Venice Meeting Highlights: Key lessons

EVOLVING CONCEPTS IN THE MANAGEMENT OF CHRONIC MYELOID LEUKEMIA

RECOMMENDATIONS FROM AN EXPERT PANEL ON BEHALF OF THE EUROPEAN LEUKEMIANET

Conclusions

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CML therapy in the imatinib era

- **CML prognosis has improved dramatically**
- **Cellular and molecular biology studies help improve prognosis and treatment**
- **However, Sokal / Hasford risk definition is still required to plan CML therapy:**
  - **age**
  - **spleen size**
  - **blood counts**
  - **blood differential**

  prior to any treatments

Imatinib in early chronic phase CML

- IRIS study (n=1106) 54 month update: imatinib continues to show good tolerability and efficacy as first line therapy for CML
- Does CCyR to imatinib have an effect on long-term outcome?
  - **Patients with a CCyR have greatest protection from progression**
  - **Time to achievement of CCyR within the first 12 months has no effect on EFS**
  - **Patients who are > 95% Ph+ at 6 mos or > 35% Ph+ (i.e. less than PCyR) at 12 mos are unlikely to achieve a CCyR**

Molecular biology

- RT-Q-PCR method of choice for monitoring residual disease / measuring BCR-ABL transcripts
- Need to know absolute concentration of BCR-ABL transcripts
- Abl probably best control gene (BCR, GUS also acceptable)
- Need to assess absolute, not relative reduction in BCR-ABL
- Labs differ in efficiency of RNA detection; comparability:
  - compare with reference samples (centrally prepared and distributed) corresponding to 100%, 1%, 0.1%, 0.01% BCR-ABL/control gene (=international scale)
  - identify BCR-ABL/control gene values corresponding to International Scale reference values
  - calculate conversion factor to identify absolute log reduction

Diagnostic and Pre-treatment Work-up

Panel recommendations:

1. Spleen assessment, blood counts and differential before any treatment

2. Sokal/Hasford prognostic groups

Response-related prognostic factors: the cytogenetic response

- In early chronic phase CML
  - CyR at 6 mos = first relevant cytogenetic prognosticator
  - CCyR at 12 mos accurately predicts freedom from progression to AP/BC in >95% of patients CCyR seems to override pretherapeutic Sokal risk

Response-related prognostic factors: the cytogenetic response

- In advanced CML
  - The more advanced the disease the less protection is afforded by CCyR →
    - In AP and BC, even CCyR should not be used as the basis to delay allogeneic transplant if this is an option
    - In late CP more rapid achievement of CCyR may be associated with superior PFS

Response-related prognostic factors: the molecular response

- Although small, a risk of losing MMolR exists
- The probability to achieve MMolR correlates to Sokal risk
- High or intermediate risk patients achieving MMolR have a risk of subsequent progression as small as low risk patients
- Shorter time to MMolR may imprve prognosis
- Most patients stopping imatinib therapy relapse, even when PCR negative
- BCR-ABL transcript levels to trigger search for mutation:
  - 2-fold rise? (Branford et al., Blood 2004)
  - consecutive rises? (Wang et al., Haematologica 2006)

Bcr-Abl Kinase Domain Mutations

- Frequency of imatinib resistance depends on stage of CML
- Major causes of resistance: BCR-ABL mutations and clonal evolution
- Prospective evaluation needed
- Some BCR-ABL mutations impair prognosis more than others, in particular on continuous imatinib therapy
- Early identification of imminent resistance might contribute to individualized therapy based on molecular data

Response Definition, Evaluation and Monitoring

- Failure: continuing imatinib treatment at the current dose is no longer appropriate for the patient, who would likely benefit more from other treatments.
- Suboptimal response: the patient may still have a substantial benefit from continuing imatinib at the current dose, but long-term outcome of the treatment would not likely be favorable. The patient is eligible for other treatments.
- Warnings: standard dose imatinib may not be the best choice. The case requires more careful monitoring. The patient may become eligible for other treatments.

Failure and suboptimal response: operational definition (ECP CML on IM 400 mg/d)

Time	Failure	Subopt Resp	Warnings
Dx	-	-	High risk Del9q+ ACA in Ph+ cells
3 mos	No HR	< CHR	
6 mos	< CHR No CR	< PCR	
12 mos	< PCR	< CCR	< MMolR
18 mos	< CCR	< MMolR	
Anytime	Loss of CHR Loss of CCR Mutation (IM-insensit.)	ACA in Ph+ cells Loss of MMolR Mutation (IM-insensit.)	Any # transcr level OCA in Ph- cells

Monitoring response

Time (Months)	3	6	9	12	
*Cytogenetics	(x)	x		x	q 6-12 mo (marrow)
RT-Q-PCR	x	x	x	x	q 3 mo
Mutational analysis	only in case of failure, suboptimal response, or sustained – confirmed increase of bcr-abl transcripts level				

*FISH should be done before treatment (del9 q+) and can be used during treatment if conventional cytogenetics fail or cannot be obtained

Treatment Policy

- Early chronic phase: initial therapy
  - Standard dose imatinib, 400 mg/d
  - Alternatives
    - IFN + HU and/or low-dose Ara-C (standard risk only)
    - High dose imatinib (experimental)
    - Allografting
    - High-risk disease, low transplantation risk
  - Trial with IM first
  - Discuss choice between IM and alloHSCT with patient
    - Little reason to deny IM trial, as early response to IM can reinforce or weaken indication for alloHSCT

Treatment Policy: Alternative therapies and indications

Intolerance	SCT or IFN ± LD Ara-C vs. New agents	Shared decision-making
Toxicity		
Failure	SCT or IM 600 or 800 mg/d	Check compliance! Rule out highly resistant mutation
Suboptimal response	IM 600 or 800 mg/d (SCT if low SCT risk and high disease risk)	
'Warnings'	Continue IM 400 mg/d	Observe! Check compliance!

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EXIT