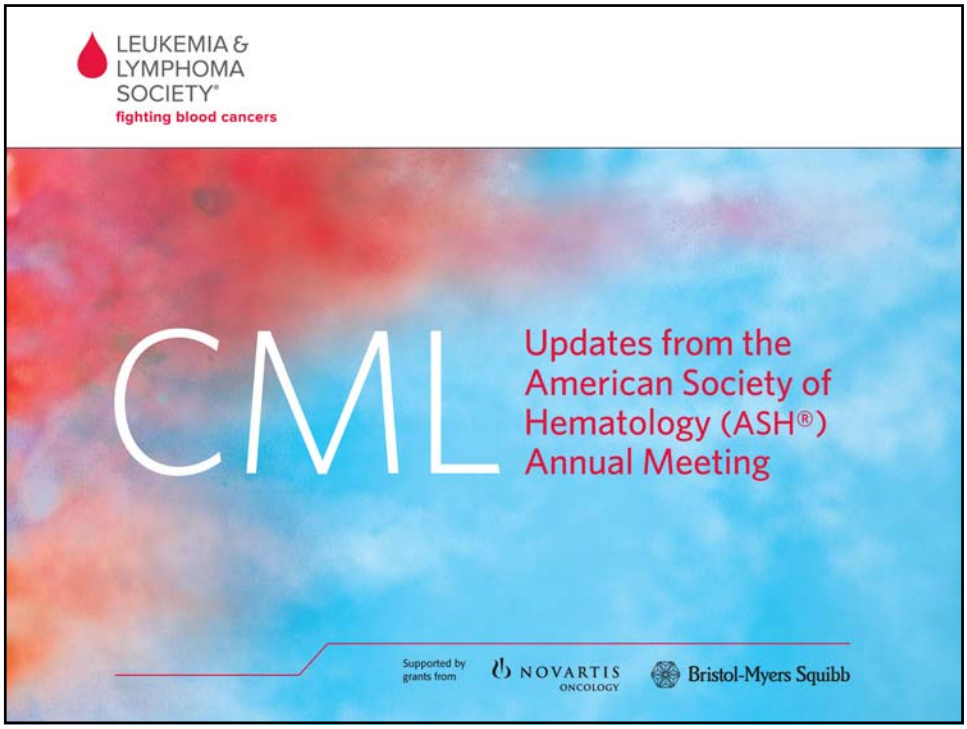
LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers
CML
Updates from the American Society of Hematology (ASH®) Annual Meeting
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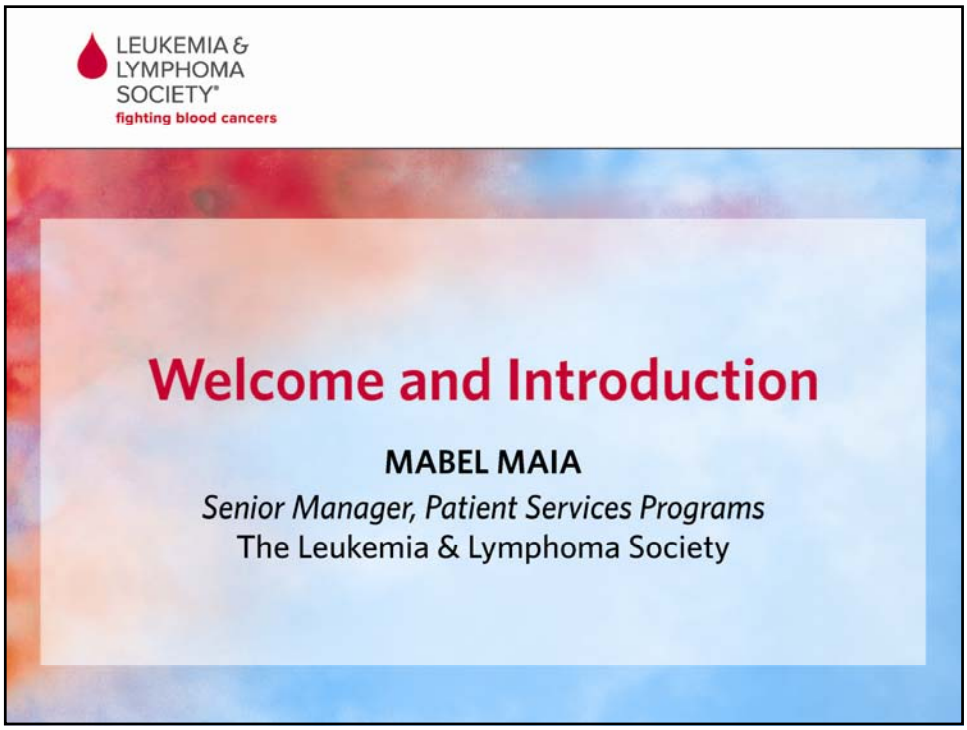
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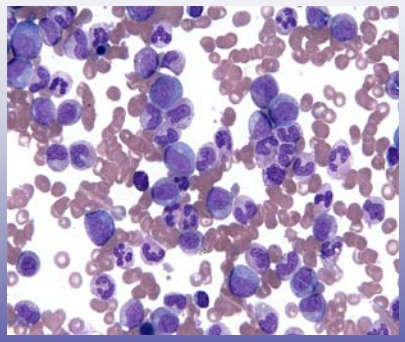
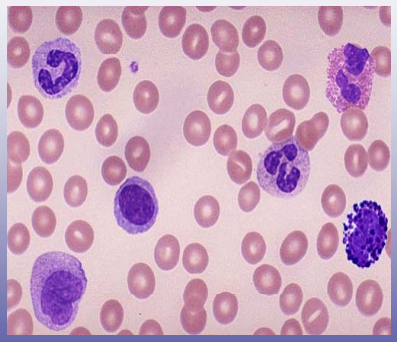
fighting blood cancers
Welcome and Introduction
MABEL MAIA
Senior Manager, Patient Services Programs
The Leukemia & Lymphoma Society

CML 2012





David L Porter, MD
University of Pennsylvania Medical Center
Abramson Cancer Center

LLS Jan 26, 2012

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CML 2012

- Current treatment options for CML patients
- Emerging therapies for CML treatment
- Quality of life issues in the treatment of patients with CML
- Role of clinical trials in the advancement of CML treatment

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Epidemiology of CML

- 1-2 per 100,000 persons
- Median age: 53 years
- Incidence increases with age
  - 12-30% of patients are >60 years old
- At diagnosis
  - 50% diagnosed by routine laboratory tests
  - 85% diagnosed in chronic phase

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Clinical Course: Can progress through 3 phases

Chronic phase	Advanced phases	
	Accelerated phase	Blast crisis
Median 4–6 years stabilization (pre-Gleevec) Few blasts, often no symptoms. Lasts months to years.	Median duration up to 1 year Blasts increase, increased symptoms, drop in healthy blood cells.	Median survival 3–6 months Blasts >30%, often resistant to chemotherapy. The speed of blast growth resembles acute leukemia AML.

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Treatment Options for CML

- No treatment
- Hydrea, Interferon
- Imatinib (Gleevec)
- Nilotinib (Tasigna)
- Dasatinib (Sprycel)
- Other tyrosine kinase inhibitors
- Bone marrow transplantation
- Investigational therapies

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Gleevec vs Ifn/AraC 5 yr Follow Up

IRIS study, NEJM 2003

Median f/u for imatinib treated patients 60 mo	5 yr
Complete Hem Response	98%
Major Cyto Response	92%
Complete Cyto Response	87%
EFS/PFS	83%/93%
Survival	89%

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Imatinib in CP CML: IRIS 8-Year Follow-Up

- **No patient progressed between year 5 and 6!**
- **1 pt progressed in year 6 and 7**
- **1 pt progressed in year 7-8.**

	CCyR, %
First-line Imatinib	82
First-line IFN+Ara-C	12
Second-line Imatinib	81
First- and Second-line IFN+Ara-C	57
8 year rate	**71**
Patients discontinuing therapy while in CCyR	13
PFS at 8 years	92%
EFS at 8 years	81%
Estimated OS at 7 years	**86%**

Deininger et al. ASH 2009; Abstract 1126

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When Gleevec Stops Working

- Dasatinib (Sprycel)
  - Newer tyrosine kinase inhibitor that inhibits bcr/abl
    - Binds 300x stronger than Gleevec
  - Bypasses most bcr/abl mutations that can develop on Gleevec
- Nilotinib (Tasigna)
  - Newer tyrosine kinase inhibitor that inhibits bcr/abl
    - Binds 30x stronger than Gleevec

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Dasatinib for Imatinib Refractory or Intolerant CML

- Complete hem response 89-92%
- Complete cyto response 59-63%
- Major molecular response 72%
- Progression free at 2 yrs 77-80%
- Survival at 2 years 89-91%
- Outcomes similar regardless of why Gleevec was stopped.

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Nilotinib in Imatinib-Resistant or -Intolerant Patients with CML in CP

- 321 pts with imatinib resistance or intolerance treated with nilotinib.
- 2 years of follow up
- Complete cytogenetic response 41%
- 2 year progression free 64%
- 2 year survival 88%

Kantarjian, H. M. et al. Blood 2007;110:3540-3546

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Nilotinib in Imatinib-Resistant or -Intolerant Patients with CML in CP: 4 yr Follow-up

le Coutre, et al. ASH 2011, Abst 3770

- 3% progression to AP/BC
- 4 year estimated survival 78%,
- No new unusual side effects
- Pleural effusions in 1% and no new cases after 2 years
- Patients treated before hematologic relapse had better outcome
- One patient died between 2 and 4 years of lung cancer but no CML related deaths.
- Therefore no cumulative toxicities, low rates of progression. Treating patients before hematologic relapse may be most effective strategy.

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Newer Tyrosine Kinase Inhibitors as Initial Therapy for CML

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Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase CML

Kantarjian H et al. N Engl J Med 2010;362:2260-2270

- N=519
- Primary end point: CCyR by 12 mo
  - CCyR at 12 mo 77% v 66% (p=0.001)
  - Major molecular response 46% v 28% (p<0.0001)
- Progression to advanced phase in 1.9% (5 pts) v 3.5% (9 pts).
- Safety profiles were similar.
- Dasatinib resulted in higher and faster CCyR and MMR at 12 mo.

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Nilotinib versus Imatinib in Newly Diagnosed CML: 3 yr Follow Up

Saglio, et al ASH 2011 abst 452

	Nilotinib 300 bid	Nilotinib 400 bid	IMatinib 400 daily
MMR by 3 yr	73%*	70%*	53%
Progression to AP/BC (No progression after 2 yr)	0.7%*	1.1%*	4.2%
PFS at 24 mo**	98%	98%*	95%
Survival at 3 yr	95%	97%	94%
Stopped drug due to side effects	9%	13%	10%

**No patient with a ≥4 log reduction in PCR signal progressed

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Nilotinib versus Imatinib in Newly Diagnosed Chronic-Phase CML:3 yr Follow Up

Saglio, et al ASH 2011 abst 452

- No new safety data, no cumulative toxicity
- 3 years of follow-up confirms the higher response to nilotinib over imatinib and an acceptable side effect profile
- Nilotinib continues to demonstrate
  - Less progression
  - Significantly faster and higher rates of MMR, MR^4, and $MR^{4.5}$
  - No difference in survival (as yet)

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Conclusions

- Nilotinib at 300 mg or 400 mg twice daily had higher response rate and less progression than imatinib in newly diagnosed CP CML.
- Dasatinib 100 mg daily induced significantly higher and faster rates of complete cytogenetic response and major molecular response compared to imatinib
- Since achieving complete cytogenetic response by 12 mo has been associated with better long-term, progression-free survival, these drugs may improve the long-term outcomes among patients with newly diagnosed CP CM.
  - It is NOT clear that either drug extends survival compared to imatinib.
  - Nilotinib (Tasigna) and Dasatinib (Sprycel) are now approved for initial therapy for CML

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Comparison of Available TKIs

	Imatinib	Dasatinib	Nilotinib
Dose	400 mg/day	100 mg/day	300-400 mg bid
BCR/ABL inhibition	1x	300X	30X
Bcr/abl mutations	-	Inhibits most imatinib-resistant mutants (except T315I)	Inhibits 32/33 imatinib-resistant mutants (except T315I)
Administration	Take with food and a large glass of water	Taken without regard to food	Avoid food 2 hr before and 1 hr after

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Toxicity	Imatinib	Dasatinib	Nilotinib	Mgt
Cramps/myalgia	+++	+	+	Hydration, Mag, quinine/tonic
Fluid retention	+++	+	+	Diuretics, dose adjust
GI: Nausea, diarrhea…	++	+	+	I and D with small meals, N fasting
Pleual effusion	-	++	-	Hold, diuretics, steroids, decrease dose
QTc prolonged	+	+	+	K, Mag, Monitor EKG
Lipase, amylase, pancreas	+	+	++	Hold, decrease dose
Rash	+	+	++	Topical steroids, hold
Neutropenia	++	+	+	Hold, dose adjust, growth factors
Thrombocytopenia	+	++	+	Hold, dose adjust

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Can tyrosine kinase inhibitor therapy be suspended or discontinued?

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Impact of dose reductions/interruptions on outcomes with dasatinib vs Imatinib in newly diagnosed CML

Jabbour et al. ASH 2011, Abst 2768

- Dose reduction/interruption in 52% dasatinib vs 36% imatinib treated patients
  - Non-hematologic toxicity 23% (D) vs 16% (I)
  - Hematologic toxicity 29% (D) vs 20% (I)
- Median duration interruption in 2 weeks
- No difference in complete cytogenetic response or major molecular response
- No significant impact when holding therapy for toxicity for short periods of time.

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Discontinuation of imatinib after complete molecular response ("STIM" study, France)

Mahon et al. ASH 2011, Abst 603

- 100 pts on imatinib and with a complete molecular remission >2 yrs
- Stopped imatinib.
- Median follow up 30 mo after stopping imatinib
- Molecular relapse in 61
  - 58 within 7 months. 3 relapses 19-22 months
  - 56/61 regained complete molecular response with retreatment
- Low risk CML and prior imatinib therapy for more than 5 years predicted for lack of relapse
- Estimated cost savings 4 million Euros

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Can tyrosine kinase inhibitor therapy be suspended or discontinued?

Preferably ONLY in the context of a clinical trial, and ONLY with the knowledge of your physician.

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Newer tyrosine kinase inhibitor therapy for CML

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Bosutinib vs Imatinib in Newly Diagnosed CML

Cortes, et al ASH 2011 abst 455

	Bosutinib 500 mg/d (n=248)	Imatinib 400 mg/d (n=250)
CCyR 18 mo	79%	79%
MMoR 18 mo	55%	45% (p<0.05)
PFS	95%	91%
Overall survival	99%	95%

**No patient with a ≥4 log reduction in PCR signal progressed

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Other Novel Agents or Trials

- Ponatinib (oral BCR-ABL inhibitor)
  - Phase II study in 403 pts with dasatinib or nilotinib resistant/intolerant CML or ALL *(Cortes, et al, ASH 2011, Abst 109)*
  - Effective in pts with T315I mutation
  - 57% failed ≥ 3 TKIs
  - Side effects similar to other TKIs
  - 25% CCyR (43% MCyR)
  - 48% CCyR with T315I mutation
  - Therefore activity in advanced and refractory CML with and without T315I.

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Long-term issues managing CML as a chronic disease

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Quality of Life for Patients with CML

- Most patients now living many years with CML but on long-term treatment
- Quality of life must be considered when considering:
  - Living with a chronic illness
  - Requiring long-term drug therapy
  - Managing chronic side-effects of medication

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Quality of Life on Long-Term Imatinib

Efficace, et al. Blood 118;4554, 2011

- 448 patients on imatinib surveyed
- Median time on imatinib 5 yrs (range 3-9 yrs)
- All patients in complete cytogenetic response
- Asked 36 questions about 8 issues:
  - Physical functioning, role limitations because of symptoms, body pain, health perceptions, vitality, social functioning, role limitations because of emotional issues, mental health
  - Compared to general population

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Quality of Life on Long-Term Imatinib

Efficace, et al. Blood 118;4554, 2011

- Overall QOL scores worse for 2 age groups
- 18-39: Significantly worse for
  - social functioning, and physical functioning.
- 40-59: Significantly worse for
  - role limitations because of symptoms, role limitations because of emotional issues, general health perceptions.
- 60-69 and ≥ 70 similar to healthy population
- QOL scores worse for women
- QOL scores for men similar to controls

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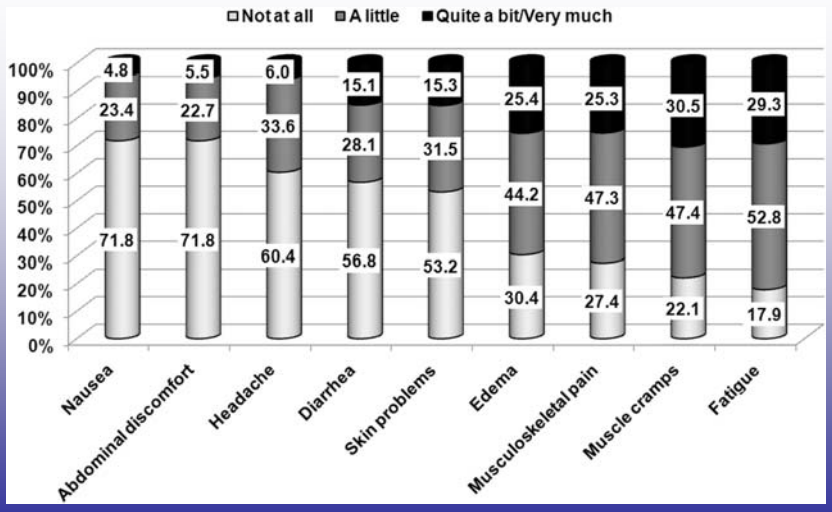
Percentage of CML patients reporting the symptom by level of severity (N = 422).



Efficace F et al. Blood 2011;118:4554-4560

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Bone Marrow Transplant for CML

- The only known “cure” for CML
- Better outcomes in chronic phase
- Currently reserved for patients with resistant CML not responding to available medication
- Can cure over 50% of patients when necessary
  - Results with siblings donors similar to using unrelated well matched donors
- Very few transplant for CML in the modern era

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Making continued progress in CML therapy

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Importance of Clinical Trials for CML

- IRIS Study compared imatinib to interferon
  - One of the best and most important trials ever conducted for CML
  - Dramatically changed treatment
- Most clinical trials are trying to make a good therapy better.
- There is medical evidence that patients who participate in clinical trials get excellent, if not better, clinical care.
- Numerous resources to access clinical trials.
  - LLS-supported TrialCheck® - www.LLS.org/clinicaltrials
  - www.clinicaltrials.gov
  - Oncolink
  - American Cancer Society
  - Other resources

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Survivorship

Treating CML, and living with CML, can be like a long distance run

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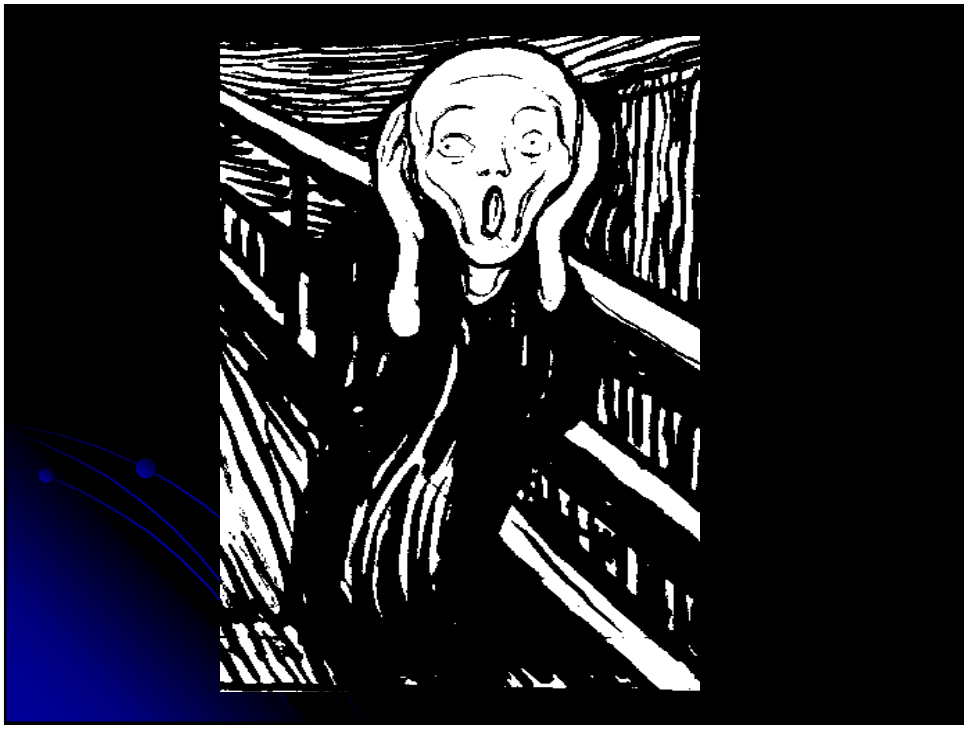

Living with Chronic Leukemia

- Adjusting to the diagnosis may take time
- Take an active role in your care
- Learn about CML, talk to care givers, patients, family and friends…
- Understand indications and goals for treatment
- Short term vs long term goals

Survivorship

- Support Groups
- Community Support
- The Leukemia & Lymphoma Society (www.LLS.org)
  - Educational programs
  - Family and other support groups
  - First connection
  - Financial assistance
- Gilda's Club/Wellness Community
- American Cancer Society
- Others

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Conclusions

- Treatment options for CML have changed dramatically in the last decade.
- Imatinib, dasatinib or nilotinib are all very effective initial therapies for CML
- CML can be managed in most patients as a chronic disease
- Intensive scientific research and rational drug development, along with the participation of hundreds/thousands of patients have let to incredible breakthroughs and changed the prognosis for patients with CML.
- Many exciting new developments are improving on already very effective treatments.

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Question and Answer Session

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MY CML TRACKER

An interactive online tool to help you keep track of appointments, questions to ask your doctor, medications, side effects, test results and more.

- Visit www.LLS.org/cmltracker

The Leukemia & Lymphoma Society's (LLS) Co-Pay Assistance Program offers financial assistance to qualified CML patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE: www.LLS.org/copay**
- **TOLL-FREE PHONE: (877) LLS-COPAY**

For more information about CML and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL: infocenter@LLS.org**