Chronic Myeloid Leukemia

2016

Goals of CML therapy:

1. Hematological response

WBC< 10 x 109/L.

No myelocyte , promyelocyte and myeloblast.

Basophile < 5%.

Platelets < 450 x109/L.

Spleen non palpable.

2.Cytogenetic response

No cytogenetic response	>95% Ph+ metaphase CBA
Minor Cy response	>35% Ph+ metaphase CBA
Major Cy response	1-35% Ph+ metaphase CBA
Complete Cy response	No Ph+ metaphases CBA, OR <1%(≤1/200) positive interphas nuclei by FISH

3.Molecular response

- Major molecular response: Ratio of BCR-ABL to ABL (or other house-keeping gene)≤0.1%(log 3 reduction) on the international scale.
- Deeper response:

Log 4 reduction i.e ratio of BCR-ABL to ABL is 0.01% on the international scale.

Log 4.5 reduction i.e ratio of BCR-ABL to ABL is 0.003% on the international scale.

Log 5 reduction i.e ratio of BCR-ABL to ABL is 0.001% on the international scale.

- Complete

When BCR-ABL level is Log 4.5 reduction i.e ratio of BCR-ABL to ABL is ≤ 0.003% on the international scale or, undetectable BCR-ABL transcripts by nested PCR in tow consecutive peripheral blood samples of adequate quality(sensitivity >10^4).

SOME OF DEFINITIONS:

Optimal response

Means there is no indication that a change of therapy may improve significantly the outcome.

Failure:

Means the risk of progression is significant. The patient should receive a different treatment, whenever available and applicable.

Warning(previously suboptimal):

Means characteristics of the disease and the response to treatment require a more careful and more frequent monitoring. That is to stay molecular and cytogenetic test within less than 3 months, and mutational analysis.

Guideline of ELN 2013

	Optimal	Warning	Failure
3months	ph≤35% and/or BCR-ABL≤10%	Ph+36-95% and/or BCR-ABL>10%	Ph+>95%
6months	Ph+ 0% and/or BCR-ABL<1%	Ph+1-35% and/or BCR-ABL1-10%	Ph+>35% and/or BCR-ABL>10%
12months	Bcr-abl≤0.1%	BCR-ABL 0.1-1%	BCR-ABL >1%
18months	NA	NA	NA
Any time	Bcr-abl≤0.1%	CCA/ph-	Loss of CCyR, mutations, CCA/ph+, confirmed loss of MMoR

In the 2013 ELN recommendations loss of MMR must be confirmed in 2 consecutive tests in order to be considered failure

Failure indicates the patient should receive another treatment

TREATMENT:

Newly chronic phase CML:

- Imatinib 400mgx1.
- Nilotinib 300mgx2, only through free of charge sample by novartis support.

If patient on imatinib treatment and develop:

- **Acceleration phase:**
  - Check for compliance.
  - Switch to another TKI: Nilotinib 400mgx2 per day or dasatinib 100mg/day or 70mgx2 or vis versa.
  - Allogenic BMT is recommended after return to chronic phase.
- **Blast transformation:**
  - Check for compliance.
  - Nilotinib 400mgx2 per day or dasatinib 100-140mgmg/day.
  - For patients in BC, options include acute leukemia type therapy (as for AML or ALL depending on phenotype) with or without 2nd generation TKI .
  - Allogenic BMT is mandatory after return to chronic phase.

If BMT is unavailable:

nilotinib 400mgx2 or dasatinib 100-140mglday plus 6mp &MTX tablets as a maintenance for those with ALL transformation.

While those with AML transformation, nilotinib 400x2mg/day or dasatinib 100-140mg/day, the remission usually is short.

Treatment of failure group patients:

- Check compliance**.**
- Nilotinib 400mgx2 or dasatinib 100-140mg/day for those on imatinib treatment while for those on nilotinib switch to dasatinib and vis versa.
- Allo BMT, if patient doesn't achieve MMoR.

Treatment of warning group patients:

- Check compliance
- Close monitoring by cytogenetic and molecular tests.
- Increase the dose of imatinib to 600-800mg/day.

Intolerance or toxicity to imatinib:

Nilotinib 300mg-400mgx2 or dasatinib 100mg/day

Pregnancy with CML:

- Interferon α during pregnancy.
- Leukopharesis.

Choice of 2nd TKI according the co-morbidity disease:

	Dasatinib	**Nilotinib**
❖ Pancreatitis	Y	N

- ❖ Cardiovascular disease……..N……Y
- ❖ Autoimmune disease……..N…….Y
- ❖ Dietaryrestriction……..Y……..N
- ❖ PostSCT……..N…….Y
- ❖ GI bleeding……N……Y
- ❖ Cardiac disease……?Y……?N

Investigations requirement at registration:

- o Complete blood count and film
- o Bone marrow study
- o Cytogenetic analysis(banding or FISH)
- o Renal function test
- o Liver function test
- o Ultrasonography of abdomen
- o Electrocardiogram with corrected QT interval value for those on nilotinib treatment
- o Blood sugar level for those on nilotinib treatment
- o Calcium, phosphorus, potassium and magnesium serum levels for those on nilotinib treatment.

Monitoring of treatment:

- Complete blood count after 2 weeks from initiation of treatment then every 4 weeks till complete hematological response is achieve.
- Both Cytogenetic study and Molecular analysis whenever possible.

Cytogenetic study:

- At 6months
- At 12months

Molecular study by Q-PCR:

- At 3months(optional)
- At 6months
- At 12months

If MMoR is achieve then follow up every 6 months.

**Regarding failure group patients, cytogenetic analysis screen after 3months of switching TKI if CCyR is achieve then Q-PCR study every 6months.

**Mutational screen always is indicated when there is loss of TKI response.

**In case of warning, the tests must be repeated at shorter intervals.

**In case of prolonged cytopenia, raising the suspicion of the development of a MDS, bone marrow examination is recommended, for morphology and cytogenetics (CBA).

**when the results of hematologica, cytogenetic, or molecular tests are borderline or not concurent, both methods or a second check are always recomended.