iCMLf Conversation with Professor Hochhaus on August 28, 2020

Answers to questions during Q&A Session

1) Does the transcript type influence treatment choice?

The impact of the type of the typical transcripts on response is still conflicting.

Reports on patients with atypical transcripts are rare. In general, patients with a shorter BCR fragment in the transcript (e1a2, e6a2, e8a2) tend to have a more aggressive disease.

However, since data is not consistent, the ELN panel did not recommend to select the treatment according to the transcript type.

2) The recent NCCN guidelines have changed the definition of a deep molecular response from MR4.5 to MR4.0. What is the consensus on this definition? Is it MR4.5 or MR4.0?

DMR has been defined as at least MR4 in the literature. It's not a question of consensus.

3) What are side effects during TFR option of the treatment?

After TKI discontinuation, patients may experience muscle and/or joint pain, which are transient symptoms of a generalized inflammation syndrome. Standard anti-inflammatory drugs may help.

4) Is rapidity of attaining DMR taken into consideration while deciding on interruption of TKI.

Speed of response might be used as a criterion in selected patients, i.e. in case of wish to get pregnant.

5) In the ELN CML recommendations 2020, fatigue is mentioned as a side effect only twice.
The first time as a cause of poor tolerance with imatinib.
The second, in the "Discussion", as "chronic low-grade fatigue" which is a pending issue with imatinib in many patients.

Patients, in any survey, study (even from pharmaceutical companies), have as main adverse effect in all TKI's, fatigue (along with joint pain, chemobrain, gastrointestinal problems...), and not in low grade...

How is it possible that 20 years later, the main adverse effect according to patients, is still "undervalued" when these recommendations are drawn up?

Patients deserve respect, to be believed, not that our own hematologists, following this ELN recommendation continue to deny that fatigue, asthenia (or other side effects) is caused by CML treatment.

How can we (Hematologists and Patient Advocates) solve this issue?

There is no need to “solve” anything, since fatigue is generally accepted as a SYMPTOM of malignant disease but also a side effect of treatment. Its not specific to any TKI and therefore not a useful criterion to select a specific treatment. ELN published a specific paper on adverse events and their treatment in LEUKEMIA (Steegmann et al.). The current recommendation paper refers to this comprehensive publication.

6) Is there a role for incorporating Kinetics of QPCR decrease (halving time & reduction ratio) in the warning or suboptimal patients and as a step for TFR?

This is included using the 10% cut point at three months. Any calculation of the early reduction is technically complex and therefore no standard procedure globally.

7) Do you recommend dose reduction either decrease dose or make it EOD before or instead of stoppage?

Not at all. Data are not convincing and a low intracellular level of TKI may lead to the selection of resistant clones. Reasons for dose reduction should be restricted to side effects and are defined in very close ranges, specific for each TKI.

8) Kinase Domain mutations should be looked for by sanger sequencing or NGS?

Either method is useful, depending on the technical availability, the sensitivity required and the number of samples per day/week in a specific lab. For the analysis of the reason for resistance, Sanger is sufficient but NGS works as well.

9) What makes the difference between successful and failing TFR patients? Are there special investigations ongoing to understand this difference in the blood, the immune system? Looking at TIGER - there should be around 350 successful and 350 failed patients - cant those patients and data been taken to further investigate the root for success?

This is one of the most active areas in CML research worldwide. We know that the aggressiveness of the CML clone play a role (high risk Sokal or ELTS), but the immune system is an important measure to keep the persisting cells silent. There is no single clue, it might be a combination of multiple effects.

10) What is the prognosis that don't achieve molecular remission by 18 months?

Lack of MMR is associated with a minimal chance to discontinue therapy later.

Lack of CCyR (<= 1% BCR-ABL1) is associated with a survival disadvantage.

11) What is the role of hyploidetical transplantation in chronic phase CML? May be used as third line after failure 2 TKIs or only in pts resistant to all available TKIs?

Haploidentical transplantation can be used for patients with aggressive disease (AP or BC) and lack of an identical related or unrelated donor. In chronic phase disease, haploidentical transplantation is being performed only if other treatment options are not available.

12) Would you also recommend the ELN guidelines for the treatment of children and younger people? Did you have pediatricians on the panel for the new guidelines?

The ELN recommendations were written for adult patients only.

13) What is your personal opinion concerning the use of imatinib in the 3rd trimester during pregnancy in case of CML progression? Is it "definitely no" or is it possible in certain individual situations?

TKIs could be used in individual patients at the end of pregnancy after organ development and maturation in case of hematological relapse to avoid harm for the mother and the baby. In case of ongoing hematologic response, I would avoid the use of TKIs even in the third trimester.