

Tomorrow's Therapies Today:

Clinical Trials for **Leukemia, Lymphoma & Myeloma**

**New Developments in
Chronic Leukemia Treatments**

David L. Porter, MD
*Director, Allogeneic Stem Cell
Transplantation and Immunotherapy
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania*

**New Developments in
Chronic Leukemia Treatment**

- Response definitions and monitoring
- Imatinib (Gleevec®) for CML
- Dasatinib (Sprycel®)
- Nilotinib (Tasigna®)
- Newer agents and trials
- Transplant for CML in the modern era
- Trends in CLL management
- Conclusions

CML Monitoring: Definitions

- Complete hematologic response (CHR)
 - Normalized complete blood count (CBC) and peripheral blood
- Cytogenetic response
 - Complete
 - Major: 1%–35% Ph+ cells
 - Partial: >35% Ph+ cells
- Major molecular response (MMR)
 - >3 log reduction in BCR-ABL transcripts from standard signal

Tomorrow's Therapies Today:

Clinical Trials for **Leukemia, Lymphoma & Myeloma**

Response Monitoring: Cytogenetics

- "Gold Standard" for treatment monitoring
- Correlates with long term progression-free survival and overall survival
- Requires marrow aspirates
- Can identify new acquired abnormalities
- Test at diagnosis and every 6 months until a complete cytogenetic response, then every 1–2 years?
- Once a CCyR is achieved, peripheral blood FISH or quantitative PCR testing may be sufficient.
 - Controversial discussion for another time

Imatinib in Newly Diagnosed Chronic Phase CML

International Randomized Interferon vs Imatinib Mesylate (IRIS) Study: Summary

- A phase III randomized trial of imatinib versus interferon
- 1106 patients participated.
- This study revolutionized therapy for CML.
 - Previously, allogeneic stem cell transplant was the only known cure for CML
 - Recommended for most appropriate patients
 - Interferon was standard medical therapy but associated with many side effects
- The IRIS trial is one of the best examples ever of the importance of clinical trials.

Tomorrow's Therapies Today:

Clinical Trials for Leukemia, Lymphoma & Myeloma

International Randomized Interferon vs Imatinib Mesylate (IRIS) Study: Summary (cont)

- Patients treated with imatinib had superior responses, lack of progression and survival compared with those treated with interferon-alpha (IFN- α) + Ara-C
 - Major cytogenetic response 92% at 5 yr
 - Complete cytogenetic response 87% at 5 yr
 - 89% overall survival at 5 years
- Imatinib demonstrated a trend towards improved survival over IFN- α + Ara-C
- Imatinib is more efficacious than IFN- α + Ara-C

Imatinib in Chronic Phase (CP) CML: IRIS 6-Year Follow-Up

	CCyR, %
• Treatment duration: 6–6.5 yrs	First-line imatinib 82
• Median dose: 400 mg	First-line IFN- α +Ara-C 12
	Second-line imatinib 81
• 34% discontinued or crossed over to Ara-C/IFN- α	6-year rate 71
	Patients discontinuing therapy while in CCyR 13
	PFS at 72 months 93%
	EFS at 72 months 83%
	Estimated OS at 6 years 88%
	OS accounting for CML only 95%

Hochhaus et al. ASH 2007; Abstract 25.

Rate of Treatment Failure on Imatinib

IRIS study, Druker et al. NEJM 2006 and ASH 2007

Time	Rate of treatment failure (or progression to AP/BC)
1 st year	3.3% (1.5)
2 nd year	7.5% (2.8)
3 rd year	4.8% (1.6)
4 th year	1.5% (0.9)
5 th year	0.9% (0.6)
6 th year	0% (0)

Tomorrow's Therapies Today:

Clinical Trials for **Leukemia, Lymphoma & Myeloma**

Treatment of CML
After Imatinib Failure

Treatment of CML After Failure of Standard-Dose Imatinib

- High-dose imatinib
- Dasatinib
 - 300x more potent than imatinib
 - Different side effects
- Nilotinib
 - 30x more potent than imatinib
 - Different side effects
- Other agents
 - Currently being tested
- Bone marrow transplant (BMT)

Treatment of CML After Failure of Standard-Dose Imatinib (cont)

- High-dose imatinib
 - Effective for inducing CHR (89%) and CCyR (38%)
- Dasatinib (300x more potent than imatinib)
 - At two years, MCyR 62%, CCyR 53%, MMR 47%
 - PFS 80%
 - OS 94%
 - Randomized trial of dasatinib vs high-dose imatinib showed benefit for dasatinib for some patients
- Nilotinib (n=321) (30x more potent than imatinib)
 - MCyR 57%, CCyR 41%
 - Duration of response 84% at 18 mos, OS 91% at 18 mos
- Each approach results in high levels of durable responses in patients with imatinib resistant or intolerant CML.

The Next Wave of Clinical Trials:
 New Tyrosine Kinase Inhibitors
 (TKIs) as Initial Therapy for CML

Dasatinib in Untreated Patients With Ph+ CML in Early CP

Response to Dasatinib (50 mg BID or 100 mg QD)	n (%) (N=39)
CCyR	34 (87)
PCyR	1 (3)
Minor CyR	1 (3)
CCyR by time, %	
3 months (n=36)	72
6 months (n=34)	88
12 months (n=25)	100
18 months (n=20)	100
MMR by time, %	
6 months (n=34)	18
12 months (n=24)	25
18 months (n=21)	57

Cortes et al. ASH 2007; Abstract 30.

Nilotinib in Untreated Patients With Ph+ CML in Early CP

Response to Nilotinib (400 mg BID)	n (%) (N=33)
CHR	33 (100)
Cytogenetic Response (n=31)	
CCyR, %	30 (97)
3 months (n=31)	96
6 months (n=20)	100
12 months (n=11)	100
Molecular Response (n=32)	
MMR, %	14 (44)
3 months (n=32)	13
6 months (n=22)	45
12 months (n=11)	45
CMR	5 (16)

Cortes et al. ASH 2007; Abstract 29.

And Still Newer Agents.....

- Imatinib is effective for the majority of patients with CP CML
- When ineffective or not tolerated, dasatinib or nilotinib show significant activity.
- Dasatinib or nilotinib appear to have very potent activity as initial therapy.
 - Will these be better than imatinib?
 - Only new clinical trials will tell!
- Still, some patients will not respond to these therapies.
 - Certain abnormalities (mutations) can be identified that predict these drugs will be ineffective (ie, T315I mutation).

Bosutinib (SKI-606) in Patients with CP CML

- 200x more potent than imatinib
- Effective against most imatinib-resistant mutations (except T315I)
- 152 patients resistant or intolerant to imatinib or failed second generation TKI were treated.
- Median duration of treatment 2.8 months (1d–19 mos)

Cortes et al. ASH 2007; Abstract 733.

Bosutinib (SKI-606) in Patients with CP CML (cont)

	No prior nilotinib or dasatinib	Prior nilotinib or dasatinib
CHR	89%	77%
MCyR	41%	20%
CCyR	30%	-
MMR	33%	16%
CMR	19%	8%

Cortes et al. ASH 2007; Abstract 733.

Tomorrow's Therapies Today:

Clinical Trials for **Leukemia, Lymphoma & Myeloma**

INNO-406 in Patients With CP CML

- 55x more potent than imatinib
- Effective against most imatinib-resistant mutations (except T315I)
- Median duration of treatment 3.7 mos (1–19 mos)
- 20 patients with advanced chronic phase CML evaluable

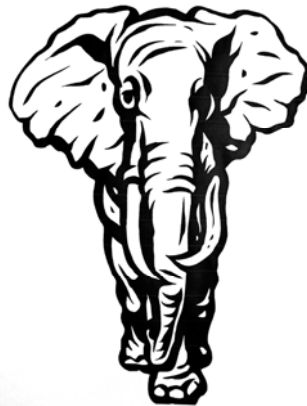
– CHR	25%
– CCyR	15%
– Partial CyR	0
- Not every patient received the optimal dose.
- Activity is noted after relatively short treatment.
- International phase II trial using optimal dose is planned.

Kantarjian, et al. ASH 2007; Abstract 469.

Other Novel Agents or Trials

- PHA-739358 (Paquette et al. ASH 2007; Abstract 1030)
 - Novel TKI against aurora kinases and Abl, including T315I
 - Dose escalation study in 9 patients
 - 2 responses: 1 CHR and 1 CCyR
 - Studies ongoing
- AP24534 (Rivera et al. ASH 2007; Abstract 1032)
 - Active against T315I mutants in the lab
 - Potentially more potent than dasatinib
 - Phase I trials planned

Bone Marrow Transplant:
The elephant in the room?



Tomorrow's Therapies Today:

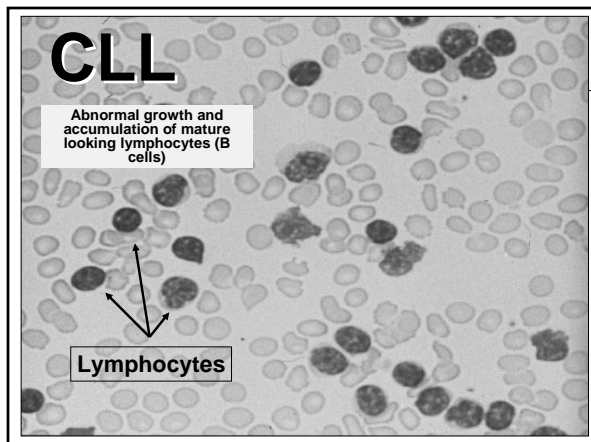
Clinical Trials for **Leukemia, Lymphoma & Myeloma**

When TKIs Fail: Is There Still a Role for Allogeneic SCT?

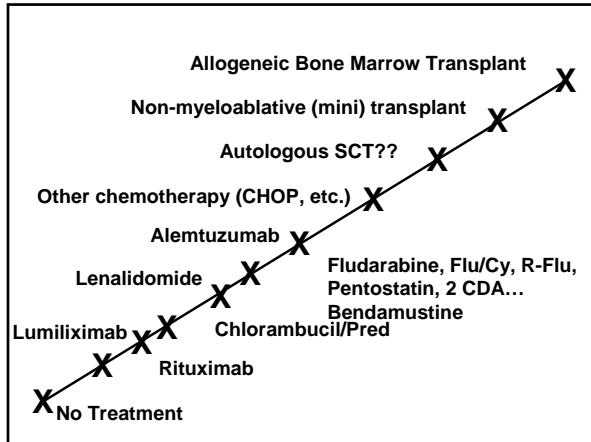
- Some patients still fail or progress after TKI therapy.
- Allogeneic SCT is the only known cure for CML.
 - Cure rates up to 70% in good-risk patients
- Limited by high treatment-related mortality
- In TKI era, no longer appropriate to apply as initial therapy because of high risk.
- However, improving safety of allogeneic SCT may improve outcomes and application.

Nonmyeloablative Allogeneic Transplant (mini-transplant) for CML

- Uses lower, and hence safer, doses of chemo or radiation therapy
- Depends on the new donor's immune system to induce a "graft-vs-leukemia" reaction, kill CML cells and cure patients
- Initial clinical trials show this approach is feasible
- Most effective, safest methods not yet defined with many unanswered questions
- Continued clinical trials are mandatory



Tomorrow's Therapies Today: *Clinical Trials for* Leukemia, Lymphoma & Myeloma



Trends in CLL: Important Topics

- Risk identification: Newer methods are being developed to better predict disease behavior and outcome to specific therapies.
- How to manage "high-risk" disease: Is treatment sooner better than later?
 - Several national and international randomized trials based on disease characteristics
- Testing new drugs for initial and later therapy
 - Bendamustine recently approved
 - Flavopiridol with or without other therapy
 - Lumiliximab (monoclonal anti-CD23 antibody)
 - FCR +/- Lumi
- Lenalidomide

Trends in CLL: Important Topics (cont)

- Is there a role for "maintenance therapy"?
 - Testing maintenance rituximab, lenalidomide
- Is it useful to achieve complete remission (treat "minimal residual disease")?
- Investigate newer transplant regimens
 - Study the role of nonmyeloablative allogeneic stem cell transplantation

Tomorrow's Therapies Today:

Clinical Trials for **Leukemia, Lymphoma & Myeloma**

Trends in Chronic Leukemias

- Dramatic progress has been made in developing newer, safer, more targeted therapies for CML and CLL.
- Results of numerous clinical trials have
 - directly changed treatment paradigms
 - improved quality of life
 - improved survival for countless patients
- New breakthroughs remain on the horizon!
- This rapid progress will continue only through continued research and newer clinical trials.
- Ultimately, all leukemia cells should look like this: