CHRONIC MYELOID LEUKEMIA UPDATE

Diana Brewer, MS, PA-C
Assistant Professor of Medicine
She/her/hers
Center for Hematologic Malignancies at *OHSU*
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DISCLOSURES

None

AGENDA

Review diagnostics, risk stratification and other considerations for new diagnosis CML

Review available therapies

Frontline therapy…how to choose

Common treatment related side effects and management

Monitoring disease status and treatment response

Suboptimal response…what to do

Intolerance and/or resistance

Dose modification…the art of medicine

Treatment free remission and TKI withdrawal syndrome

INTRO

CML is a chronic disease, and for many requires lifelong therapy and monitoring…

Incidence is 1-1.2 cases per 100,000 adults

Accounts for 15% of newly diagnosed cases of leukemia

Characterized by the balanced translocation of t(9;22) ->BCR/ABL1 oncogene which translates into a BCR/ABL1 oncoprotein

Therapeutic landscape of CML has profoundly changed since the success of targeted therapy

As a consequence, resulting in the growing prevalence of CML worldwide

DIAGNOSTIC WORK UP

-BM aspirate required for morphology [blasts & basophils] to identify phase of dz & cytogenetics

-BM biopsy to identify nests of blasts or degree of fibrosis

-QPCR (qualitative) to identify type of BCR/ABL1 transcripts (2-4% have atypical)

-PCR (quantitative) not required at dx but essential for monitoring dz status & tx response

-FISH, especially if Ph- by cytogenetics

-Physical exam [spleen and liver]

-biochemical profile: CMP [LDH, Phos, uric acid), HgbA1C, pancreatic enzymes, lipid panel, Hep B

-Imaging: EKGs, +/- ECHO

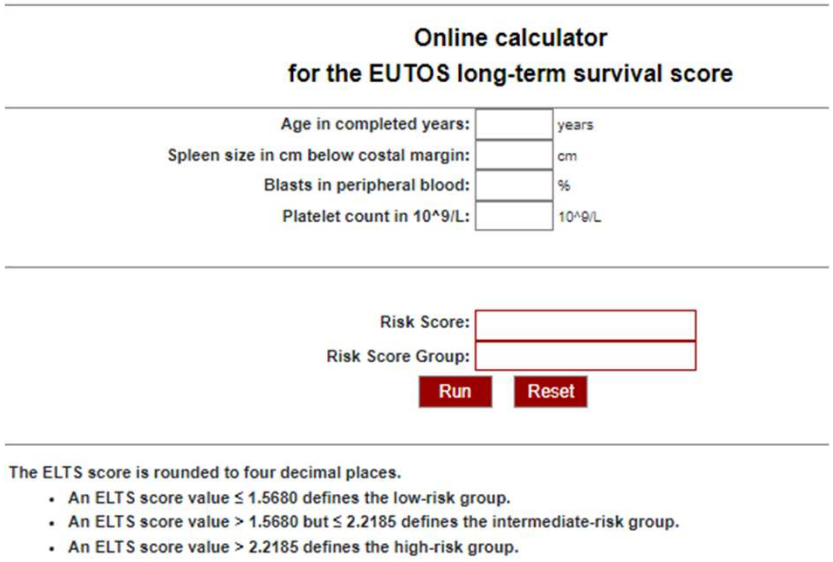
RISK STRATIFICATION

EURO Long Term Leukemia Score [ETLS] ELTS-Score (leukemia-net.org)

ELTS score =

$$0.0025 \times (\text{age in years}/10)^3 + 0.0615 \times \text{spleen size LCM} + 0.1052 \times \text{blasts in PB} + 0.4104 \times (\text{plt count}/1000)^{-0.5}$$

Developed to predict the probability of dying from CML (leukemia-related death, LRD)



Online calculator
for the EUTOS long-term survival score

Age in completed years:		years
Spleen size in cm below costal margin:		cm
Blasts in peripheral blood:		%
Platelet count in 10^9/L:		10^9/L

Risk Score:
Risk Score Group:
Run Reset

The ELTS score is rounded to four decimal places.

- An ELTS score value ≤ 1.5680 defines the low-risk group.
- An ELTS score value > 1.5680 but ≤ 2.2185 defines the intermediate-risk group.
- An ELTS score value > 2.2185 defines the high-risk group.

AVAILABLE THERAPIES

1GTKI = imatinib

2GTKI =dasatinib, nilotinib, bosutinib

3GTKI =ponatinib, asciminib

***Alternatives*:**

PEG-INF

Omacetaxine

HSCT

Clinical Trial

FIRST LINE TREATMENT FOR CP-CML

Imatinib	**400 mg**	**QD**
Dasatinib	100 mg	QD
Nilotinib	300 mg	BID
Bosutinib	400 mg	QD

HOW TO CHOOSE…

Clinical trials w/2GTKIs reported significantly deeper & faster responses however had no impact on survival prolongation c/w 1GTKI

Choice of treatment depends on individual tx goals, risk assessment & comorbidities

Patient risk status at dx [ETLS] including additional cytogenetic aberrations [ACAs] =warning as these herald early dz acceleration and molecular clonal evolution [ASXL1, DNMT3A, RUNX1 and other genes] have been observed ~25% of CP-CML at dx

TKI ADVERSE EVENTS & RISKS

Imatinib	Myelosuppression, Fluid retention, CHF, Hepatoxicity, GI toxicities, Hypothyroidism, Dermatologic toxicities, Toxicities from Long-Term Use*
dasatinib	Myelosuppression, Bleeding-related events, Fluid retention, CV toxicities, PAH, QTc prolongation, Severe dermatologic reactions
nilotininb	Myelosuppression, *QTc prolongation, AOEs, Pancreatitis, Hepatoxicity, Electrolyte abnormalities
bosutinib	Myelosuppression, GI toxicities, Hepatoxicity, CV toxicities, Fluid Retention, Renal Toxicities
ponatinib	Myelosuppression, AOEs, VTEs, Heart failure, Hepatoxicity, Pancreatitis, Myelosuppression, Arrhythmias, HTN
asciminib	Myelosuppression, Pancreatitis, HTN, CV toxicities

COMMON TREATMENT RELATED SIDE EFFECTS

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib
myelosuppression	✓ *	✓ *	✓ *	✓ *	✓ *	✓ *
edema	✓ *	✓ *		✓ *		
GI-N/V, D, C	✓ *	✓ *	✓ *	✓ *	✓ *	✓ *
Headache	✓ *	✓ *	✓ *	✓ *	✓ *	✓ *
Muscle cramping	✓ *					
Myalgia/ arthralgia	✓ *	✓ *	✓ *	✓ *	✓ *	✓ *
fatigue	✓ *	✓ *	✓ *	✓ *	✓ *	✓ *
rash	✓ *	✓ *	✓ *	✓ *	✓ *	✓ *
Alopecia			✓ *			
Pyrexia	✓ *		✓ *	✓ *	✓ *	
URI symptoms			✓ *	✓ *		✓ *

MANAGEMENT OF SIDE EFFECTS

Fatigue	r/o other etiologies & correct, rest, exercise, lifestyle modification
Myalgias/Arthralgias/ Bone pain	NSAIDs (if able), rarely short term opioids, collaboration w/supportive care team
Rash/Pruritis	Topicals steroids and/or antihistamines, treatment interruption, oral steroids
Myelosuppression	May require dose interruption and/or reduction, growth factors
Muscle Cramping	Electrolyte repletion; K+, Phos, Mg+ (Ca+ citrate), hydration, vitamin D level
Edema/Fluid Retention	Adapt to changes in metabolism, low Na+ diet, diuretics
Constipation	Diet modification, hydration, stools softeners, psyllium seed or other fiber, laxatives
Diarrhea	Diet modification, antidiarrheals (loperamide), psyllium seed, acidophilus
Dyspepsia/Heartburn	Diet modification/avoidance triggers, antacids, H2 blockers or PPIs

MONITORING

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤0.01% (MR^4).

A change of treatment may be considered if MMR is not reached by 36–48 months.

NA not applicable, *ACA* additional chromosome abnormalities in Ph+ cells, *ELTS* EUTOS long term survival score.

[a]Loss of MMR (BCR-ABL1 > 0.1%) indicates failure after TFR

HOCHHAUS, A., BACCARANI, M., SILVER, R.T. *ET AL.* EUROPEAN LEUKEMIANET 2020 RECOMMENDATIONS FOR TREATING CHRONIC MYELOID LEUKEMIA. *LEUKEMIA* **34**, 966–984 (2020). HTTPS://DOI.ORG/10.1038/S41375-020-0776-2

LEVELS OF RESPONSE

CCyR = < or =1%

MMR (MR3) = < or =0.1%

MR4 = < or =0.01%

MR4.5 = < or =0.0032%

MR5 = < or =0.001%

“Complete molecular response” should be referred to as “molecularly undetectable leukemia”

DEEP MOLECULAR RESPONSE

Study	5 years (%)	10 years (%)
CML-IV		
Imatinib	MR4 68	81
	MR4.5 53	72
ENESTnd		
Nilotinib	MR4 66	73
	MR4.5 54	64
Imatinib	MR4 42	56
	MR4.5 35	45
Dasision		
Dasatinib	MR4.5 42	N/A
Imatinib	MR4.5 33	N/A
BFORE		
Bosutinib	MR4 58	N/A
	MR4.5 46	N/A
Imatinib	MR4 48	N/A
	MR4.5 35	N/A

CUMULATIVE INCIDENCE OF DMR AT 5 & 10 YEARS

SUBOPTIMAL RESPONSE…WHAT TO DO?

Optimal response: BCR/ABL <0.1% IS =MMR

PCR > than 10% at 3 months indicates tx failure

Consider reasons why…

Close/frequent monitoring

Dose adjustments

Abl sequencing

KD Mutations:

T315i	Ponatinib or Asciminib
F317L/V/I/C, T315A	Nilotinib, Bosutinib, Ponatinib or Asciminib
V299L	Nilotinib, Ponatinib
Y253H, E255V/K, F359V/L/C	Dasatinib, Bosutinib, Ponatinib

INTOLERANCE AND/OR RESISTANCE

Change of therapy is recommended in the case of intolerance* or when molecular milestones are not met

Abl sequencing, BM & cytogenetics

For CML post failure on frontline tx; options include 2GTKIs & 3GTKIs

Considerations include; risk/benefit (hx of prior AEs & risk of AEs w/TKIs), dz status, age, comorbidities, cytogenetics & mutational status

For T315i, options include ponatinib, asciminib or HSCT [who have failed at least 2 TKIs, and for those with advanced dz] *for those who fail their 1st 2GTKI d/t true resistance need more potent therapy

DOSE MODIFICATION…FINE TUNING

Intolerance/Suboptimal Response

*address side effects (distinction b/w adverse events)/adherence

*decrease or increase dosage

*close monitoring

*switch therapy

*HSCT/Clinical trial

Optimal Disease Control

*Goal: maximize treatment response while minimizing treatment related side effects & long term risks

*dose reduction

*possible precursor to TFR

*close monitoring

TREATMENT FREE REMISSION

What to consider…

Reasoning for treatment discontinuation

Shared decision making & education: ~50% probability of success

Eligibility criteria; various factors *duration of deep molecular response [DMR]

Close monitoring; typical timeline for progression within the 1st six-twelve months

TKI withdrawal Syndrome; hyperinflammatory syndrome of musculoskeletal and/or joint pain affecting ~20-30% of patients

Threshold to resume therapy, loss of MMR with PCR >0.1% IS

CRITERIA FOR TFR

Eligibility

Must:

- CML in 1st CP only
- High quality PCR monitoring
- Adherence to more frequent monitoring

Maybe:

- 1L or 2L if intolerance as reason for switching
- Typical transcripts [e13a2 or e14a2)
- TKI > 5 years (or >4 years for 2GTKI)
- DMR (MR4 or better) >2 years
- No prior tx failure

Monitoring

Quantitative PCRs:

First 6 months: q monthly

Months 6-12: q 2 months

1 year milestone and beyond: q 3 mos

Indefinite monitoring: *those w/good adherence and undetectable for many years can consider monitoring q 3-6 months.

ON THE HORIZON

Considerations for clinical trials…

?Role for asciminib in 1L therapy

ATP competitive TKIs/potential new 3GTKI:

- HQP1351 (olverembatinib) w/focus on 3L therapy and/or patients with T315i mutation
- PF-114 –for wild-type and mutated BCR/ABL including T315i
- K0706 (vodobatinib) in vitro data notable against most mutations (not T315i)

Combination therapies w/other anticancer agents [INF, chemotherapy, immunomodulators]

2nd attempt TFR

QUESTIONS?

THANK YOU

brewerd@ohsu.edu