
- Access to clinical trials critical

Chronic Lymphocytic Leukemia

- Initial evaluation
  - Flow cytometry for CD38, ZAP-70
  - FISH for cytogenetics
  - Complex flow cytometry to exclude other lymphocytic leukemias
- 16 "acceptable" chemotherapy options

Chronic Myeloid Leukemia

- Requires BM bx to diagnose phase
  - Phase determines treatment options
- Relapses can be predicted by
  - Hematologic response
  - Minor cytogenetic response
  - Major cytogenetic response
- Requires access and experience with FISH and PCR
  - And time to interpret results

Non-Hodgkin Lymphoma

- Now over 30 recognized entitites
- Diagnosis requires correlation of clinical history, histology and complex flow cytometry and/or immunohistochemistry
- FISH analysis in selected cases
- Numerous "acceptable" regimens and treatment pathways

Multiple Myeloma

- FISH results inform progression and recurrence risk
  - deletion 13, deletion 17, t(4;14), t(11;14), t(14;16)
- ~16 different chemo options
- Bone marrow transplant may be an important option
- Inappropriate choice of chemo may make transplant feasible

Informing Patients of New Diagnosis

- Reassure without false hope
- Encourage patient to fully understand treatment options before deciding course of action
  - Treatment is not what they expect
- Consider tertiary referral early
  - Care may often then be delivered in community
  - 2nd opinion before treatment initiation is critical

Access to Trials is Critical

- For most hematologic malignancies
  - Consideration of an appropriate clinical trial is the nationally accepted standard of care
- Nationally
  - ~3% of patients with cancer will be treated on a clinical trial
- For my family
  - With the exception of chronic phase CML, I would hope that an appropriate clinical trial would be available and offered

For my family…

With the exception of chronic phase CML, I would hope that an appropriate clinical trial would be available and offered

Thanks!

Questions?