Chronic Myeloid Leukemia

Updates on recent clinical papers

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Overview

- CML background
- 2009 European LeukemiaNet Guidelines
- Updated data from ENEST and DASISION trials

Chronic Myeloid Leukemia

- Clonal myeloproliferative disorder of pluripotent stem cells
  - Increase proliferation, decrease apoptosis
  - Cytogenetic hallmark: Ph chromosome
  - Molecular hallmark: Bcr-Abl; Bcr-Abl initiation causative event in CML
- Epidemiology
  - Median age – 45 to 55 years old
  - 15 – 20% of all leukemias in adults

Faderl S, et.al. N Engl J Med. 1999

CML – Disease Course

Chronic Phase	Progressive Disease	
	Accelerated phase	Blast Crisis
Median 5 - 6 years stabilization	Median duration 6 – 9 months	Median survival 3 – 6 months

Faderl S, et.al. N Engl J Med. 1999

Historical versus Current Perspective

Parameter	Historical (until 2000)	Current (since 2000)
Course	Fatal	Indolent
Prognosis	Poor	Excellent
Median survival, yrs	3 - 6	≥ 25
Frontline treatment	Allogeneic SCT, interferon alfa, hydroxyurea	Imatinib
Second-line treatments	Not established	Allogeneic SCT, novel TKIs

Faderl S, et.al. N Engl J Med. 1999
Druker BJ et.al. N Engl J Med. 2001

Imatinib: IRIS 8-year Update

- IRIS established imatinib as standard initial therapy for chronic phase CML
- 8-year update of IRIS
  - 304 of 553 (55%) remained on study, 98.4% of these patients were on imatinib, 1.6% remained on IFN/Ara-C
  - No new safety issue identified
  - Estimated EFS at 8 years = 81%
  - Estimated rate without AP/BC at 8 years = 92%
  - Overall survival (ITT) = 85%, Survival: Death associated with CML = 93%

Deininger M et.al. Blood 2009

European LeukemiaNet (ELN) CML Guidelines 2009

An update from the 2006 ELN CML Guidelines

Baccarani M, et.al. J Clin Oncol.2009

ELN 2009: Definition of Response and Monitoring

	Definition	Monitoring
Hematological Response (Complete) CHR	Platelet count < 450 x 10^9/L WBC count < 10 x 10^9/L Differential wo immature granulocytes & w < 5% basophils Non-palpable spleen	Check at diagnosis, then q2w until complete response achieved & confirmed, then q3m unless otherwise specified
Cytogenetic Response	Complete (CCyR): Ph+ none Partial (PCyR): Ph+ 1 – 35% Minor: Ph+ 36 – 65% Minimal: Ph+ 66 – 95% None: Ph+ > 95%	Check at diagnosis, at 3rd mo, at 6mo, then q6m until complete response achieved and confirmed
Molecular Response (BCR-ABL: control gene ratio according to international scale)	'Complete': transcript non-detectable Major (MMR): ≤ 0.1%	RT-Q-PCR: Check q3m, then at least q6m Mutational analysis only incase of failure, suboptimal response or increased level of transcript

Baccarani M, et.al. J Clin Oncol.2009

ELN 2009: Classification of Responses

Months	Optimal response	Suboptimal response	Failure	Warning
3	CHR & at least minor CyR	No CyR	< CHR	NA
6	At least PCyR	< PCyR	No CyR	NA
12	CCyR	PCyR	< PCyR	< MMR
18	MMR	< MMR	< CCyR	NA
Anytime	Stable or improving MMR	Loss of MMR Low IM IC50 mutations	Loss of CHR Loss of CCyR High IM IC50 mutations Ph+ CCA	Any rise in transcript levels Ph-CCA

Baccarani M, et.al. J Clin Oncol.2009

ELN 2009: Classification of Responses

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3	CHR & **at least minor CyR**	**No CyR**	**< CHR**	NA
6	At least PCyR	< PCyR	No CyR	NA
12	CCyR	PCyR	< PCyR	< MMR
18	MMR	< MMR	< CCyR	NA
Anytime	**Stable or improving MMR**	Loss of MMR Low IM IC50 mutations	Loss of CHR Loss of CCyR High IM IC50 mutations **Ph+ CCA**	Any rise in transcript levels Ph-CCA ****del9q+****

Baccarani M, et.al. J Clin Oncol.2009

Summary of ELN Treatment Recommendations 2009

Response	Second-line	Third line
Intolerance	Nilotinib, Dasatinib	
Suboptimal response	Imatinib 600 or 800 mg QD Nilotinib, Dasatinib Check compliance	Continue nilotinib, dasatinib AlloHSCT if warning (prior hematologic resistance, mutations) EBMT risk<2
Failure	Nilotinib, Dasatinib or alloHSCT in pts in progression or with T315I mutation Check compliance	AlloHSCT
Warnings	Continue Imatinib 400 mg/d Observe Check compliance	

Baccarani M, et.al. J Clin Oncol.2009

Summary of ELN Treatment Recommendations 2009

- **Imatinib dose escalation is an option in suboptimal response but is no longer recommended after failure of response**
- **2nd line treatment: high dose imatinib, nilotinib or dasatinib in all patients**
- **Provisional definition of response to 2nd generation TKIs introduced**

Baccarani M, et.al. J Clin Oncol.2009

ELN 2009: Allogeneic HSCT in CML

At Diagnosis (Front-line)	In pts presenting in AP or BP Pretreatment with a TKI recommended
Imatinib failure	In pts who have already progressed to AP or BP Pretreatment with 2nd generation TKI is recommended In patients with T315I mutation
Imatinib failure OR Suboptimal response to 2nd generation TKIs (3rd line)	In all eligible pts, depending on response and on EBMT risk score

Baccarani M, et.al. J Clin Oncol.2009

Nilotinib Demonstrates Superior Efficacy compared with Imatinib in patients with Newly diagnosed CML-CP: Results From the International Randomized Phase III ENESTnd Trial

Giuseppe Saglio, Dong-Wook Kim, Surapol Issaragrisil, Philipp le Coutre, Josy Reiffers, Clarisse Lobo, Ricardo Pasquini, Richard Clark, Timothy Hughes, Andreas Hochhaus, Neil Gallagher, Albert Hoenekopp, Mei Dong, Ariful Haque, Hagop Kantarjian and Richard Larson

Study design and Endpoints

N = 846
(217 centers, 35 countries)
Randomized,
follow-up 5 years

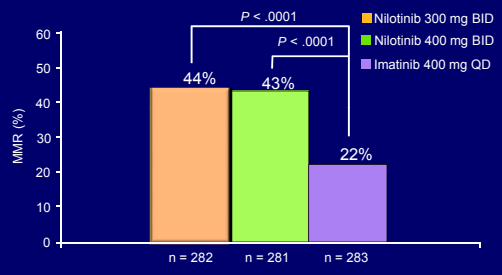
- Nilotinib 300 mg BID (n = 282)
- Nilotinib 400 mg BID (n = 281)
- Imatinib 400 mg QD (n = 283)

Stratified by Sokal risk score

- o Primary endpoint: MMR at 12 months
- o Secondary endpoint: CCyR by 12 months
- o Other endpoints: Time to and duration of MMR and CCyR, EFS, PFS, time to AP/blast, OS

Larson RA, et al. ASCO 2010. Abstract 6501. Saglio G, et al. N Engl J Med. 2010

ENESTnd: Primary Endpoint (MMR rate at 12 Mos)



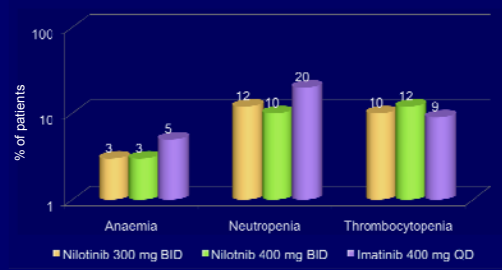
Larson RA, et al. ASCO 2010. Abstract 6501. Saglio G, et al. N Engl J Med. 2010

ENESTnd: CCyR Rates by 12 Mos and Overall

- **Among patients who had cytogenetic assessment at 18 mos (n = 442/846), the rates of CCyR were**
  - **Nilotinib 300 mg BID 99%**
  - **Nilotinib 400 mg BID 99%**
  - **Imatinib 89%**
- **Overall progression to AP/BC**
  - **Nilotinib 300 mg BID 0.7%**
  - **Nilotinib 400 mg BID 0.4%**
  - **Imatinib 4.2%**

Larson RA, et al. ASCO 2010. Abstract 6501. Saglio G, et al. N Engl J Med. 2010

ENESTnd: Grade 3/4 Myelosuppression



Larson RA, et al. ASCO 2010. Abstract 6501. Saglio G, et al. N Engl J Med. 2010

ENESTnd: Key Summary

- Nilotinib is superior to imatinib with significantly higher rates of MMR and CCyR, at both 300 mg BID and 400 mg BID
- Significantly fewer patients on nilotinib progressed compared to imatinib
- Nilotinib is superior to imatinib across all Sokal risk groups, generally more tolerable
- Incidence of AEs leading to discontinuation was lowest in the nilotinib 300 mg BID arm (Grade3/4 46% vs 52%)
- Based on these results nilotinib may become the new standard of care in newly diagnosed CML **(FDA granted accelerated approval of nilotinib at 300 mg BID for the treatment of newly diagnosed Ph+ CP CML on 17th June 2010)**

Larson RA, et al. ASCO 2010. Abstract 6501. Saglio G, et al. N Engl J Med. 2010

Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase CML: A Randomized Phase III Trial The DASISION Study

Hagop Kantarjian, Neil P.Shah, Andreas Hochhaus, Jorge Cortes, Sandip Shah, Manuel Ayala, Beatriz Moiraghi, Zhixiang Shen, Jiri Mayer, Ricardo Pasquini, Charles Chuah, Eric Bleickardt, M.Brigid Bradley, Chao Zhu, Ted Szatrowski, David Shapiro, Michele Baccarani

Study design and Endpoints

N = 519
(108 centers, 26 countries)
Randomized,
follow-up 5 years

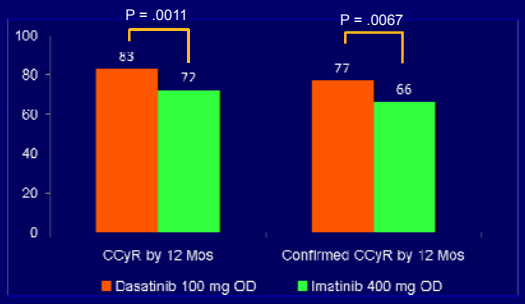
- Dasatinib 100 mg QD (n = 259)
- Imatinib 400 mg QD (n = 260)

Stratified by Hasford risk score

- o Primary endpoint: CCyR at 12 months
- o Secondary endpoint: CCyR no Ph+ metaphases in BM, MMR
- o Other endpoints: Time to MMR and CCyR, PFS, OS

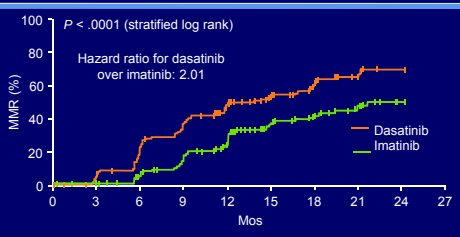
Kantarjian et.al. N EnglJ Med 2010

DASISION: Primary Endpoint (CCyR rate by 12 mo)



Kantarjian et.al. N EnglJ Med 2010

DASISION: Secondary Endpoints



- Patients more likely to achieve MMR at any time with Dasatinib (median time to MMR 6.3mos with dasatinib vs 9.2 mos with imatinib)
- MMR at 12 mos: dasatinib (46%) versus imatinib (28%)
- Progression to AP/BP: Dasatinib 1.9% vs Imatinib 3.5%

Kantarjian et.al. N EnglJ Med 2010

DASISION: Key Summary

- Dasatinib associated with superior efficacy compared to imatinib as 1st line treatment of CP-CML
  - Higher and faster rates of CCyR, confirmed CCyR and MMR
- Dasatinib generally well tolerated
  - Low rates of grade 3/4 hematologic toxicity
  - Pleural effusion (10%) more frequent in dasatinib (92% with PE achieved 12mo CcyR, 1.2% stopped treatment)
- Results support use of dasatinib as 1st line therapy patients with newly diagnosed CP-CML

Kantarjian et.al. N Engl J Med 2010

Special Considerations

- Adverse events specific to TKIs:
  - Imatinib [Edema (periorbital) and muscle cramps]
  - Dasatinib [Pleural effusion (5% w once a day dosing), thrombocytopenia]
  - Nilotinib (Liver enzymes elevations, QTc prolongation, elevation of lipase)
- Mutational analysis in guiding choice of TKIs
  - Dasatinib (Y253F/H, E255K/V, F359C/I)
  - Nilotinib (V299L, F317L/V)
  - Clinical trial e.g. AP24534, HHT, LBH589, AlloHSCT (T315I)
- Increasing resistance to TKIs
- Potential drug interactions (major CYP3A4 substrates), food-drug interactions (nilotinib to be taken on empty stomach)

Sawyer LC, N Engl J Med 2010
Burgess et al, PNAS, 2005
Bradeen et al, Blood 2006