

٠	DISCLOSURES Advances in Chronic Myeloid Leukemia	PAGE 2	
	Alison Wakoff Loren, MD, MSCE, has no affiliations to disclose.		
	BEATING CANCER IS IN OUR BLOOD.	LLUKLMIA S LYMPHOMA SOCIETY	
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## Learning Objectives

- Treatment advances for chronic myeloid leukemia (CML)
- The concept of treatment-free remission
- Supportive care and side- effects management
- $\bullet$  How communicating with your healthcare team can improve your quality-of-life

#### A Few Basics: What is CML?

- Cancer of bone marrow stem cells
- Three phases: chronic, accelerated, blast
- Most patients are diagnosed in chronic phase
   Often without symptoms
- Untreated, all patients progress to accelerated / blast phase within 3-5 years

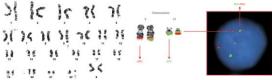




Atlas of Haematological Cytology (online). 2016 [cit. 2018-9-16]. Available from WWW: http://www.leukem cell.org/atlas.

#### A Few Basics: What is CML?

 Characterized by a translocation between chromosomes 9 and 22, denoted as t(9;22) which results in an abnormal juxtaposition of two genes, bcr and abl

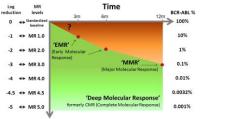


Images courtesy of Spandidos Publications and The Lancet

### How Do We Know If Treatment is Working?

- Hematologic response (CBC [complete blood count])
  - Normal blood counts
- Cytogenetic response (bone marrow cytogenetics ["karyotype"])
  - Major (MCyR): < 35% of cells have the Philadelphia chromosome
  - Complete (CCyR): 0% of cells have the Philadelphia chromosome
- Molecular response (Quantitative PCR, International Scale [qPCR, IS])
  - MR3 (0.1%) aka "major molecular response" or MMR
  - MR4.5 (0.01 0.001%)
  - Complete or deep molecular response (CMR or DMR):  $\underline{\textit{no}}$  detectable bcr/abl

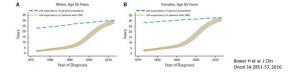
#### How Do We Know if Treatment is Working?



Baccarani M, Soverini S. Blood 124:469-47, 2014.

#### Impact of TKIs

- Until imatinib approved (FDA 2001), most patients treated with supportive care, hydroxyurea, interferon, and allogeneic hematopoietic cell transplantation ("bone marrow transplant")
- Tyrosine kinase inhibitors ("TKIs") have revolutionized this disease



#### Treatment Advances for CML: TKIs

- Bosutinib
  - Overcomes most imatinib-resistant mutations
  - Approved for 1st line therapy in late 2017
  - BELA trial (2012), 502 patients: bosutinib 500 mg vs imatinib 400 mg,
  - evaluated at 12 months

     CCyR (primary endpoint) equivalent: 70% (B) vs 68% (I)

     MMR better for bosutinis: 41% (B) vs 27% (I)

     BEFORE trial (2017), 536 patients: bosutinib 400 mg vs imatinib 400 mg, evaluated at 12 months
    - MMR (primary endpoint) better for bosutinib: 47% (B) vs 37% (I)
       CCyR also better for bosutinib: 77% (B) vs 66% (I)

    - Significantly more diarrhea (8% vs 1%) with bosutinib

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Treatment Advances for CML: TKIs	
Ponatinib     The only commercially available TKI effective for patients with T315I	
mutations	
Significant cardiovascular risks     Radotinib*	
Structurally similar to imatinib and nilotinib	
<ul> <li>Approved in Korea for 1<sup>st</sup> line and later therapy</li> <li>2<sup>nd</sup> line: 77 patients (2014)</li> </ul>	
<ul> <li>MCyR 65%, CCyR 47%, MMR 14% at 12 months</li> <li>1st line radotinib 300 mg vs imatinib 400 mg: 241 patients</li> </ul>	
MMR 52% (R) vs 32% (I), CCyR 91% (R) vs 77% (I)     *Radotinib is not FDA-approved	
Kim SH et al. Haematologica 99(7): 1191-1196, 2014. Kwak IY et al. Clin Cancer Res Dec 2017, Epub ahead of print.	
Number Et al. Call Canada To See 2017, 2000 united of partic	
Treatment Advances for CML	
Treatment Advances for Civil	
• Asciminib (ABL001)*	
Potent and selective inhibitor of BCR-ABL	
Different site from other TKIs, allowing possible co-treatment	
Promising early data     Resistance may occur	
ABL mutations Proteins that pump drug out of the cells	
4 open clinical trials, alone or in combination with existing TKIs	
*Asciminib is not FDA approved	
Schoepfer J et al. J Med Chem, Sep 2018. Epub ahead of print.	
Treatment Advances for CML	
Tarantina laulania stara sella (ISCs)	
<ul> <li>Targeting leukemic stem cells (LSCs)</li> <li>JAK2 and STAT5 pathways: ruxolitinib</li> </ul>	
PPARy inhibitors: pioglitazone     Autophagy inhibitors: hydoxychloroquine	
<ul> <li>Immune activation: IFNα, IL-1 receptor antagonists, others</li> </ul>	
Bhatia R. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):115-120	

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Treatment-Free Remission	
<ul> <li>Dec 2017: FDA approved a discontinuation indication for nilotinib</li> <li>History:         <ul> <li>2007: 12 patients on imatinib with undetectable bcr/abl &gt; 2 years</li> </ul> </li> </ul>	
<ul> <li>6 remained in remission</li> <li>2010: STIM trial: 100 patients (69 with 1-year follow up)</li> </ul>	
<ul> <li>39 patients (43%) remained in remission</li> <li>Longer duration of imatinib predicted freedom from relapse</li> <li>2013: TWISTER, and others, confirmed that for about 40-50% of patients,</li> </ul>	
long-term treatment-free remission is possible  Rousselot P et al. Blood 109:58-60, 2007.	
Mahon FX et al. Lancet Oncol 11:1029-35, 2010. Ross DM et al. Blood 122(4)-515-22, 2013.	
Treatment-Free Remission: Who is eligible?	
Ability to monitor bcr/abl transcript on IS testing     b2a2 or b3a2 transcript	-
<ul> <li>No prior resistance to TKIs</li> <li>Some recent studies suggest some 2<sup>nd</sup> line patients may be successfully discontinued</li> </ul>	
<ul> <li>No prior accelerated or blast phase</li> <li>Minimum of 3 – 5 years on TKI, but longer (8 years) is preferred</li> </ul>	
<ul> <li>Minimum of 12 months undetectable bcr/abl on IS testing, but longer (2 years) is preferred</li> </ul>	
Willingness to comply with intensive follow up qPCR testing	
Criteria Green Yellow Red	

Institutional criteria met (per table 1)	Yes		No		
Sokal score at diagnosis	Non-high	High			
BCR-ABL transcript at diagnosis	Typical - B2A2 or B3A2 (e13a2 or e14a2)	Atypical, but can be accurately quantified	Not quantifiable		
CML past history	CP only	Resistance or KD mutation	Prior AP or BC		
Response to first line TKI therapy	Optimal	Warning	Failure < 3 years		
Duration of all TKI therapy	> 8 years	3-8 years			
Depth of deep molecular response	MR4.5	MR4.0	Not in MR4.0		
Duration of deep molecular response monitored in a standardized laboratory	> 2 years	1–2 years	< 1 year		
All green lights: strong recommendation to consider TKI withdrawal					
Any yellow lights: only consider TKI withdrawal in high priority circumstances (e.g. significant toxicity or planned pregnancy)					
Any red lights: TKI withdrawai not recommended except in clinical trial					

Hughes TP and Ross DM. Blood 128(1): 17-23, 2016.

Treatment Free Remission: How to monitor?	
Most patients relapse within 6-9 months     qPCR for bcr/abl in IS lab with prompt results:	
Every 4 weeks during year 1     Every 6 weeks during year 2     Every 12 weeks during year 3 and thereafter	
<ul> <li>Upon loss of response, re-initiate effective TKI therapy immediately and monitor bcr/abl every 2 weeks until MMR is regained / sustained</li> </ul>	
Nilotinib (and imatinib) withdrawal syndromes have been described     Not all patients wish to discontinue therapy	
Supportive Care: Managing Side Effects	
Unfortunately, most patients with CML will not be eligible for a trial of treatment-free remission	
<ul><li>How to live well on these medications?</li><li>Side effects are common (60-80% of patients)</li></ul>	
<ul> <li>3 areas of concern</li> <li>Physical (side effects and health risks)</li> <li>Psychological</li> </ul>	
Financial ("TKI handcuffs")	
Supportive Care: Side Effects	
Imatinib     Once daily, with or without food     Muscle cramps, swelling, rash,     Rash, constipation, nausea	
Dasatinib     Ossed drike with or without food     Second drike with or without food     Second drike with or without food	
Once daily, without our of the standard effusion in up to 30% of patients     Low blood counts, especially platelets     Nausea	
Notice fail, 1 hour before / 2 hours after eating  Notice fail, 1 hour before / 2 hours after eating	
ALL: FATIGUE!!!!	

	Imatinib		
	Once daily		Once daily
Cramps/myalgia Fluid retention	+++		+
GI: Nausea,	++	GI: Nausea,	+
diarrhea		diarrhea	
Pleural effusion	-		++
Prolonged QTc	+		+
Pancreatitis Rash	+		+
Neutropenia	++		+
Thrombocytopenia	+		++
portive Ca	re: M	ortive Car	ledical
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II TKIs except imatinib increase risk of cardiac events:			
rolonged "QTc" inte			
Congestive heart fail	lure		
atinib Ieural effusions			
ulmonary hyperten	nsion		
			11: - 1
portive Ca	re: M	ortive Car	iedical
:inib 1etabolic risks: elev	ated bloo		od glucose
atinib			ou Biucose,
igh blood pressure		h blood pressure	
Arterial clots (heart a patients	attack, str	erial clots (heart a ients	roke, clots i

- Patients should consider routine cardiology care and/or referral to an "onco-cardiologist"

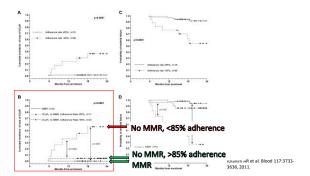
• Generic price ~\$96,000/year

Experts in CML, Blood 121:4439-42, 2013. Cole AL and Dusetzina SB. Health Aff 37(5):738-742, 2018.

# Communication with your team

- Medication does not work if you don't take it!
- Non-adherence is common (30-70% of patients)
- Adherence is a major predictor of response:
  - Patients who took > 90% of their doses had a 94.5% probability of achieving MMR, compared to patients who took < 90% of doses, who had a 28% incidence of MMR)
  - Treatment adherence is the only independent predictor of achieving CMR.
  - Patients with suboptimal responses missed 24% of doses, as opposed to those with optimal responses, who missed 7% of doses.

Marin D et al. J Clin Oncol 28(14):2381-8, 2010. Noens L et al. Blood 113(22):5401-11, 2009.



#### Communication with your team

- Insurance and marital status impact the survival of patients under age  $65\ \mbox{with CML}$ 
  - Medicaid patients: 83% increased risk of death
  - Uninsured patients: 93% increased risk of death
  - Single (vs married): 65% increased risk of death
- Talking with your doctor about your concerns physical, psychological, financial can help us take better care of you!

Perry AM et al. Cancer 123:2561-9, 2017.

٠	Q&A SESSION Advances in Chronic Myeloid Leukemia	PAGE 28	
	Ask a question by phone:     Press star (*) then the number 1 on your keypad.		
	<ul> <li>Ask a question by web:</li> <li>Click "Ask a question"</li> <li>Type your question</li> </ul>		
	<ul> <li>Click "Submit"</li> <li>Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.</li> </ul>		
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٠	LLS EDUCATION & SUPPORT RESOURCES	PAGE <b>29</b>	
	Information Specialists Master's level oncody professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.  EMAL: Inforenter BLL Sorg TOLL-FREE PHONE: 1-800-955-4572  Free Education Booklets:  - www.LLS org/booklets  Free Telephone/Web Programs:  - www.LLS org/brograms  Live, weekly Online Chats:  - www.LLS.org/chat		
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٠	LLS EDUCATION & SUPPORT RESOURCES	PAGE 30	
	LLS Podcast, The Bloodline with LLS Lates in the specific and patient guide leterors is understanding patients year. Rebedding and patient specific leterors is understanding patients year. Rebedding and patients patients year. Rebedding year.      Education Videos Fractions videos about survivorship, treatment, disease upstates and other topics: year. LL Society and patients patients.      Patil Robinson Kaufmann First Connection Program	ng	
	Peer to gee program that matches restly diagnosed patents a their families wind LLS profit acconnection  • Free Nutrition Consults		
	Telephore and email consultations with a Registered Dietistan with A Registered Dietistan with A Registered Dietistan with A Coaks  What to Ask  Other Support Resources  LIS Community, discussion boards, blogs, support groups, financial sections and from warm Lis digitations.	ak.	