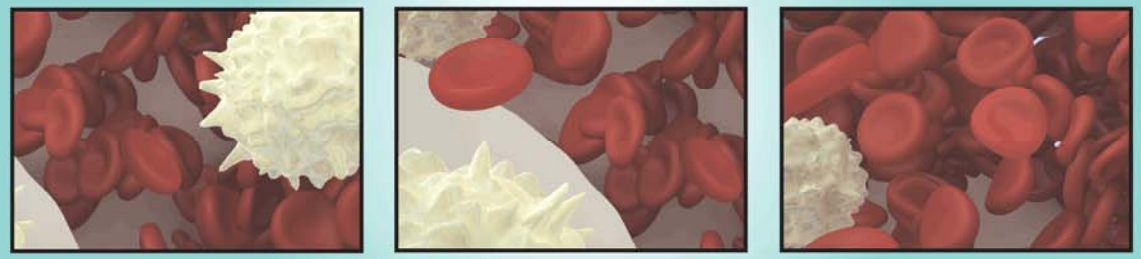
THE MDS FOUNDATION PRESENTS

The Myelodysplastic Syndromes: Challenges and Strategies for Effective Outpatient Management



May 3, 2012 ✣ *New Orleans, Louisiana*

Meeting space has been assigned to provide a satellite symposium co-sponsored by The Myelodysplastic Syndromes Foundation and the Foundation for Care Management via an educational grant during the Oncology Nursing Society's (ONS) 37th Annual Congress, May 3–6, 2012 in New Orleans, Louisiana. The Oncology Nursing Society's assignment of meeting space does not imply product endorsement nor does the Oncology Nursing Society assume any responsibility for the educational content of the symposium.

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FCM
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Scientific Update: Recent Advances in Strategies for the Treatment of Myelodysplastic Syndromes: From Prognosis to Treatment Selection

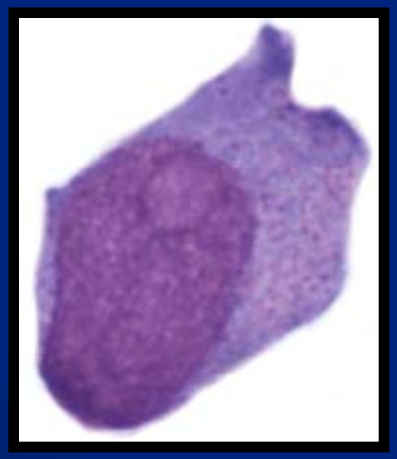
Jean A. Ridgeway MSN, APN, NP-C, AOCN

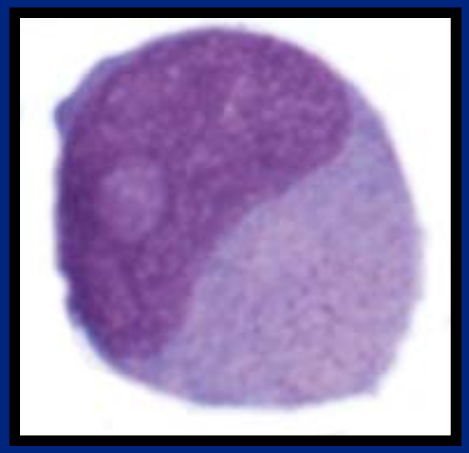
University of Chicago Medicine

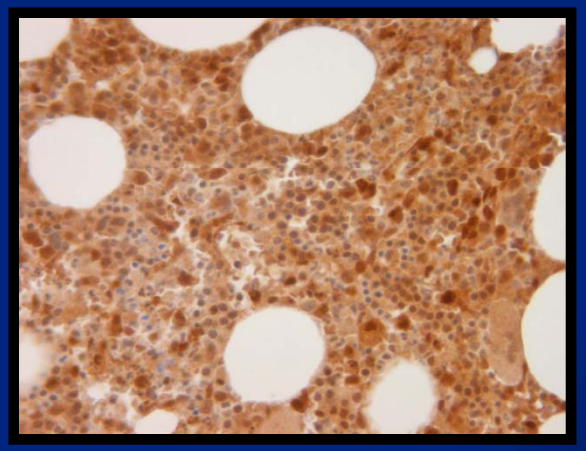
Adult Hematologic Malignancy/Stem Cell Transplant Nurse Practitioner

We've come along way

- Initially, MDS diagnosis focused solely on cell morphology and blast counts





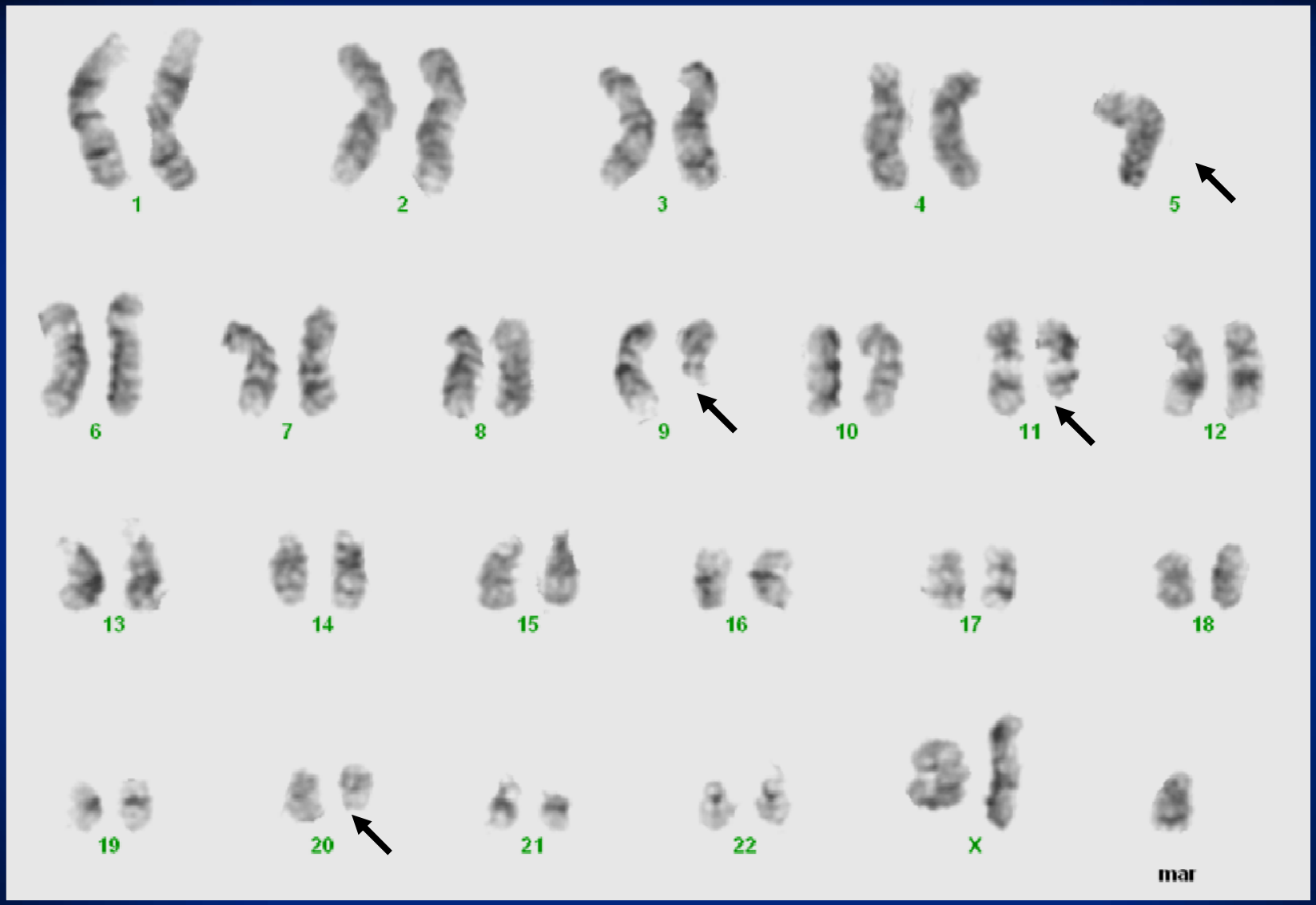


Images courtesy of John Bennett, MD and Alan List, MD

Cytogenetics

- Cytogenetic advances began to influence the understanding of MDS in the 1990's
- Advances in cytogenetic analysis have demonstrated that MDS is characterized by multiple cytogenetic defects
- Cytogenetics continue to affect the diagnosis, prognosis and treatment of MDS

Westers et al., 2011, Vardiman et al, 2008.



46,XX[9]

46,XX,-5, del(9)(q21q34),del(11)(q21q23),del(20)(q11.2q13.3),+mar[11]

Diagnostic Advances
Cytogenetic Attributes

- Conventional metaphase cytogenetic (MC)analysis
  - Gold standard in karyotypic analysis
- Examines 20 actively dividing cells in metaphase
- Identifies chromosomal abnormalities
- MC cannot detect abnormalities in non-dividing cells
  - This has led to development of new technologies to enhance sensitivity of karyotype analysis

Westers et al., 2011, Vardiman et al, 2008.

Single-Nucleotide Polymorphism (SNP) Array

- Overcomes limitations of MC
- Detects copy number alterations below the limit of standard cytogenetic analysis detection
- Identifies abnormalities in non dividing cells
- Allows for identification of abnormalities in specific genes that have prognostic significance
  - Some which have demonstrated differential responses to therapy
    - TET2 gene
    - TP53 gene

Gondek et al., 2008; Maciejewski & Mufti, 2008; Graubert, 2011, Tiu et al, 2011; Garcia-Manero, 2010

TET-2

- Produces an enzyme that affects DNA methylation state
- Its dysregulation may have a role in epigenetic alterations in MDS
- Mutated TET2 is an independent prognostic factor for increased response rate to azacitidine therapy
- Cytogenetic Location: 4q24

Itzykson et al. *Blood*. 2010; 116

TP53

- Mutation of TP53 is an independent predictor of poor prognosis MDS
- Mutation of TP53 predicts inferior response to hypomethylating agents and lenalidomide
- Cytogenetic Location: 17p13.1
- The official name of this gene is “tumor protein p53.”

Bejar et al 2011, Tiu et al, 2011

Diagnostic Advances: Molecular Attributes

- Flow Cytometry (FC)
- Based on quantitative and/or qualitative cell receptor or internal protein expression
- Studies point to need for additional refinement and standardization of quantification measures
- CD34-related parameters are good candidates
  - CD34+ stem cell compartment in MDS is altered

Westers et al., 2011, Vardiman et al, 2008.

Classification Systems

- French-American-British (FAB) System
  - Based on morphology and blast percentage
- World Health Organization System
  - Added cytogenetics to FAB
  - Decreased % blasts to <20% for MDS
- MD Anderson Cancer Center discordance with review of outside slides
  - Diagnostic complexity of MDS
  - Need and value of expert hematopathologists
  - Diagnostic discrepancies between referral and tertiary care centers

Vardiman et al. *Blood.* 2009;114:937-951.
Steensma. *Hematology Am Soc Hematol Educ Prog.* 2009;645-655.

Myelodysplastic Syndromes: Classification Systems

FAB	WHO	WHO 2008	DYSPLASIA	BLAST % (BM/PB)
Refractory anemia (RA)	RA Myelodysplastic syndromes, unclassified (MDS-U) Refractory cytopenia with multilineage dysplasia (RCMD) Del(5q)	RC with unilineage dysplasia (RCUD) RA Refractory neutropenia Refractory thrombocytopenia RCMD Isolated del(5q) MDS-U	Erythroid Nonerythroid Nonerythroid Erythroid + other Erythroid + megakaryocytic Unilineage + pancytopenia or RCMD/RCUD with 1% PB blasts	All: < 5/≤ 1
Refractory anemia with ringed sideroblasts (RARS)	RARS RCMD-RS	RARS RCMD-RS	Erythroid only Erythroid + other (all > 15% RS)	< 5/< 1
Refractory anemia with excess blasts (RAEB)	RAEB-1 RAEB-2	RAEB-1 RAEB-2	≥ 1 lineage ≥ 1 lineage	5–9/2–4 10–19/5–19 ± Auer rods
RAEB in transformation	Acute myeloid leukemia (AML)	AML	Myeloid ± other	≥ 20/—
Chronic myelomonocytic leukemia (CMML)	MDS/myeloproliferative disorder (MPD) CMML Juvenile MML (JMML) Atypical chronic myeloid leukemia (aCML) MDS/MPD-U	MDS/myeloproliferative neoplasm (MPN) CMML JMML BCR-ABL–negative CML MDS/MPD-U	Variable > 1 × 10^9/L monocytosis	All: < 20/—

From: Ridgeway et al, 2012

Classification and Prognostic Scorings Systems*

- 1997 IPSS(FAB): 816pts/3 databases
  - Marrow blasts, cytogenetics, cytopenias
- 2001 WHO classification
  - Dysplastic subgroups, RAEB-1,2, del(5q)
- 2007 WPSS: 1165pts/3 DBs
  - WHO subgroups, IPSS cytogenetics, RBC Transfusions
  - New cytogenetic classification: 2900 pts/4 databases
- 2011 IWG-PM Refined consensus system (IPSS-R)
  - 7012 pts/18databases

*Preliminary data – final attributes and scores to be finalized by the IWG-PM

Greenberg, P. on behalf of the IWG-PM – MDS Symposium, ASH December 2011 – with permission

International Prognostic Scoring System (IPSS)

- Developed to understand independent variable for predicting clinical outcomes
- 3 areas of risk scores are identified
  - Cytopenias, bone marrow blasts, cytogenetics
- 4 risk groups are identified
  - Low
  - Intermediate 1
  - Intermediate 2
  - High
- 4 median survival estimates
  - Low—5.7 years
  - Intermediate 1—3.5 years
  - Intermediate 2—1.2 years
  - High—0.4 year

Greenberg et al. *J Natl Compr Canc Netw*, 2011

IPSS Risk Categories and Survival †

Variable/Score	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	<5	5-10	---	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Risk Category	Numeric Score	Patient Distribution	Median Survival†	Evolution to AML
Low	0	31%	5.7 years	9.4
Int-1	0.5-1.0	39%	3.5 years	3.3
Int-2	1.5-2.0	22%	1.2 years	1.1
High	≥ 2.5	8%	0.4 years	0.2

† **Data generated prior to active therapies**

Greenberg et al. *Blood*. 1997;89:2079-2088 [published correction in *Blood*. 1998;91:1100].

Aims for Refining IPSS

- Determine impact of newer features for prognostic power
- Incorporate larger cytogenetic subgroups & re-assess their prognostic impact
- Analyze depth of cytopenias
- Provide better prognostic ability
- Maintain continuity, feasibility, flexibility

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IPSS-R
18 Databases -11 Countries
7012 patients

- Austria
- Brazil
- Czech Rep
- France
- Germany
- Italy
- Japan
- Netherlands
- Scotland
- Spain
- USA

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International Working Group-for Prognosis in MDS (IWG-PM)

- Data vetted from data bases from 18 institutions
  - Primary untreated, accuracy, completeness, cytogenetics, outcomes
- Further assessed cytogenetics: standard ISCN
  - Cytogenetic committee review
- Data review, statistical weighting for predictive power
- Data analysis
- Final IPSS-R model generated

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Inclusion criteria

- Primary MDS (FAB or WHO)
  - Marrow blasts ≤30%
  - PB blasts ≤19%
  - WBC ≤ 12,000/mm3 (ANC ≤8,000)
  - ≥2 months stable disease
- Marrow blasts, cytogenetics, hgb, ANC, platelet levels documented
- No disease-altering therapy during chronic phase
- Valid survival data
- Age ≥ 16yo

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Poor Prognostic Indices Considered in the IPSS-R

- PRBC transfusion dependency
  - Depth of anemia, iron overload
- Laboratory parameters
  - LDS>ULN, elevated β_2 microglobulin
- Comorbidity index/score
  - Cardiac most common
- Bone marrow features
  - Fibrosis, clustered CD34+ cells, megakaryocytic dysplasia, ↑cellularity, ↑angiogenesis
- Flow cytometry
  - CD34 coexpression: CD7, 117, 56, 44
- Modified cytogenetic subgroups

Greenberg et al, Leuk Res. 2011;35:S6. Abstract 14
Zipperer et al. Leuk Res. 2011;35:S20. Abstract 55

Combined Data Base Variables*

- 7012 patients
- Age: 71 yo (median)
- M:F 1.5:1
- Median follow up: 3.9yr
- Classification Systems
  - FAB 7000 pts
  - WHO 5504 pts (79%)
  - WPSS 2325 pts (33%)

- Additional Diagnostic Attributes:
  - RAEBt 6%
  - CMMol 9%
  - 5q- 4%
  - Ferritin 43%
  - TD - RBC 13% (32% w/data)
  - BM fibrosis 19%
  - LDH 61%
  - B2M 13%
  - PS-ECOG 36%

*Preliminary data – final attributes and scores to be finalized by the IWG-PM

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Combined Data Base Variables (cont.)*

- Cytogenetics (n=7001)
  - IPSS – current and 1997:
    - Good – 75% (74%)
    - Intermediate: 13% (15%)
    - Poor: 12% (11%)
    - IPSS-R; V good/good/int/poor/v poor: 4/72/13/4/7%
- IPSS categories, n=7008
  - Low/int1/int2/high 37/40/16/7% (‘97:33/38/22/7)
- WPSS categories, n=2325
  - 22/32/20/20/4/5 (‘07;23/28/19/23/7)

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IPSS-R:
Modified Cytogenetic Prognostic Subgroups

- Very Good: 60.8 months
  - del(11q), -Y
- Good:48.5 months
  - Normal, del(20q), del(5q) alone and double, del(12p)
- Intermediate: 24 months
  - +8, 7q-, i(17q), +19, +21, any other single or double, independent clones
- Poor: 14 months
  - der(3)q21/q26, -7, double including 7q-, complex (3 abnormalities)
- Very Poor: 5.7 months
  - Complex (>3 abnormalities)

Greenberg et al, *Leuk Res*. 2011;35:S6. Abstract 14
Schanz et. al., *J Clin Oncol :* 30:820, 2012

IPSS-R for MDS: Prognostic Score Values/Risk Groups*

	0	1	1.5	1.5	2.5	3.5	5
Cyto	Very Good		Good		Int	Poor	Very Poor
Blasts	<5%			5-10%	11-30%		
Hgb	≥10			<10			
Plt	≥100		<100				
ANC	≥0.8	<0.8					

Risk Groups

1. Very Low: 0-2
2. Good: >2-3.5
3. Intermediate: >3.5-5
4. High: >5-6
5. Very High: >6

*Preliminary data – final attributes and scores to be finalized by the IWG-PM

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IPSS-R:
Prognostic Subgroup Clinical Outcomes*

	1 Very Low	2 Good	3 Intermediate	4 Poor	5 Very High
OS	8.7	5.3	3.0	1.6	0.8
AML, 25%	NR	10.7	4.0	1.4	0.8

* Medians, years

*Preliminary data – final attributes and scores to be finalized by the IWG-PM

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Therapeutic Strategies for MDS

- Low-Risk
  - Management of symptomatic cytopenias and symptoms
    - PRBC, ESAs
    - Immunomodulatory Agents
    - Immunosuppressive Agents
    - Thrombopoietin receptor agonists
      - Romiplostim, eltrombopag
- High Risk
  - Prolonged survival
    - Hypomethylating agents, HCT

From: Ridgeway et al, 2012, *CJON*

Mechanisms of Action of Therapies Under Investigation

AGENT	TARGET	MOA	TRIAL/POPULATION	RESPONSE	GRADE 3/4 AES
ARRY-614[a]	P38/Tie-2	Antineoplastic, anti-inflammatory, and antiangiogenic activity	Phase I/low or Int-1 risk (N = 100)	–	–
Entinostat (SNDX-275/MS-275)[b]	Histone DAC	Class 1 HDAC1 and HDAC3 inhibitor	Combination with azacitidine; phase III/high risk (N = 150)[c]	HR and CyR did not differ between AZA/Pbo versus AZA/entinostat	• Thrombo: 63% • Fatigue 23%
Erlotinib[d]	EGFR signaling leads to DNA synthesis and proliferation	Tyrosine kinase inhibitor that blocks EGFR signaling	Phase II/Int-2 and high risk (N = 24)[e]	ORR: 17%	• Diarrhea: 21% • Thrombo: 17% • Rash: 17%
Everolimus (RAD-001)[f]	mTOR	Inhibitor of mTOR that induces G_1 arrest	Phase II/low and Int-1 risk (not yet recruiting)[g]	–	–
Ezatiostat[h]	GST P1-1	Stimulates proliferation of myeloid precursors	Phase I/Int-2 (N = 45)	HI: 38%	• Neutropenia: 7%
ON-0110.Na[i]	Polo-1 kinase, PI3K, AKT	Inhibits mitotic progression and induces apoptosis	Phase II/Int-1, Int-2, high risk (N = 10)[j]	ORR: 50%	• GI: 10% • Dysuria: 10% • Fatigue: 10% • Epistaxis: 10% • No heme toxicities
Panobinostat (LBH589)[k]	Histone DAC	Pan DAC inhibitor, inhibits differentiation and induces apoptosis	Phase II/relapsed or refractory MDS (N = 10)[l]	70% had stable disease	• Thrombo: 80% • Neutropenia: 70% • Leukopenia: 60% • Anemia: 50% • Febrile neutropenia: 20%

From: Ridgeway et al, 2012, *CJON*

Scientific Developments in Management of MDS

- Risk-adapted treatment selection—IPSS
- Low-Int-1: improve hematopoiesis
  - Int-2: survival
  - Additional prognostic factors have been identified and the IPSS-R is being introduced
- Outcomes shift to include survival
- Identification of novel therapeutic targets
  - Molecular/tissue studies continue to clarify and identify existing and new targets
    - FC
    - TET-2
    - TP53 mutations

Kurtin, S. 2011, *JAdPrO*, Bejar et al 2011, Tiu et al, 2011

Practical Tools for Optimal Management of Myelodysplastic Syndromes

Sandra Kurtin, RN, MS, AOCN, ANP-C
Nurse Practitioner
Clinical Assistant Professor of Medicine
Adjunct Clinical Assistant Professor of Nursing
The University of Arizona Cancer Center

The Facts About MDS

- The average age at diagnosis is 73 years
- MDS remains an incurable ***malignancy*** for the majority of patients
- Allogeneic-HCT is the only potential “cure”
- The leading cause of death is the disease itself (~80%)
- Risk-stratified treatment strategies are key to optimal therapeutic outcomes

Dayyani et al., 2010; Kurtin et al, 2012

IPSS Risk Categories and Survival

Variable/Score	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	<5	5-10	---	11-20	21-30*
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

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Int-2	1.5-2.0	22%	1.2 years	1.1
High	≥ 2.5	8%	0.4 years	0.2

Life expectancy at 75 years US	**12.5 years**
Life expectancy at 65 years US	**19.8 years**

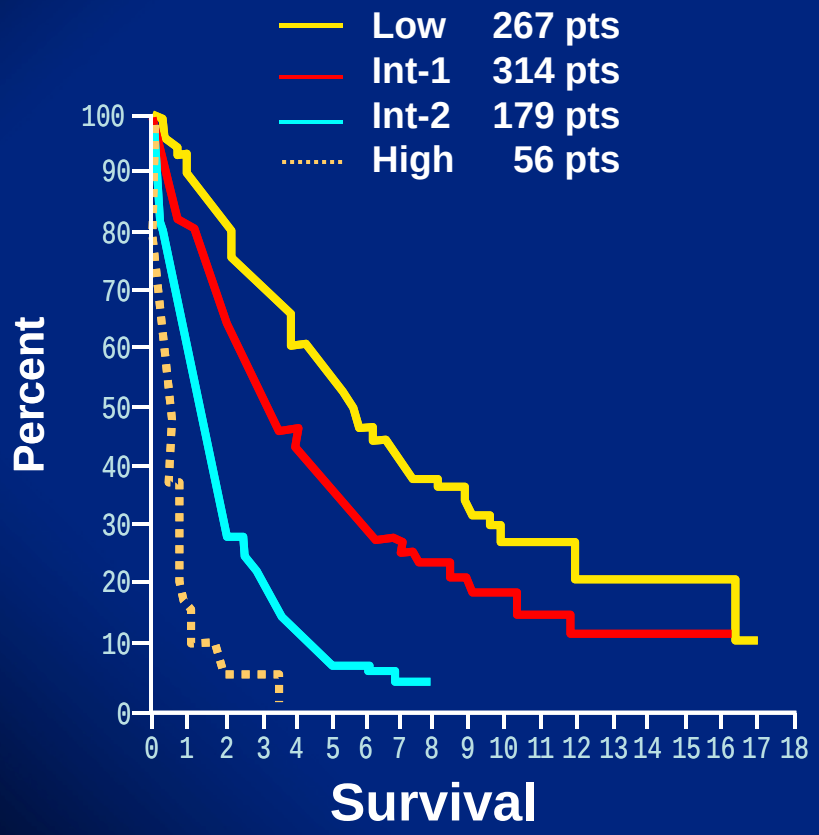
† **Data generated prior to active therapies**

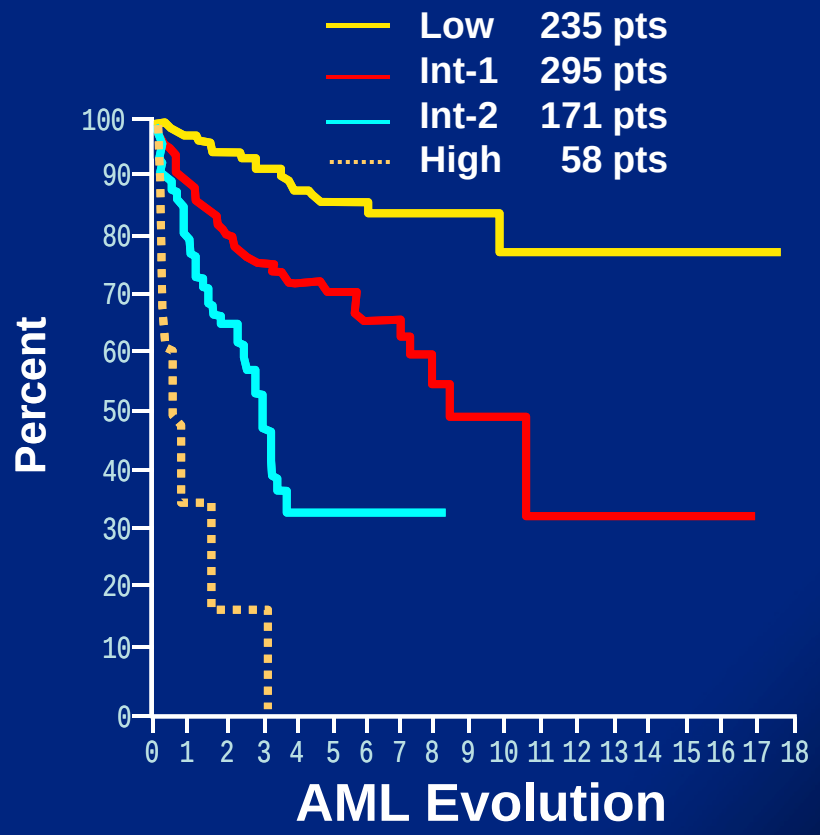
* **> 20% blasts denotes AML**

US Social Security Administration, 2010.

Greenberg et al. *Blood*. 1997;89:2079-2088 [published correction in *Blood*. 1998;91:1100].

Survival and AML Evolution by IPSS Classification





From diagnosis in untreated patients

Reprinted with permission from Greenberg et al. *Blood*. 1997;89:2079-2088 [published correction in *Blood*. 1998;91:1100].

Current and Revised IPSS with Survival and Risk of Leukemic Transformation

Current IPSS n=816				Proposed Revisions : R-IPSS n=4417		
Category	Score	Median Survival (yrs)	Evolution to AML yrs (25%)	Revised Risk Category	Median Survival (yrs)	Evolution to AML yrs (25%)
				Very Low	6.8	NR
Low	0	5.7	9.4	Low	4.3	10.1
Intermediate-1	0.5-1.0	3.5	3.3	Intermediate	2.3	2.8
Intermediate-2	1.5-2.0	1.2	1.1	High	1.5	1.2
High:	≥2.5	0.4	0.2	Very High	0.9	0.7

Greenberg et al. *Leukemia Research*. 2011;35:S6, Abstract 14.
Greenberg et al. *JNCCN*. 2011;9:30-56

Co-morbidities and MDS

- 600 consecutive patients evaluated at MD Anderson using Adult Co-morbidity Evaluation-27 (ACE-27)
- Median overall survival
  - Overall - 18.6 months (*P*<.001 for all)
  - No co-morbidities - 31.8 months
  - Mild – 16.8 months (HR 1.3)
  - Moderate – 15.2 months (HR 1.6)
  - Severe – 9.7 months (HR 2.3)
- Patients with severe co-morbidities have a 50% decrease in median survival independent of age or IPSS risk group.
  - Low-risk – 43 months
  - Intermediate risk – 23 months
  - High-risk – 9 months

Nagvi et al. *J Clin Oncol*. 2011;e-pub ahead of print May 2,2011

Functional Status, Frailty and Co-morbidities

- Functional Status: Measures by ECOG and KPS
  - ADLs:
    - ability to bath, dress, toilet and maintain continence, transfer, and eat independently
  - IADLs:
    - finances, shopping, housekeeping, transportation, and self-medication
- Co-Morbidities
- Frailty:
  - weight loss, weakness, poor nutritional intake, cognitive impairment and poor endurance
  - Cardiovascular Health Study (n=5317): frailty associated with hospitalization, falls, declining ADLs including diminished mobility, and death ($p<.001$)

Kumar et al, CA Cancer J Clin. 2010. Doi:10.3322/caac.20059.
Balducci & Extermann, Oncologist. 2000;5:224–237

NCCN Senior Adult Oncology General Approach to Therapy

Patient Characteristics	Approach to Treatment
Functionally independent without comorbidities	Candidates for most forms of therapy with consideration of goals of treatment/expected outcomes
Intermediate functional impairment unable to tolerate intensive life-prolonging curative therapy	Application of individualized pharmacologic approach
Major functional impairments or complex comorbidities	Candidates for palliative therapies only
Poor prognosis and limited functional status	Symptom management and supportive care

Saif and Lichtman. *Crit Rev Oncol Hematol*. 2009;72:155-169.
Kurtin. *J Adv Pract Oncol*. 2010;1:119-129.

MDS, Transfusions, and Survival

- 2,253 newly diagnosed MDS patients
  - median age of 77
- Transfusion dependent patients with MDS
  - higher incidence of dyspnea, hepatic disease, and infections (all $p<0.001$)
  - 82% experienced a cardiac event within 3 years of follow-up ($p<0.001$).
  - increased risk of death (age-adjusted) when compared to other MDS patients (HR 2.41, 95% CI, P<.001)

Goldberg, S.L., Chen, E., Corral, M., Guo, A., Mody-Patel, N., Pecora, A.L. & Laouri, M. (2010) Incidence and Clinical Complications of Myelodysplastic Syndomres Among United States Medicare Beneficiaries. *J Clin Oncol*;28:2847-2852. DOI: 10.1200/JCO.2009.25.2395

Pivotal Trials for FDA Approved Agents

REGISTRATION TRIALS

Azacitidine	Lenalidomide	Decitabine
CALBG 9221—phase I/II (2000) Efficacy & Safety **CALGB 8421—phase II**	**MDS 001—phase I/II (2002) Efficacy & Safety**	**D 0007—phase I/II (2003) Efficacy & Safety**

CONFIRMATORY AND EXPANSION TRIALS

AZA—001

Phase III international multicenter
Expansion trial
Int-2–high-risk MDS

First survival data for active therapies in MDS

MDS—002

Phase II multicenter trial
lenalidomide in non-del(5q) low–Int-1 MDS confirmed activity in non-(del)5q MDS safety and efficacy

MDS—003

Phase II multicenter trial
Lenalidomide in del(5q) led to FDA approval based on efficacy and safety

ADOPT Trial

Phase III randomized multicenter trial
Established new dosing guidelines
Decitabine 20 mg/m^2 IV given over 1 hour days 1-5

Outpatient treatment feasible

Kurtin and Demakos. *Clin J Oncol Nurs*. 2010;14:3. doi:10.1188/10.CJON.E24-E39.

Individualized Treatment

- Treatment Triggers: Initiation of disease modifying therapy
  - Transfusion dependence
  - Progressive or symptomatic cytopenias
  - Increasing blasts
  - High-risk disease
- Individualized treatment selection
  - Performance status (good vs poor)
  - Comorbidities
  - IPSS risk category (low/Int-1 vs Int-2/high)
    - Low/Int-1: improve hematopoiesis
    - Int-2/high: survival
  - Primary vs secondary MDS
  - Cytogenetic status (del[5q], complex karyotype)
  - Lifestyle

NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes—v.2.2011. Kurtin and Demakos. *Clin J Oncol Nurs*. 2010;14:3. doi:10.1188/10.CJON.E24-E39.

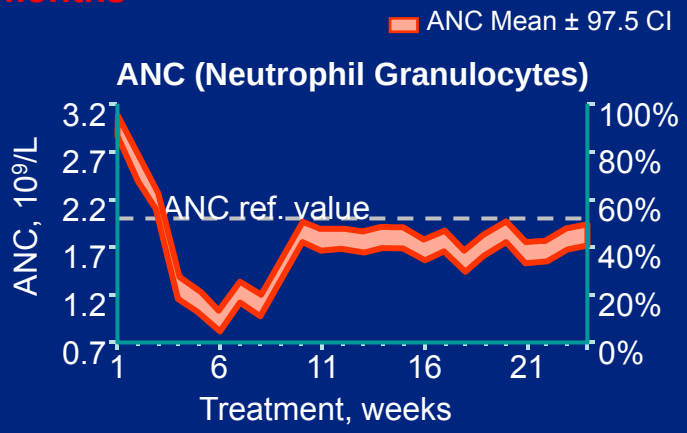
Key Principles of Therapy in MDS Treatment Goals and Duration

- MDS is not curable without allogeneic HCT
  - Not an option for the majority of patients
- Not every patient will have a complete response
  - Hematologic improvement, stable disease, and transfusion independence are good things
- Treatment should continue until disease progression or unacceptable toxicity
  - Methylation is a continuous process and is associated with leukemogenesis
  - Limited FDA approved agents currently available

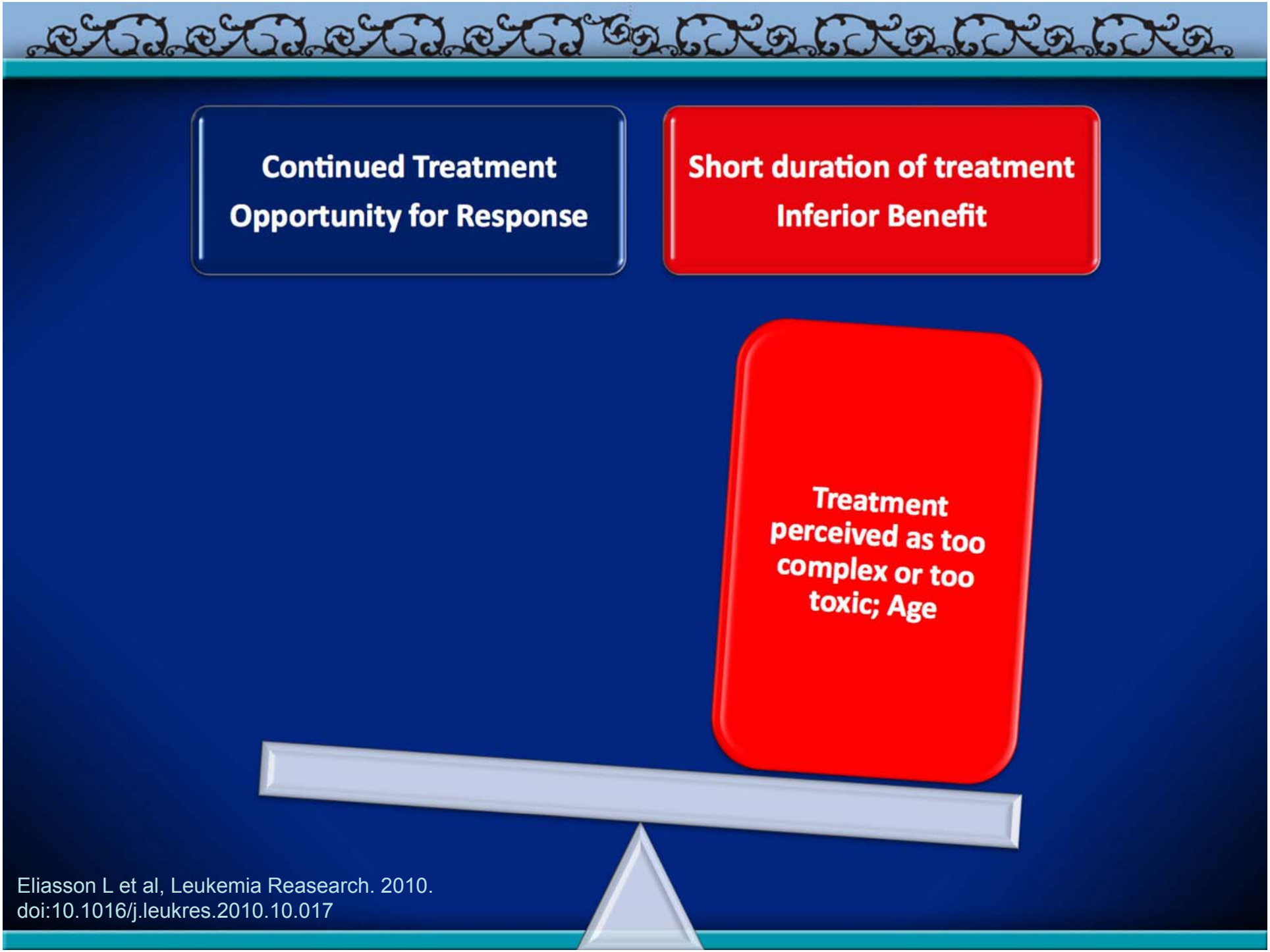
Kurtin and Demakos. *Clin J Oncol Nurs*. 2010;14:3. doi:10.1188/10.CJON.E24-E39.
Kurtin, S. JAdPrO, 2011, submitted for publication

The Challenge:
Getting Through the First Few Cycles of Treatment

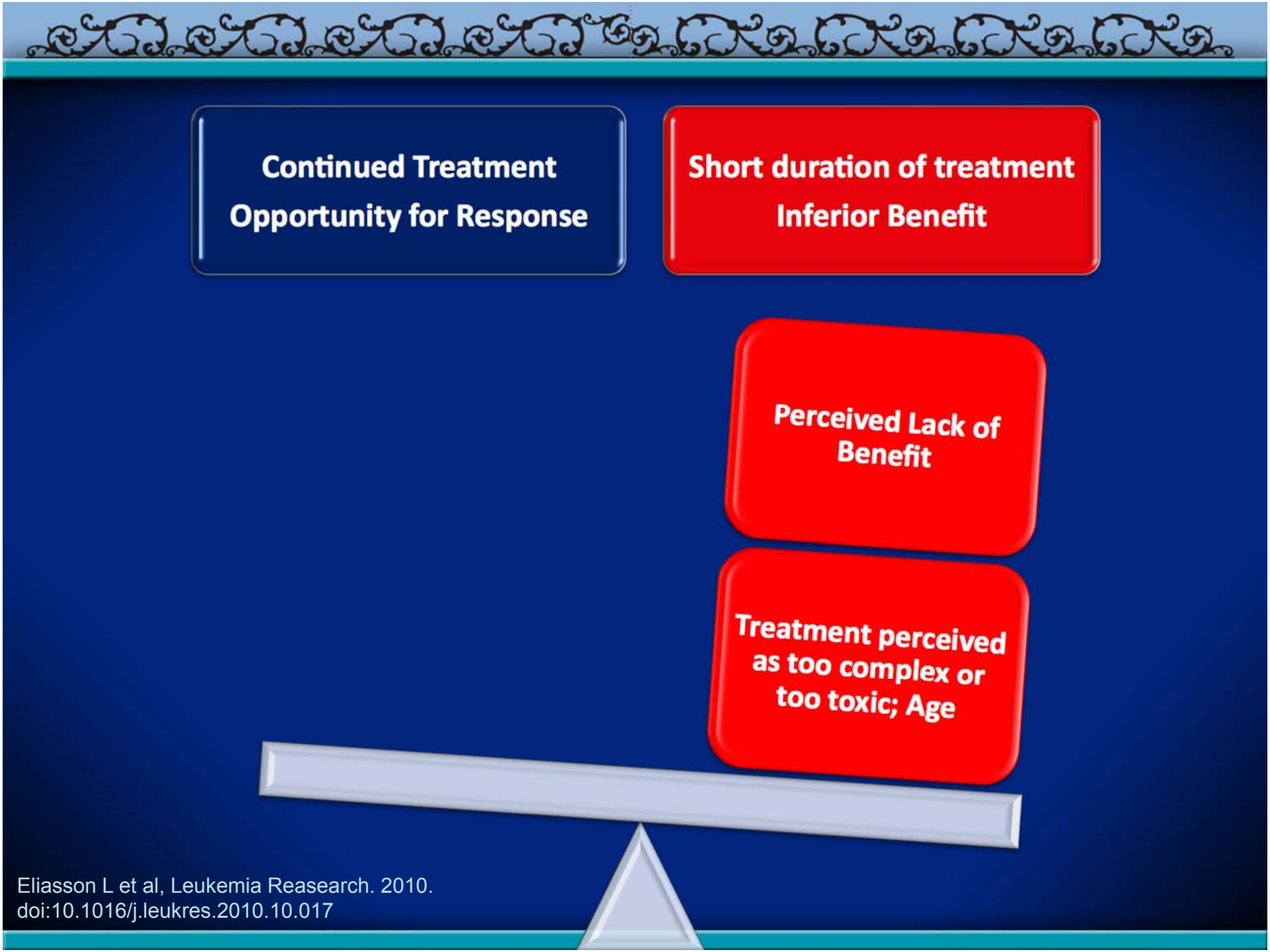
- **Time is required for the best response: a minimum of 4-6 months**
- **Cytopenias often get worse before they get better**
- **This may be concerning to the patient (*and providers*)**
- **There are strategies for management**
  - Dose modifications/delays
  - Supportive care
  - Set expectations and provide support



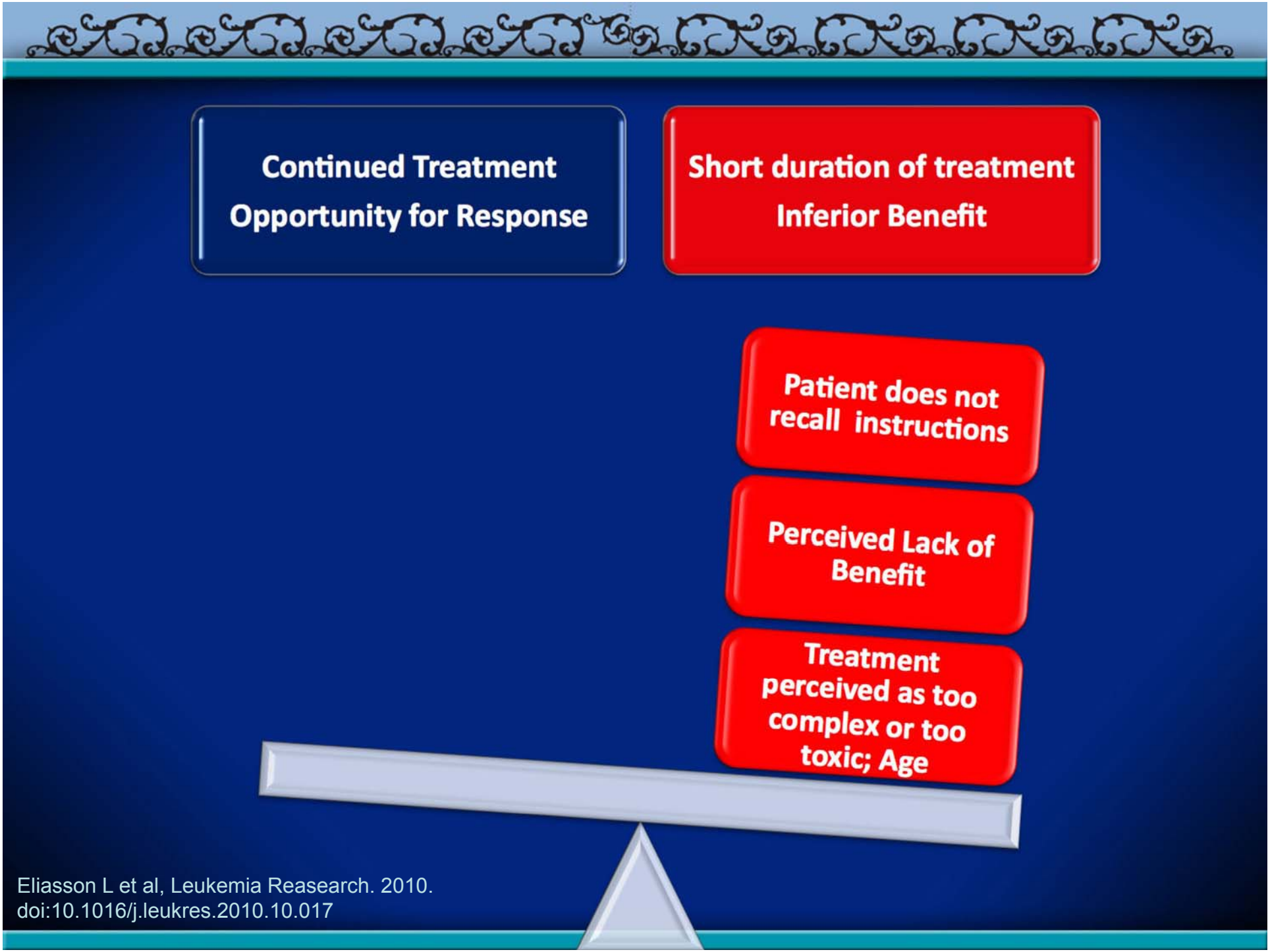
Sekeres and List. *Clin Leuk.* 2008;2:28-33.



Eliasson L et al, Leukemia Reasearch. 2010.
doi:10.1016/j.leukres.2010.10.017



Eliasson L et al, Leukemia Reasearch. 2010.
doi:10.1016/j.leukres.2010.10.017



Eliasson L et al, Leukemia Reasearch. 2010.
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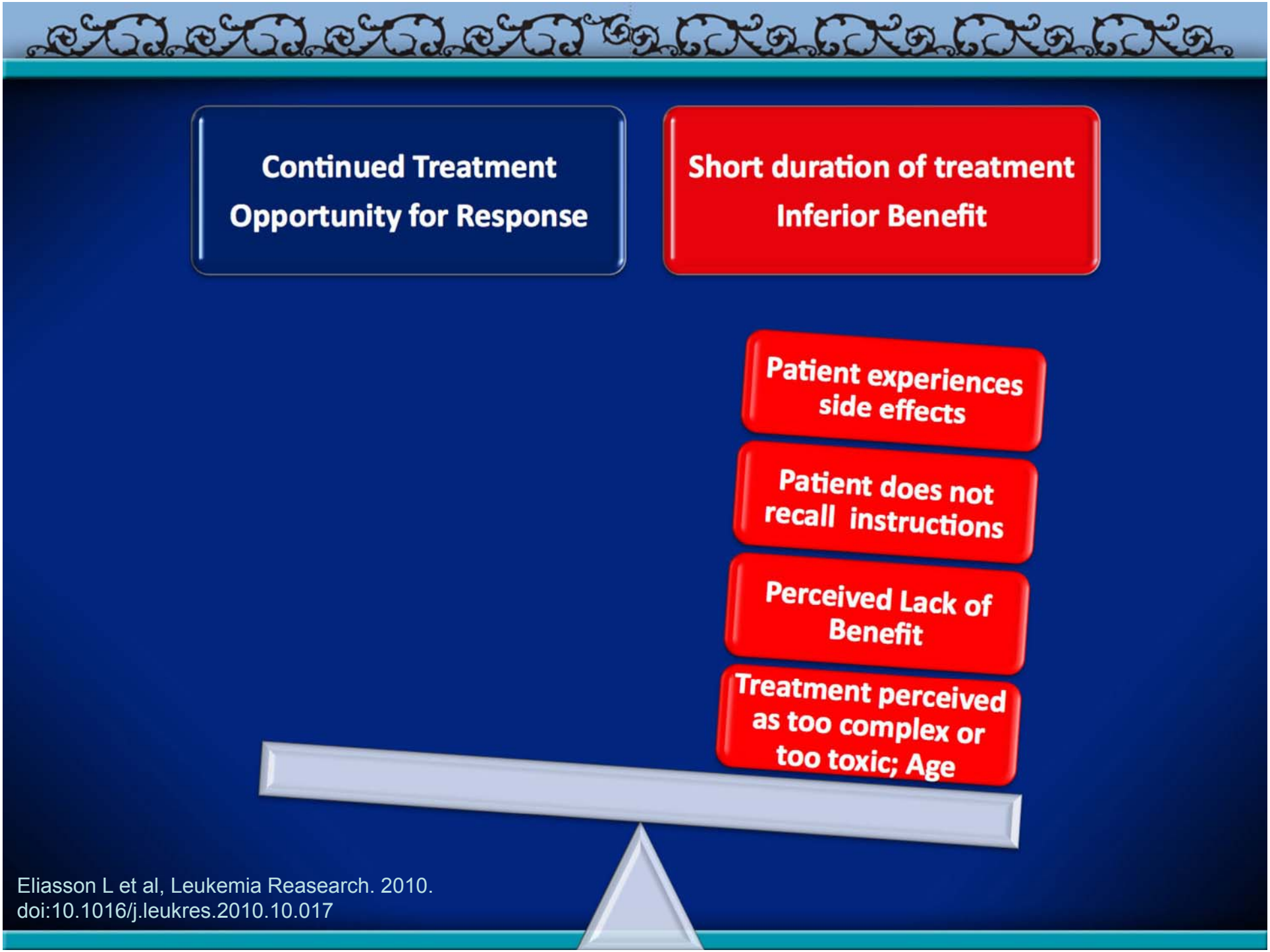
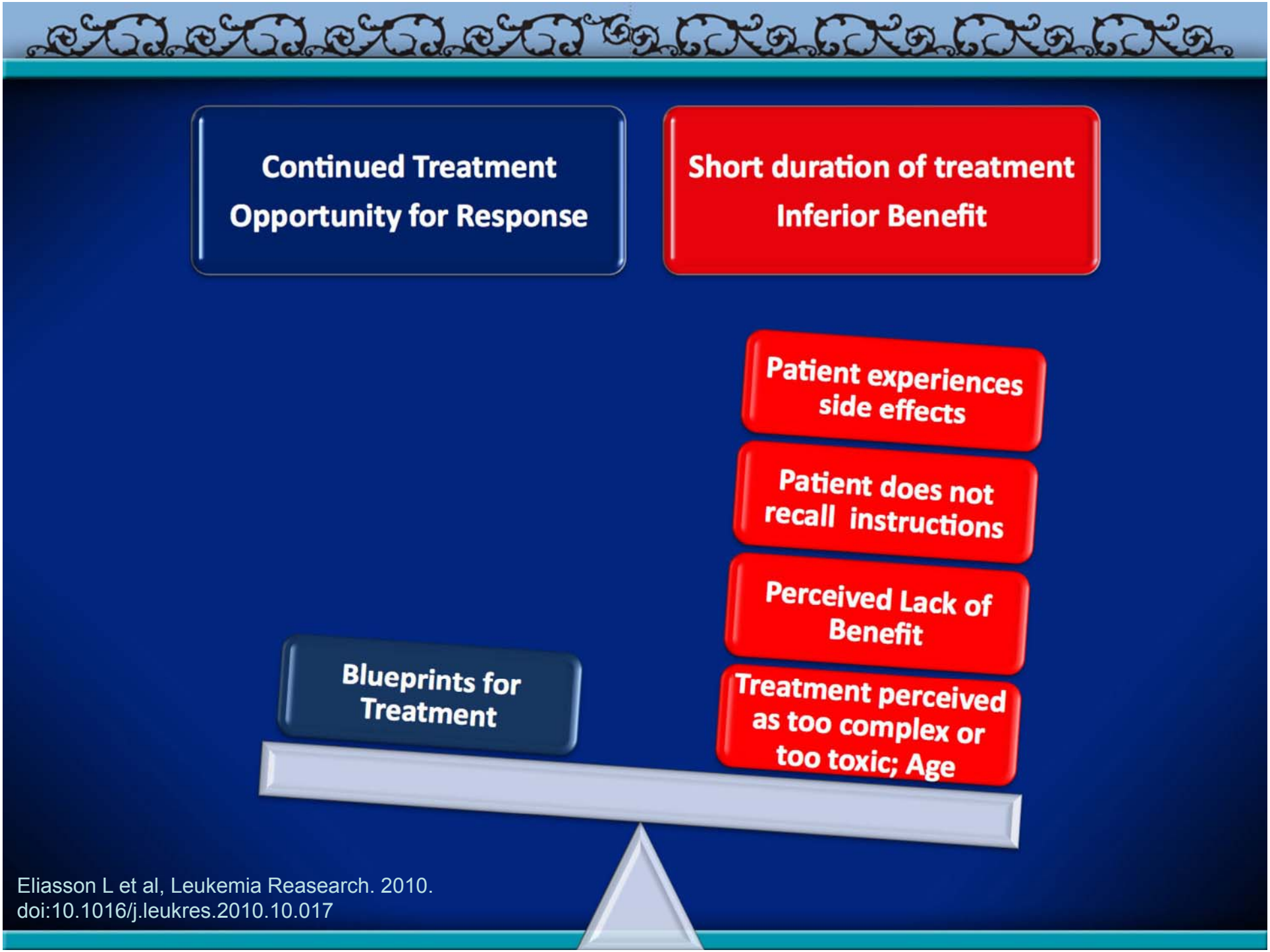
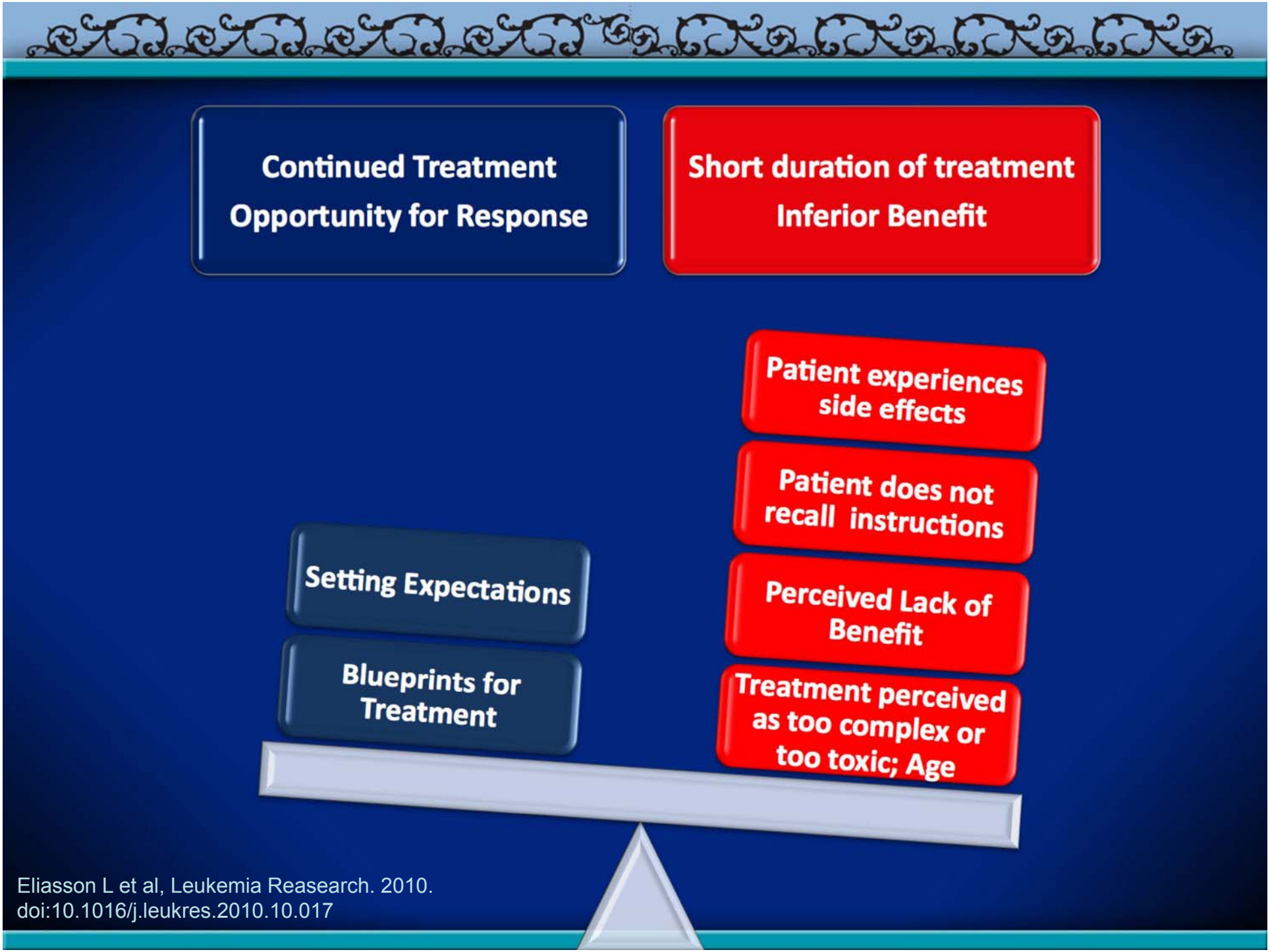


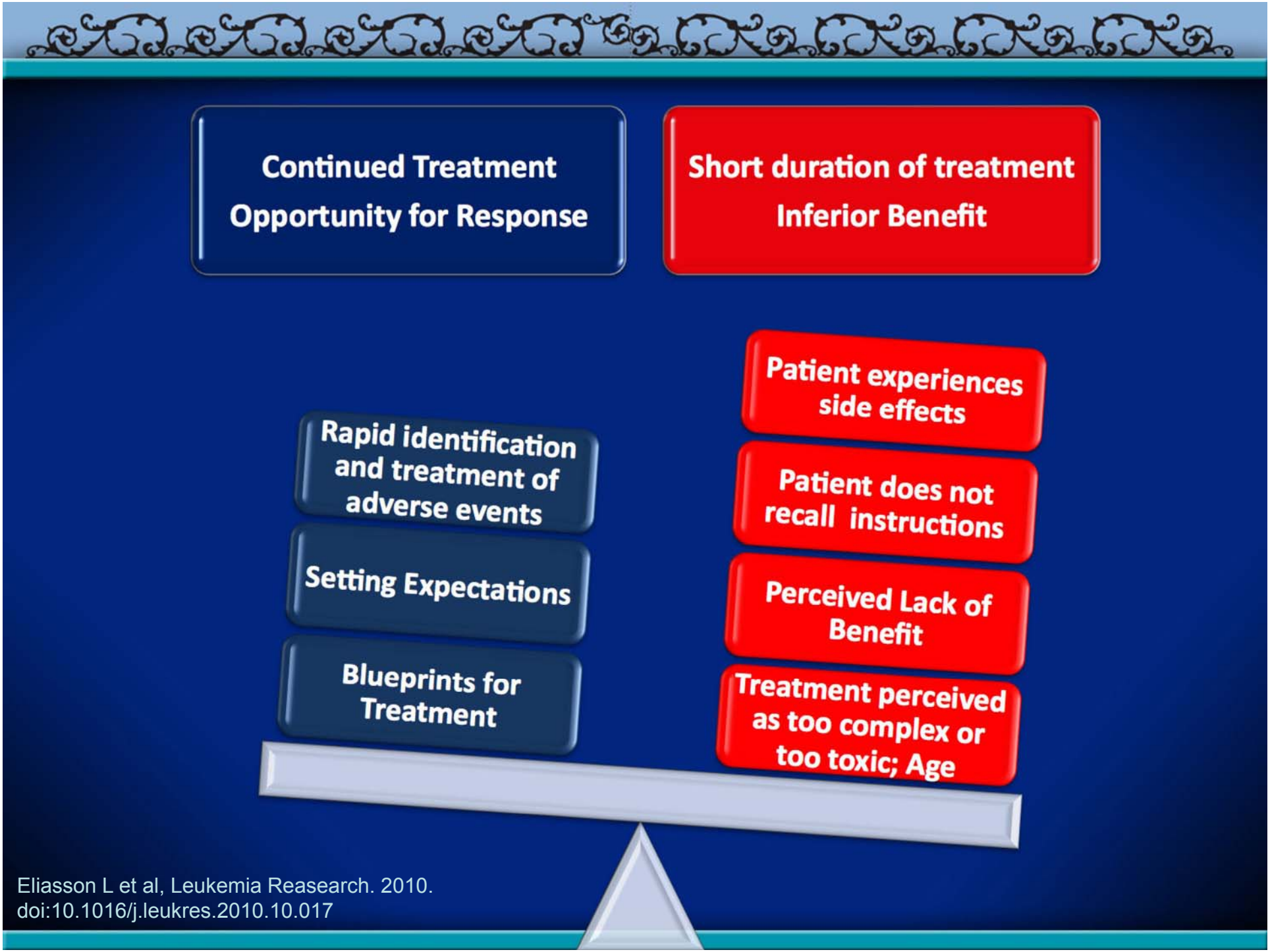
Eliasson L et al, Leukemia Reasearch. 2010.
doi:10.1016/j.leukres.2010.10.017



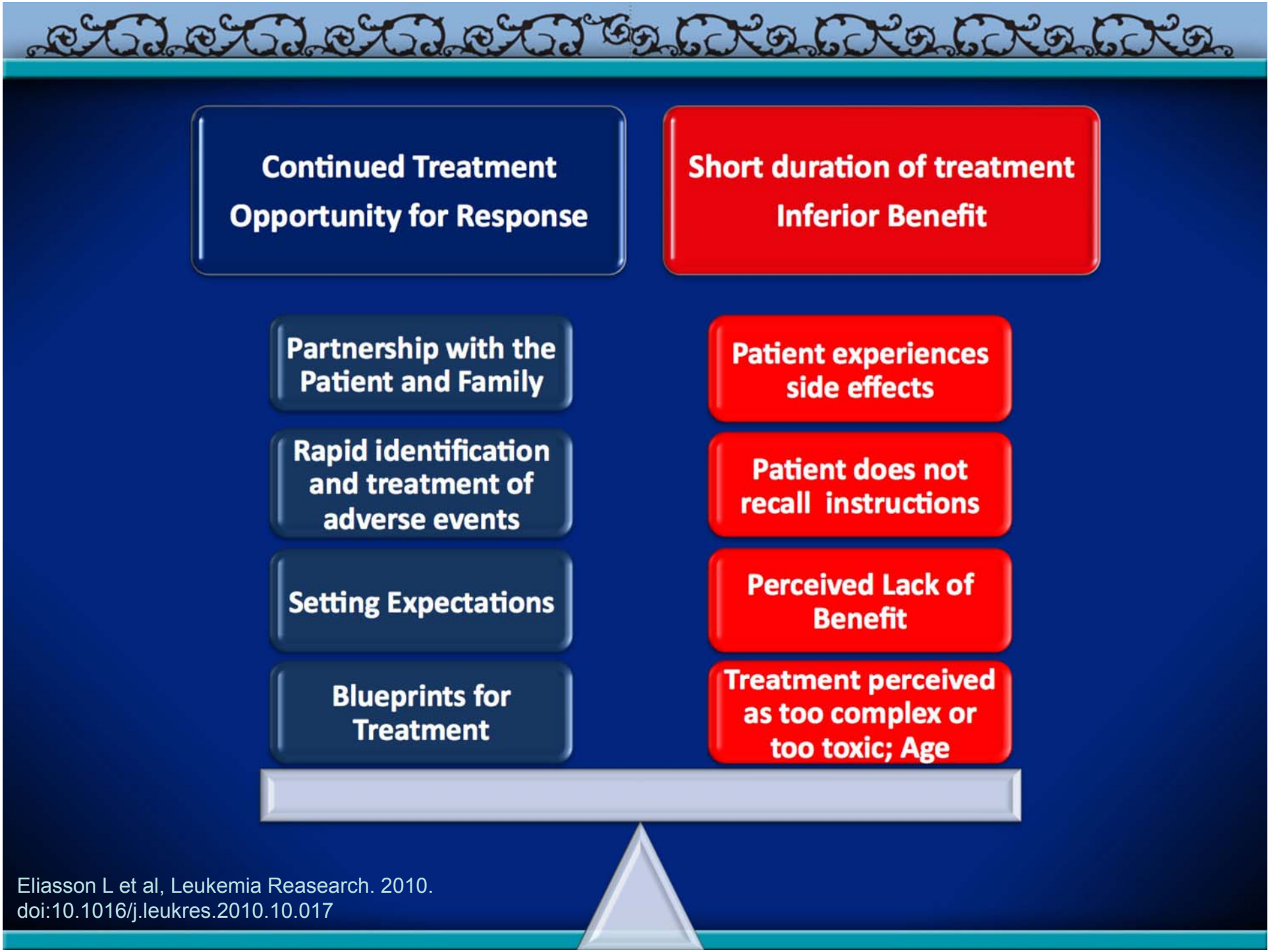
Eliasson L et al, Leukemia Reasearch. 2010.
doi:10.1016/j.leukres.2010.10.017



Eliasson L et al, Leukemia Reasearch. 2010.
doi:10.1016/j.leukres.2010.10.017



Eliasson L et al, Leukemia Reasearch. 2010.
doi:10.1016/j.leukres.2010.10.017



Eliasson L et al, Leukemia Reasearch. 2010.
doi:10.1016/j.leukres.2010.10.017

Sub-Group Analysis of the AZA-001: Elderly patients ≥75 years with high risk disease

- 87 elderly ≥ 75 years
- High risk disease: IPSS: Int-2 or High
- AZA significantly improved OS compared to BSC
  - 2 year OS rates 55% vs 15% ($p<0.001$)
- AZA generally well-tolerated
  - Adverse events most common in the first 2 cycles

AE (grade 3/ 4	Cycle1-2		Cycle 3-4		Cycle 5-6	
	AZA	BSC	AZA	BSC	AZA	BSC
Anemia (%)	2	1	0	1	2	0
Neutropenia (%)	15	6	8	3	7	2
Thrombocytopenia (%)	14	10	8	2	5	0
Fatigue (%)	0	0	1	1	1	0
Pyrexia (%)	0	0	1	1	1	0

Seymour et al. 2010, Crit Rev Onc/Heme 76;218-227.

Setting Expectations and Empowering the Patient and Family

- Setting Expectations: Blueprints for Treatment
  - Cytopenias are **expected**
  - Require close monitoring during the first 8-12 weeks of therapy.
    - Create a plan for follow-up
  - Likely to improve with treatment response but may not return to normal - “new normal”
- Empower the patient and family to track, report and manage
    - Treatment tracker, Transfusion records
    - Early identification of AEs, how and when to report or manage

Kurtin and Demakos. *Clin J Oncol Nurs*. 2010;14:3. doi:10.1188/10.CJON.E24-E39.
Kurtin. *JAdPrO* , 2011

THE UNIVERSITY OF ARIZONA CANCER CENTER

Patient Identification:
Name:
DOB:
MR#
Visit#

DIAGNOSIS: MDS	**ICD 9: 238.7**	**REGIMEN: Lenalidomide**	HT: CM	WT: KG	BSA: M^2

Approved Indications:

References:

List A et al, (2006) Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med*, 355,1456-1465.
List, A et al, (2005). Efficacy of lenalidomide in myelodysplastic syndromes. *New Eng J Med*, 352(6), 549-557
Raza, A., et al, (2007) Phase 2 study of lenalidomide in Low- Intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. Blood, 111(1), 86-93.

Allergies (Drug, Food, Environmental)_____
□ No Known Drug Allergies □ No Known Food Allergies □ No Known Environmental Allergies

COURSE #:_____of_____			**Start date for cycle #1 of therapy: _____**	
MEDICATION AND DOSE		**PATIENT'S DOSE**	**ROUTE**	**ADMINISTRATION TIME, AND FREQUENCY**
1	**Lenalidomide (Revlimid®)**	**□ 10 mg** **□ 5mg**	**By mouth**	**Once tablet daily with or without food at the same time each day** **□ Days 1-21 every 28 days** **□ Daily** **□ Other: _____**

Begin Therapy:(day 1) _____

Treatment Parameters: Do Not Initiate Treatment If: (will use clinic standards if not indicated)	**WBC <** **PLT <** **Bilirubin >** **ANC <** **CR >**

Protocol modification (reason):	**Effective date:**	
Other Provider Signature:	**ID #**	**Date/Time:**
Attending Provider Signature:	**ID #**	**Date/Time:**

Kurtin, S. et al. (2012) Digital Object Identifier:10.1188/12.CJON.S1.23-35

PRE-TREATMENT EVALUATION:		
1	Informed Consent	□ Consent form signed: Date: _____ (included in HER)
2	Registration with Revassist ®: www.revassist.com	Must be prescribed through Revassist program for safety Celgene Customer Care Center toll-free at 1-888-423-5436
3	Pre-treatment laboratory	□ CBC, differential, platelet count □ Complete Metabolic Panel □ Serum erythropoietin level □ TSH, serum testosterone (men only)
4	Pre-treatment patient education	□ Consultation with Clinical Coordinator/Patient Navigator □ Chemotherapy education course: Date: □ Treatment and Transfusion tracking tool □ Lenalidomide (Revlimid ®) patient information packet
5	~~Referral to financial coordinator~~	□
6	Common Adverse Events	• Myelosuppression – most common • Rash – generally transient, pruritus is common in early phase of treatment • Diarrhea • Use with caution in renal impairment – refer to Micromedex • Analog of Thalidomide- Lenalidomide is nonteratogenic in animal studies
FOLLOW-UP PROTOCOL:		
1	Weekly laboratory analysis for first 8 weeks	□ CBC, differential, platelet count □ Complete Metabolic Panel
2	Provider/ Nursing Visit for toxicity check, reinforcement of teaching (first 8 weeks)	□ Provider visit (99214) □ weekly □ every other week □ Other □ Nursing visit (99211)) □ weekly □ every other week □ Other
3		

Kurtin, S. et al. (2012) Digital Object Identifier:10.1188/12.CJON.S1.23-35

Transfusion Tracker

Name: **John Smith**
DOB: **10/01/1939** Blasts (%): ____
Initial Diagnosis: **Refractory Cytopenias with Multilineage Dysplasia (RCMD) – September 1, 2000**

Gender (M) F Patient ID #: **12345678**
Cytogenetics: **46, XY, del(5)(q13q33)[13]/46,XY[7]**
IPSS Score (low) / intermediate-1 / intermediate-2 / high

Date of First Transfusion/Number of Lifetime Transfusions: **September 30, 2000 / 6 units**

Date of transfusion	Days/weeks since last transfusion	Number of units transfused	Total # of transfusions	Transfusion complications	Serum Ferritin (µg/L)	Hemoglobin (g/dL)	White blood cell/absolute neutrophil counts (cells/µl)	Platelets/µL
10/5/2001	60	2 PRBC	8	None	221	8.4	2300 / 759	193,000
12/7/2001	60	2 PRBC	10	None		8.2	2700 / 1404	185,000
2/11/2002	66	2 PRBC	12	None		7.8	2900 / 1219	200,000
3/22/2002	39	2 PRBC	14	None	223	8.1	2600 / 899	193,000
4/2/2002		0	14	n/a		9.1	2700 / 1728	193,000
4/16/2002		0	14	n/a		7.6	2600 / 1170	140,000
4/22/2002	31	2 PRBC	16	None		7.6	1800 / 510	119,000
4/24/2002		0	16	n/a		8.9	1500 / 300	112,000
4/26/2002		0	16	n/a		8.6	1100 / 546	105,000
4/30/2002		0	16	n/a		8.6	1000 / 140	78,000
5/10/2002		0	16	n/a		8.65	1100 / 660	68,000
5/14/2002		0	16	n/a		9.0	1900 / 1102	61,000
5/21/2002		0	16	n/a		10.2	2600 / 1300	58,000
5/28/2002		0	16	n/a		11.3	3000 / 1350	53,000
6/4/2002		0	16	n/a		11.3	3100 / 1178	61,000
6/11/2002		0	16	n/a	315	11.7	2200 / 858	57,000
9/9/2011	3427 days	0	16	n/a	288	12.3	3700 / 1820	105,000

DATE	OTHER THERAPIES	NOTES
4/2/2002	MDS-001 Trial started Lenalidomide 25 mg/day	
4/22/2001	Two units of PRBCs transfused	
4/24/2002	Lenalidomide held due to neutropenia and thrombocytopenia	
5/21/2002	Resumed treatment with Lenalidomide at 10 mg/day	
10/8/2003	Lenalidomide held due to neutropenia and thrombocytopenia, no transfusions since 4/22/2002	
11/4/2003	Resumed Lenalidomide 5mg daily	
3/11/2004	Lenalidomide changed to 21 days on 7 days off – syncopated schedule due to protocol modification	
9/9/2011	Continue on Lenalidomide 5 mg daily 21/28 days	

MDS TRANSFUSION TRACKER

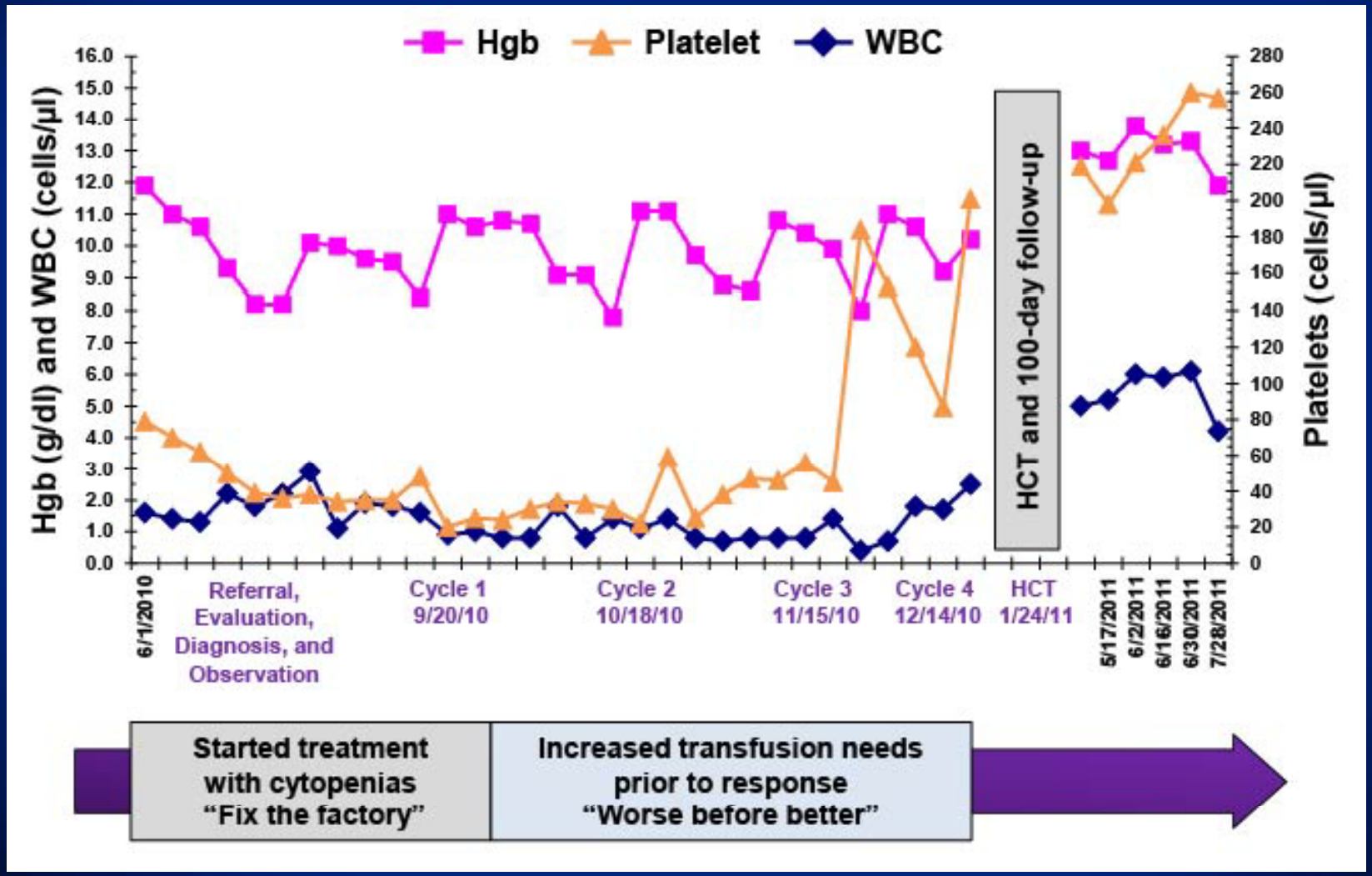
Kurtin, S. et al. (2012) Digital Object Identifier:10.1188/12.CJON.S1.23-35

Strategies to Minimize Adverse Events

- Supportive care is essential for all patients with MDS to improve quality of life
  - Transfusion support, Growth factors, management of infections, management of co-morbidities, chelation therapy, referrals to supportive services
- Minimize AEs in patients on active therapies
  - Dose adjustment, drug holidays, or administration of growth factors to allow safe continuation of therapy.
  - Clear guidelines to the patient and family for early reporting of AEs or strategies for independent management

Kurtin and Demakos. *Clin J Oncol Nurs*. 2010;14:3. doi:10.1188/10.CJON.E24-E39.
Kurtin. *JAdPrO* , 2011

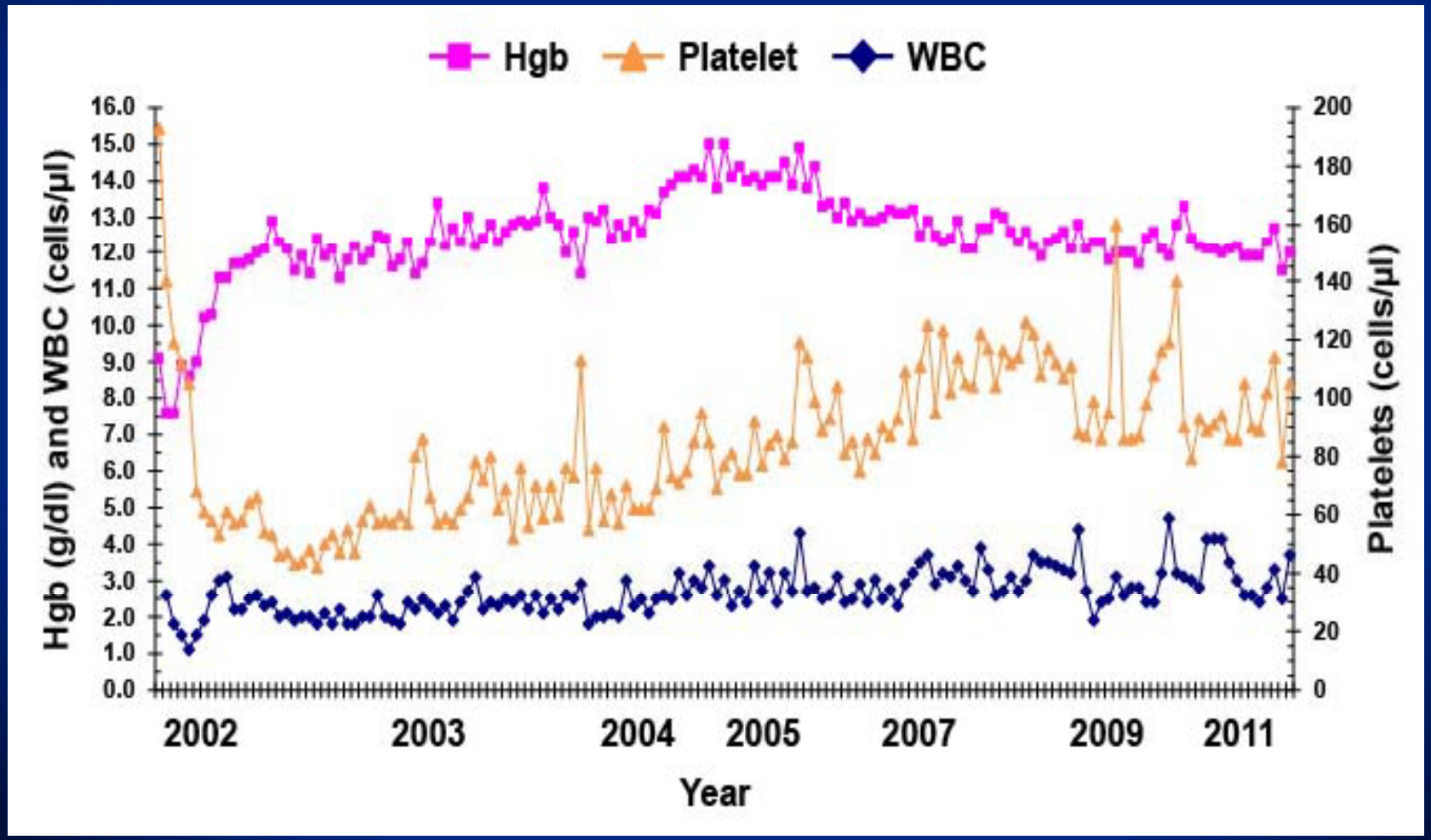
Trilineage Response Following 4 Cycles of Azacitidine



Kurtin, S. et al. (2012) Digital Object Identifier:10.1188/12.CJON.S1.23-35

Patient Response Over 9 Years of Lenalidomide Treatment

Sustained Moderate But Asymptomatic Cytopenias–A New "Normal"



Kurtin, S. et al. (2012) Digital Object Identifier:10.1188/12.CJON.S1.23-35

Passion for the Patients ***LIVING*** with MDS

Patient and Family Support Throughout the Continuum of Care

Jayshree Shah
APN-C, AOCN, MSN, BSN, BS, RN, CCRP
John Theurer Cancer Center
Hackensack University Medical Center
Leukemia Division

Key Principles for Educating the Patient and Caregiver

- Understand Disease State
- Available treatment options
- Expected duration of therapy
- Potential adverse events
- Strategies for taking an active role in their care
- Effective patient, caregiver and HCP communication results in better outcome

Kurtin et al, *CJON*, 2012

Factors noted to limit treatment options

- Fear of toxicity
- Limited expectation of benefit
- Ageism
- Cost of treatment
- Strain on caregivers[1]
- Several surveys of patients & providers have underscored the ambiguity in describing MDS as a myeloid malignancy resulting in reluctance to offer disease modifying treatments based on risk analysis [2]

1. Carreca& Balducci, 2009; Kurtin 2010
2. Kurtin & Demakos, 2010; Sekeres, 2011;Sekeres et al., 2011

Common Adverse Events

- All agents
  - Myelosuppression (may also be disease related)
    - Anemia, neutropenia, thrombocytopenia
  - Nausea and vomiting
  - Constipation
  - Renal and hepatic toxicities
- Drug-specific adverse events
  - Azacitidine: injection-site reactions
  - Lenalidomide: rash, pruritus, diarrhea, safety program for lenalidomide
- Iron overload
  - Chelation therapy may be associated with cytopenias, renal and hepatic toxicities

Kurtin and Demakos. *Clin J Oncol Nurs*. 2010;14:3. doi:10.1188/10.CJON.E24-E39.
Scott and Deeg. *Annu Rev Med*. 2010;53:345-358.
Kurtin. *Oncology: Nurse Edition.* 2007;21:41-48.

Transfusion Risks: Iron Overload

- Each unit of PRBC adds 250 mg of unexcretable iron into the patient's blood
  - At 20-40 RBC transfusions (5-10 g iron)
  - Elevated serum ferritin (1,000-2,000 mg/L), liver, and/or cardiac iron
- Iron accumulation results in end-organ damage

ORGANS	COMORBIDITIES & END EFFECTS
Heart	Increase risk of cardiac –related event, myocardial infarction, congestive heart failure, arrhythmias
Liver	Increase risk of cirrhosis, hepatic dysfunction w/elevated levels,
Endocrine	Leads to hypogonadism, hypothyroidism, and diabetes

Which Patients With MDS Are Likely to Benefit Most From Management of Iron Overload?

Transfusion status	• Transfusion dependence • Requiring 2 units/month for > 1 year • Received 20-30 packed RBC units
Serum ferritin	• 1,000 ug/L (MDS Foundation) • > 2,500 ug/L (NCCN) • Or evidence of significant tissue iron overload with continued transfusion dependence
MDS risk	• IPSS: Low- or int-1 • WHO: RA, RARS, and 5q
Patient profile	• Candidates for allografts • Life expectancy > 1 year • Free of comorbidities that limit prognosis • A need to preserve organ function

Jabbour et al. *Oncologist*. 2009;14:489-496.
NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes—v.2.2010.

FDA Approved Iron Chelation Therapies

Parameters	Deferoxamine (Desferal)	Deferasirox (Exjade)	Deferiprone (Ferriprox)	Phlebotomy
Dosage	i.m. 0.5 – 1 mg/day s.c. 20-40 mg/kg/day	p.o. 20-40 mg kg/day	p.o. 75 mg/kg/day	Venipuncture
Half-life (hours)	6	8-16	2-3	n/a
Schedule	Administered over 8-24 hours, 5-7 days/week	Once a daily	Three times daily	1-2 weekly
Routes of iron excretion	Urine, stool	Urine, stool	Urine	n/a
Toxicities & adverse effects	Ocular, auditory, localized site injection reaction, allergic reaction, growth and skeletal abnormalities	Renal, hepatic, rash, myelosuppression, GI disturbances	GI, hepatic disturbances myelosuppression	Non-invasive
Website	www.desferal.net	www.us.exjade.com	www.ferriprox.com	n/a

Shah et al, *CJON*, 2012

Iron Chelation Therapy: Safety and Patient Monitoring

- Pancytopenia
  - Neutropenia, agranulocytosis, thrombocytopenia have been reported in MDS patients
    - Baseline and regular monitoring
- Auditory
  - High-frequency hearing loss, decreased hearing
    - Baseline and yearly audiology evaluation
- Ocular
  - Cataracts, lens opacities, increased pressure, retinal disorders
    - Baseline and yearly slit-eye and fundoscopic exam

Malcovati et al. *J Clin Oncol*. 2005;23:7594-7603. Jabbour et al. *Oncologist*. 2009;14:489-496. Kurtin. *Oncology: Nurse Edition.* 2007;21:41-48. Kurtin. 2008. https://www.meniscus.com/mds-cll-mm.

Iron Chelation Therapy: Safety and Patient Monitoring *(cont)*

- Renal toxicity
  - Increase in serum creatinine
    - Rare cases of acute renal failure have been reported
  - Intermittent proteinuria
    - Baseline and regular monitoring
    - Dose delay or reduction may be necessary
- Hepatotoxicity
  - Elevated transaminase levels
    - Baseline and regular monitoring
    - Dose delay or reduction may be necessary
- Gastrointestinal toxicity
  - Diarrhea
    - May use antidiarrheal medications
    - Dose reduction may be necessary
  - Nausea
    - Take at bedtime
    - Avoid taking with dairy products

Malcovati et al. *J Clin Oncol*. 2005;23:7594-7603. Jabbour et al. *Oncologist*. 2009;14:489-496. Kurtin. *Oncology: Nurse Edition.* 2007;21:41-48. Kurtin. 2008. https://www.meniscus.com/mds-cll-mm.

Guidelines for Monitoring Chelation Therapy

Test	Baseline	During therapy
Serum ferritin	X	Every three months
Serum transaminase levels	X	Monthly
Serum creatinine	X	Monthly
Liver iron stores (T2 MRI)	X	Annually
Granulocyte levels	X	Monthly for MDS pts
Myocardial iron stores (T2 MRI)	X	Annually
Auditory testing	X	Annually
Ophthalmic testing	X	Annually

Malcovati et al. *J Clin Oncol*. 2005;23:7594-7603. Jabbour et al. *Oncologist*. 2009;14:489-496.
Kurtin. *Oncology: Nurse Edition.* 2007;21:41-48. Kurtin. 2008. https://www.meniscus.com/mds-cll-mm.

Building Blocks of Hope:

A Patient and Care Giver Guide for

LIVING with MDS

International Nursing Leadership Board

The MDS Foundation

The Building Blocks of Hope
Answering Common Questions About MDS

- Understanding the Diagnosis of MDS
- How is MDS diagnosed?
- What are my treatment options?
- What are the common side effects of treatment, and what can be done to control them?
- What new treatments are on the horizon to treat patients with MDS?
- What are the consequences of blood transfusion?
- Should I receive iron chelation therapy?
- How do I select a bone marrow transplant center?
- What can I do to keep myself healthy?

Kurtin, et al. (2012) *CJON*

What Can I do To Stay Healthy?

- Balanced Diet
- Daily Activity/Exercise
- Avoid Infection
- Avoid Bleeding
- Continue to Enjoy Things You Love - *LIVE*
- Get Enough Rest
- Take Advantage of Available Resources
- Ask for Help When Needed
- Be an Active Participant in Building Hope

Kurtin, et al. (2012) *CJON*

Key Points for Patients & Family Living with MDS

- Supportive care
- Advocate and ask questions
- Formulate a plan
- Engage in activities
- Track & Talk
- You

Navigating the Web for MDS: Web-based Resources for Patients and Health Care Providers

Sara M. Tinsley, ARNP, AOCN
Nurse Practitioner
Moffitt

Supporting the MDS Patient, their Caregivers and Health Care Providers

- Myelodysplastic syndromes are a class of incurable diseases requiring compassionate, clear, and consistent communication among healthcare providers (HCPs), patients , and caregivers
- The majority of patients and caregivers want to understand their disease, prognosis, available treatment options, expected duration of therapy, potential adverse events, and strategies for taking an active role in their care

Supporting the MDS Patient, their Caregivers and Health Care Providers

- Effective patient, caregiver, and HCP communication will promote patient and caregiver participation in the decision making process and self-care
- A number of Web-based resources provide resources for patients, caregivers and health care providers

http://cjon.sup.mds-foundation.org

MDS-Specific Organizations
(alphabetical order)

- **Life Beyond Limits**
  - *http://mdslifebeyondlimits.org*
  - Brings together an independent group of MDS experts to raise awareness of ageism in access to care for patients with MDS
- **MDS Beacon**
  - *http://mdsbeacon.com*
  - Objective and unbiased news and other information related to MDS

MDS-Specific Organizations
(alphabetical order)

- **MDS Foundation**
  - *http://mds-foundation.org*
  - Multidisciplinary, international, nonprofit organization dedicated to the education of professionals, patients, and caregivers; facilitation and support of clinical trials; and development and support of patient advocacy groups
- **United Kingdom MDS Patient Support Group**
  - *http://mdspatientsupport.org.uk*
  - Offers support, information, referral advice, and patient information in the United Kingdom

http://www.mds-foundation.org/

http://www.mds-foundation.org/global-patient-support-groups/

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Clinical Trials

Clinical trials study new interventions (drugs or procedures) to evaluate their safety and effectiveness in humans. Trials follow a careful set of steps, allowing for the systematic gathering of information to answer questions and confirm hypotheses that were formed earlier, in either laboratory experiments or preliminary trials.

If you are an MDS patient, you may wish to discuss a trial with your primary treating physician to see if you qualify as a candidate.

Announcing New MDS Trial

- CLINICAL RESEARCH TRIAL WITH RIGOSERTIB (ON01910.Na)
- www.onconova.com
- www.mdstrial.com

Click here for a list of international trials.

To submit information on your clinical trials for publication, you

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MDS Foundation Store

http://www.mds-foundation.org/clinical-trials/

Organizations That Include MDS Within the Scope of Hematologic Malignancies

- **Aplastic Anemia and MDS Foundation**
  - *http://www.aamds.org*
  - Nonprofi t health organization dedicated to supporting patients and families living with aplastic anemia, MDS, paroxysmal nocturnal hemoglobinuria, and related bone marrow failure disease
- **Leukaemia and Lymphoma Research Foundation**
  - *http://leukaemialymphomaresearch.org*
  - Programs for support of all of the different blood cancers for patients and their families

Aplastic Anemia & MDS
INTERNATIONAL FOUNDATION

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HEALTH PROFESSIONALS

- eInsider for Health Professionals
- Patient Education Materials
- CME
- Treating MDS Toolkit
- MDS Mobile App

RESOURCES FOR

- Patients & Caregivers
- Health Professionals
- Members of the Media

ONLINE LEARNING CENTER

Health Professionals

Treating MDS Toolkit

TREATING MDS
Your Partner in Patient Care

Health professionals are the primary source of information for patients. The purpose of this toolkit is to provide resources for healthcare providers to communicate with and support patients with MDS. These materials will help you share the necessary information efficiently and effectively.

The toolkit contents are based on the needs identified by MDS patients in the survey conducted by AA&MDSIF and summarized in **The Oncologist** in 2011 (Perceptions of Disease State, Treatment Outcomes, and Prognosis Amon

http://www.aamds.org/treating-mds-toolkit

Organizations That Include MDS Within the Scope of Hematologic Malignancies

- **Leukaemia Care**
  - *http://www.leukaemiacare.org.uk*
  - Resources for people affected by Hodgkin, non-Hodgkin, and other lymphomas; myeloma; MDS; aplastic anemia; and myeloproliferative disorders
- **Leukemia and Lymphoma Society**
  - *http://www.lls.org*
  - Mission is to cure leukemia, lymphoma, Hodgkin disease, and myeloma and improve the quality of life of patients and their families

http://www.lls.org/#/diseaseinformation/myelodysplasticsyndromes/

http://www.lls.org/#/researchershealthcareprofessionals/

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Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) is the name of a group of conditions that occur when the blood-forming cells in the bone marrow are damaged. This damage leads to low numbers of one or more type of blood cells. If you (or a loved one) are worried about developing a myelodysplastic syndrome, have just been diagnosed, are going through treatment, or are trying to stay well after treatment, the Detailed Guide or Overview can help you find the answers you need.

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Circle Of Sharing™ helps cancer

Clinical Trials »

Clinical trials are studies in which

Bone Marrow and Peripheral Blood Stem Cell

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- Detailed Guide
- Overview Guide

HOW CAN WE HELP YOU?

http://www.cancer.org/cancer/myelodysplasticsyndrome/index.cancer.org/

Managing Cancer-Related Fatigue

Watch an intro video

Start the class

This presentation is for general information only. It is not intended as medical advice and should not be used as a substitute for talking with your doctor or nurse who knows your medical needs.

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American Cancer Society®

https://americancancersociety.adobeconnect.com/_a300451731/fatigue/_ncer.org/

Financial Assistance Programs

- American Cancer Society: *http://cancer.org*
- Anthony Nolan Trust: *http://anthonynolan.org*
- CancerCare Co-Payment Assistance Foundation: *http://cancercarecopay.org*
- Cancer Financial Assistance Coalition*:* *http://cancerfac.org*
- Chronic Disease Fund: *http://cdfund.org*
- HealthWell Foundation: *http://healthwellfoundation.org*
- Lance Armstrong Foundation: *http://livestrong.org*

Financial Assistance Programs

- Leukemia and Lymphoma Society: *http://lls.org/copay*
- MacMillan Cancer Support:
  http://macmillan.org.uk/Home.aspx
- Patient Advocate Foundation Program/Co-Pay Relief Program: *http://copay.org*
- Patient Handbook: Insurance and Reimbursement Resources for MDS Patients: A Guide to Assistance Programs in the U.S.: *http://mds-foundation.org/for-patients-visitors*

The MDS Foundation International Nurse Leadership Board

http://mds-foundation.org/nursing-leadership-board-nlb/

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  San Francisco, California, United States
- **Sara M. Tinsley, ARNP, AOCN**
  Tampa, Florida, United States

MDS Patient Outreach and Advocacy Program

Patients or caregivers may contact the patient liaison directly by calling

(toll-free) 800-637-0839

or via

e-mail to

ahassan@mds-foundation.org