LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

CML

Expert Information About Diagnosis and Treatment

Supported by grants from NOVARTIS ONCOLOGY Bristol-Myers Squibb

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Welcome and Introduction

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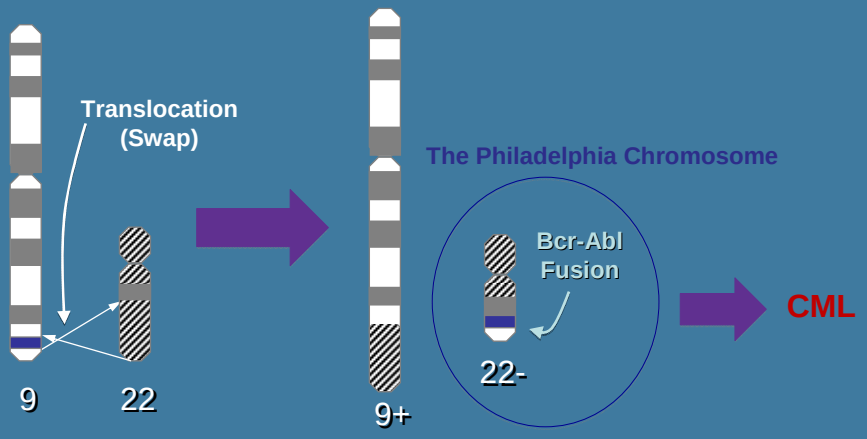
What Causes CML?

- Chromosome translocation ('swap') in marrow cells that divide and repopulate the blood (progenitor cells)
- Not inherited; few known exposure risks
- One of few cancers with discrete, singular "driver"
  - The Philadelphia chromosome (Ph)
    - easy to identify
    - central to the diagnosis
    - common genetic error happening in dividing blood cells that rarely causes disease

The Philadelphia Chromosome



Profiling the CML at Diagnosis

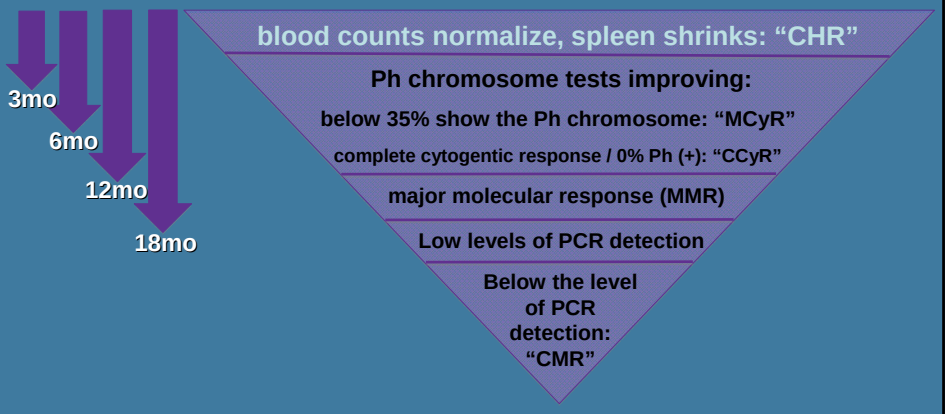
- Blood testing:
  - Triggers the consideration of CML
  - Confirming the Philadelphia chromosome
- Chronic phase (most) or more advanced stage?
  - Bone marrow studies important at diagnosis
- The Sokal “score”- helps predict response
  - % blasts, basophils, spleen size, platelet count, and age
- Discussion of bone marrow transplant: define the option
  - Rarely performed but still a curative option to be used in certain circumstances

Response after Diagnosis

"CML treatment and response is a marathon, not a sprint"

-Landmarks of response occur over time, with expected improvements needed to consider treatment successful…

Response in CML: Shrinking the Iceberg

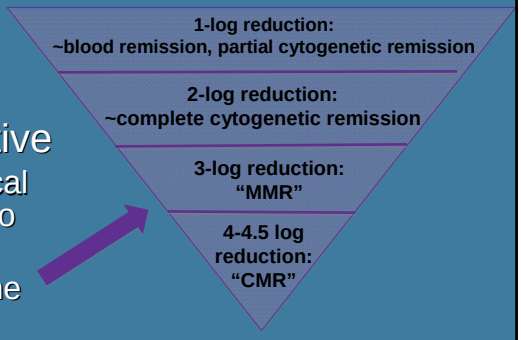


What's Considered a Good Response?

- 3 mo: complete blood remission, beginning of cytogenetic (chromosome) response
  - Bone marrow testing now recommended @3mo
    - Early opportunity to address delayed/missed response
- 6-12 mo: majority / complete cytogenetic response
  - Complete bone marrow remission (CCyR) key to long term remission and reduction in risk of relapse
- 12-18 mo and beyond: molecular (PCR) response
  - Major molecular response= 3 log reduction= further 10x reduction in volume of CML beyond CCyR

PCR testing in CML: the Bulk of Monitoring

- Detects 1 leukemia cell in 1,000 to 1 million normal cells
- Can be qualitative
  - Present or undetectable
- Needs to be quantitative
  - Gives a relative, numerical (%) of leukemia related to normal DNA/RNA
  - Should be reported on the international scale (IS)



PCR Monitoring

- Different labs will have different results
  - Standardization to the international scale is necessary and is being worked on; only a few labs in the US use
  - Until then – use the same lab so trends can be followed
- Negative results depend on the quality of the sample and the quality of the lab
  - "Complete Molecular Response" or "PCR negative" may not be fixed points or agreed levels
  - Meaning of achieving these levels unclear: logically desirable but necessity unproven to date

When Should a Change in Therapy Be Considered?

- Lack of a complete blood response after 3 months
  - potentially if no cytogenetic response
- No cytogenetic response after 6 months of therapy
- Still greater than 35% Ph+ after 1 year of therapy

Current targets of response are based on treatment with imatinib (Gleevec®)- But initial treatment choice is different in 2011…

Nilotinib or Dasatinib for Newly Diagnosed Patients with Chronic Phase CML: Proven Options

- Early data (1-2 yrs) suggests higher rates and faster responses, both cytogenetic and molecular
- Protection from progression to accelerated/blast phase
- Side effect profile narrower
  - Drug-specific side effects possible

Is it Safe to Stop treatment in “PCR Undetectable” or “CMR” Patients?

- Small studies, follow up averages < 2 yrs
- Some patients (~40%) have not shown evidence of CML returning (PCR turning (+))
- Too early; no tool to predict and concern over “quality” of remission regained if lost after stopping
- ‘Cure’ (remission without treatment) in CML the current focus of research

When Should Stem Cell Transplant Be the Main Focus of Treatment?

- When CML has been or has moved into an advanced stage and long term remission is less likely
- If chronic phase CML is brittle and little/no response is occurring even with switching to newer treatment
- When certain types of “resistance” to treatment are identified
  - Specific mutations in the BCR-ABL target such as the ‘T315I’ mutation- until promising novel therapies like ponatinib are available

Conclusions

- Mutliple options when chronic phase CML is diagnosed
  - Nilotinib, Dasatinib, or Imatinib
  - Important dialogue about ‘best fit’ for each patient based on medical history, side effect risk, preferences, etc
- Tailoring therapy for each patient possible / necessary
  - Intolerance to medication- even lower intensity side effects that are chronic- is grounds to consider switch
  - Having side effects addressed to boost likelihood of perfect or near-perfect adherence to therapy key

Question and Answer Session