ASH Report #1

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Update on stopping CML treatment with Tyrosine Kinase Inhibitors in deep molecular response

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Tyrosine kinase inhibitors (TKI) have dramatically improved survival of CML and made it a chronic disease. However, life-long therapy is still advised according to expert recommendations and the product labels of current TKI treatments.

Depending on the choice of TKI, about 40-70% of CML patients reach a deep molecular response, meaning a BCR-ABL ratio of 0.01% (MR4) or below. Given it had been observed that some patients were able to stop treatment in deep remission without a recurrence of the disease, the effectiveness of stopping TKI treatment of CML patients at large having a sustained, deep molecular response is a key question that is being investigated in various studies, and is probably the most debated CML topic at this year's ASH.

Similar to the findings presented last year, about half of the patients in deep molecular response (MR4, BCR-ABL ratio better than 0.01%) can safely stop TKI treatment, while the other half needs to restart therapy when the PCR rises again above MMR after stopping. Most patients who lose their deep remission then seem to experience a quick rise in PCR counts, so monitoring in short intervals and quick re-start of therapy seems crucial. And while most patients lose their remission within the first 6 months after stopping, the European
EURO-SKI study, the largest CML TKI stop study to date, has shown that some patients do so even after three years, so doing regular PCRs for years, potentially life-long, seems to be required.

The reasons why one half of patients can safely stop and the other half can’t, as well as how the withdrawal symptoms should be managed that about one third of patients are experiencing after stopping any of the TKIs, are not yet well understood. So far, we now know from EURO-SKI that a longer a patient has received TKI treatment prior to stopping treatment, and the longer a patient had a deep molecular response (MR4), the higher the probability is that the patient will be able to stop therapy successfully. Hence today, stopping treatment is a difficult trade-off between getting rid of expensive, potentially annoying therapies, and letting time pass until the residual CML is almost extinct – and until research has advanced towards understanding the mechanisms better, or even developing a cure.

It is still not officially recommended to stop outside of trials today, given PCR monitoring and swiftness of therapy re-start might not be as strict “out in the field” than within a clinical trial – even though many CML experts seem to support stopping as part of clinical practice already today. However, everything we know about stopping today has been observed within trials using very frequent, best quality PCR testing and very strict protocols. Given CML patients who are eligible to stop treatment (MR4) are already in the “safe haven” and are very unlikely to suffer from disease progression when on continuous treatment, even one single patient progressing or even dying due to poor monitoring or too late detection of "stop failure" would be one too many.

As more patients achieve MR4 when treated with the 2nd generation TKIs Nilotinib or Dasatinib and because frontline treatment with these drugs prevent progression of the disease in the months after diagnosis, many CML experts tend to treat patients with these (albeit much more expensive) drugs. However, it is estimated that two thirds of CML patients are on Imatinib today, and hence switching them to Nilotinib or Dasatinib in order to accelerate the achievement of MR4 is quite popular, supported also by the marketing interests of the pharmaceutical companies to have as many patients on 2nd generation drugs at times when Imatinib becoming generic. However, the ENESTGoal and ENESTPath trials have demonstrated that a relatively small number of patients have suffered from severe side effects under Nilotinib (mainly cardiovascular side effects) or Dasatinib (mainly pleural effusions), which also needs to be considered in the risk/benefit assessment when switching from Imatinib to another drug just for the sake of improving response to stop treatment. In the specific case of Nilotinib, switching from a once-a-day-with-food drug to Nilotinib with twice-daily intake and fasting periods needs to be explained to the patient – as this will not only affect his quality of life until the patient is ready to stop, but also when stoppings fails and therapy re-starts. The Australian TWISTER study which has provided patients with Imatinib front-line treatment and early escalation to higher dose Imatinib and switch to Nilotinib depending on response rates might demonstrate another feasible alternative to get ready to stop.

So the questions that still need answers remain:

- What is the fraction of patients that can safely stop treatment in a decentralized, but standardized monitoring?
- What is the optimal duration of TKI treatment and of MR4 remission before trying to stop?
- What are the prognostic factors for remaining in molecular relapse-free remission 6 months after stopping, besides duration of TKI therapy and duration of MR4 response?
- Is there a role of individual immune effects and immunological pee-treatments (like Interferon)?
- If a patient is treated with imatinib and have not reached stable MR4, does he/she need to switch to a second-generation drug to be able to stop, or does it just take longer to get into the required remission using Imatinib? What is the effect/side-effect trade-off?
- Are patients losing their chance to stop by stopping (too) early and then failing on their first stop attempt?
- For how many years and how frequently do we need to monitor CML patients in therapy-free remission – in the first months but also years after – until we can say they are safe?
• How to manage withdrawal symptoms, e.g. of those patients that suffer from severe pain after stopping treatment?

To better understand the current status of knowledge and what is being done in the studies to answer those questions, we are now summarizing the most interesting findings from the stop studies presented at this year’s ASH in more detail below.

As a final thought, with all the (justified) hype around stopping treatment as an important option to get CML patients independent of treatment, we should not forget that only about 25%-35% of CML patients will ever be able to stop treatment successfully using current TKIs. Around 70% of patients may get to MR4 and try stopping, but only half of them will be successful. This means that unless we find more effective, potentially curative treatments, around two thirds of all CML patients will be in need of continuous treatment. On treatment, they will live a long life with, as we see from 15 years’ history of TKI treatment, a good quality of life and little long-term risks. Patients achieving MMR under continued treatment are already in the “safe haven”. With the discussions around therapy-free remission, we should not give them the feeling that they have missed something or even failed therapy goals, and we should also not put pressure on those that decided for staying on treatment despite their response would qualify to stop treatment.

EURO-SKI: Largest STOP study

The EURO-SKI (ClinicalTrials.gov No. NCT01596114) is the largest multi-national CML stop study to date. Given it is a purely academia-driven study without sponsorship of a pharmaceutical company, it has some interesting features that other studies do not have, like enrolling patients with the three competing TKIs Imatinib, Nilotinib and Dasatinib, and academic sub-studies which investigate the biological mechanisms that may decide between individual success or failure of stopping.

In EURO-SKI, 821 chronic phase CML patients were enrolled after a minimum of 3 years of TKI treatment, which had shown no prior TKI treatment failure and which had achieved MR4 (BCR-ABL <0.01%) for a duration of at least one year. Patients stopped treatment after enrolment, and had to re-start when the PCR rose above major molecular response (MMR, BCR-ABL 0.1%) at any one point. For ASH, the data of 755 patients was analysed. Of those, the median age was 60, the median duration of TKI treatment before stopping was 7.5 years, and the median duration of MR4 before stopping was 4.7 years.

Of these 755 patients, 373 lost MMR and 4 died in remission. The median follow-up was 26 months (range 1-36). 39% patients had to restart therapy due to loss of MMR in the first 6 months. After 36 months, 52% had to restart therapy. However, some patients lost MMR after more than 30 months – even though this occurs only rarely, EURO-SKI has demonstrated that there seems to be no “plateau” after 3 years, so all patients who stop need to stay on continuous PCR monitoring even years after stopping treatment.
At the time of evaluation, most patients who had to re-start therapy regained a deep molecular response, and importantly, no progression to advanced disease phase was noted. The analysis demonstrated that no significant association between age, gender, depth of molecular response (MR4.5 vs. no MR4.5) or any variable part of the Sokal, EURO, EUTOS, or ELTS risk scores and the success of stopping after 6 months of treatment stop.

There was also no difference between patients whether they had MR4.5 or undetectable residual disease prior to stopping treatment. However, treatment duration with imatinib prior to stopping, the duration of MR4 remission before stopping, and the duration of Interferon pre-treatment were positively influential to the success rate. One additional year of treatment increased the chance to stay in MMR at 6 months after stopping by 13%. In addition, the success rate of stopping at 6 months was 65.5% for all patients treated longer than for 5.8 years and 42.6% for patients treated shorter than for 5.8 years. In addition, patients who had an MR4 for more than 3.1 years had a significantly higher chance to stop successfully.

About one third of patients who stopped treatment experienced “TKI withdrawal symptoms”, mostly musculoskeletal pain, after stopping treatment, including pain in the bones, joints and muscles.

From an economic point of view, just looking at the 596 patients on study who had received Imatinib as first line treatment, 279 patients had stopped but had to restart treatment, and 317 had stopped treatment and were still without treatment to date, in total 8092 months of imatinib treatment were saved. With an average monthly cost of 2252 EUR for Imatinib in the 11 European countries (range: 1.73 - 3.370 Euro per month), the total estimated savings of drug costs to the healthcare systems of EURO-SKI amounted to 22 million EUR. From that perspective, it is a pity this study did not receive public funding. (Mahon, ASH-Abstract 787; Pfirrmann, Abstract 789)

**ENESTop trial**

ENESTop is a Novartis-sponsored, ongoing, single-arm, phase 2 study (ClinicalTrials.gov, NCT01698905), and is the longest running study which is investigating to stop Nilotinib treatment in deep molecular remission after switching from Imatinib (= second line Nilotinib).

126 patients in chronic phase who had received at least 3 years of total TKI therapy (at least 4 weeks of Imatinib, followed by at least 2 years of Nilotinib) prior to the study and had achieved a sustained MR4.5 (BCR-ABL ratio at least 0.0032%) on Nilotinib were analyzed. After enrollment on the study, patients continued Nilotinib treatment in a 1-year consolidation phase, and those who were continuously at MR4.5 or below were eligible to stop treatment. Patients with a loss of MR4 reinitiated Nilotinib treatment.

Of those 126 patients in ENESTop who were eligible to stop NIL, 57.9% maintained therapy-free remission at 48 weeks.

A subgroup analysis analyzed whether the reasons for switching from imatinib to Nilotinib prior to the study had any influence on the success rate in stopping treatment. These categories were relatedness to safety (intolerance), loss of response or treatment failure (resistance), and the physician’s clinical judgment (physician preference). There was no significant difference.

**ENESTfreedom study: Stopping first-line Nilotinib**

The Novartis-sponsored ENESTfreedom study enrolled patients who had Nilotinib as a first-line therapy for at least 2 years and who had achieved MR4.5 (BCR-ABL 0.0032%). They then continued on Nilotinib for at least one year. If no PCR in that year demonstrated a rise above MR4 (0.01%), patients stopped treatment. Patients who lost MMR (BCR-ABL above 0.1%) restarted Nilotinib treatment.

Amongst the patients that were analyzed in this report, at 48 weeks, 48.4% of patients who stopped hat to re-start therapy.

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Almost every fourth patient who stopped treatment suffered from musculoskeletal pain after stopping, while such a pain was only present in every seventh patient during treatment.

When looking at quality of life before, during and after stopping treatment, there was little difference. According to the study investigators, this may be related to patients already having a relatively high quality of life prior to stopping treatment, given that they had tolerated at least 2 years of Nilotinib prior to enrollment in the study. This suggests that the higher frequency of musculoskeletal pain in the stop phase did not substantially impact the quality of life of patients. Although many patients have fears about TFR, reported levels of anxiety/depression were similar before and after stopping treatment but decreased among patients who restarted treatment. (However we objected to these findings in our informal discussions with experts during ASH, as this is strong contrast to the experience we have in our daily work supporting CML patients).

**ENESTgoal: Switching from Imatinib to Nilotinib between MMR and MR4.5 and then stopping treatment**

The Novartis-sponsored ENESTgoal study enrolled patients who had a PCR below MMR (BCR-ABL ≤ 0.1%) and above MR4.5 (BCR-ABL1 ≤ 0.0032%) after at least one year of Imatinib treatment. They were then switched to Nilotinib when entering the study and were monitored for at least 2 years. If they had achieved MR4.5, they were treated for another 2 years on Nilotinib. If no PCR in those last 2 years was above MR4, (BCR-ABL ≤ 0.01%), patients stopped treatment. If patients lost MMR, they had to restart Nilotinib treatment.

Two thirds of patients who achieved MMR on Imatinib but not MR4.5 achieved MR4.5 after switching to Nilotinib on study. By the time of the analysis, 4 patients had entered the stopping phase, of which 3 had to restart Nilotinib after 70, 99, and 153 days; all regained MR4.5 with Nilotinib retreatment.

Adverse events reported in more than 10 patients during Nilotinib treatment included fatigue (22 patients = 37%), constipation (15 patients = 25%), rash (14 patients = 24%), headache (12 patients = 20%), abdominal pain and pruritus (11 patients = 19% each), and diarrhea, lipase increased, and weight decreased (10 patients each = 17%). The majority of events were grade 1/2. Serious Nilotinib related AEs were unstable angina, arterial stenosis, pericardial effusion, peripheral arterial occlusive disease, and transient ischemic attack (1 patient each). No deaths occurred on study.

**ENESTpath: Switching from Imatinib to Nilotinib when not in MR4, and then stopping treatment**

ENESTPath is Novartis-sponsored, randomized, phase 3 study which has enrolled 619 patients who had shown a complete cytogenetic response, but not MR4, after at least 24 months of treatment with Imatinib. After enrollment, patients were randomized to different study arms where different durations of consolidation therapy on Nilotinib were defined. Patients were assigned to receive 2x 300 mg Nilotinib per day for either 24 months (study arm 1) or 36 months (study arm 2). Patients with at least stable MR4 (BCR-ABL <0.01%) for at least 12 months entered the stopping phase.

The present analysis reports the results of the first 300 patients. No new safety concerns were observed during the 24 months of consolidation with Nilotinib. The majority of the adverse events were low grade, like pruritus (19%), hypercholesterolemia (14.0%), rash (10.7%), asthenia (10%), and arthralgia (10%). However, grade 3 or 4 cardiovascular events were experienced by 6.7% of patients including ischemic heart disease (4.7%), peripheral artery occlusive disease (1.7%), and ischemic cerebrovascular events (0.7%).

**DASASTOP: Stopping Dasatinib in deep molecular remission**

The phase-II DASFREE study is investigating to stop Dasatinib treatment in the first and second line setting. Patients had to be on Dasatinib for at least two years, and for at least 1 year in sustained MR4.5 (BCR-ABL <0.032%). The trigger for restarting Dasatinib was the loss of MMR. 71 patients were enrolled, of which 30 patients were evaluable at the 1 year mark. 37% of patients lost MMR after stopping treatment, but regained...
MMR after restarting treatment. Duration of treatment had a positive influence on the success of stopping. There were no progressions of the disease, and those who had molecular relapse had them early and could achieve responses again with Dasatinib.

After discontinuation, 5 patients had musculoskeletal adverse events; in 2 patients, these adverse events were attributed to the withdrawal from Dasatinib. Additional adverse events following discontinuation included hypertension (17%) and skin disorders (13%). (Shah, Abstract 1895)

**DESTINY Study: Stopping on stable MMR and dose reductions**

While most STOP studies investigate stopping TKI therapy after the achievement of at least a stable MR4 (BCR-ABL below 0.01%), the British De-Escalation and Stopping Therapy with Imatinib,Nilotinib or Sprycel (DESTINY) study investigates a decrease the TKI dose to half of the standard dose after achieving MMR (BCR-ABL 0.1%) for 12 months, followed by a complete stop of treatment. Key entry requirements included receiving the same TKI since diagnosis except if switched for intolerance against the initial treatment; TKI treatment for at least 3 years, and all PCR tests in the past 12 months with MMR (BCR-ABL 0.1%) or below. Patients had to restart full dose of the initial TKI treatment when losing MMR.

At study entry, 148 patients were receiving imatinib, 16 nilotinib and 10 dasatinib. After 12 months of half-dose therapy (imatinib 200mg daily, nilotinib 200mg twice daily or dasatinib 50mg daily), stopping failure was lower in patients with stable MR4 at entry (3 of 125 patients; 2.4%) than in those in MMR but not MR4 (9 of 49 patients; 18.4%). The median time to loss of MMR was shorter in those that had MMR at study entry than those in MR4. No progression to advanced phase or loss of cytogenetic response was seen. All 12 patients with loss of MMR regained MMR within 4 months after restart of full dose TKI. During the first 3 months of halved TKI dosing but not thereafter, the number of patient-reported common TKI side effects decreased. Interestingly, musculoskeletal symptoms were reported by 36 patients (21%) after stopping treatment – even though they were typically mild and transient, they may mean that TKI withdrawal symptoms observed in all STOP studies do not seem to be avoided by lowering the dose in an interim period before stopping treatment.

According to the investigators, in CML patients with stable MMR or better, decreasing TKI treatment to half the standard dose appears safe, and is associated with improvement in TKI related side effects. The authors think that many patients with stable responses may be overtreated. However, the DESTINY results also demonstrate that the reduction in dose may already lead to rising PCR, especially when the response has not been below MR4 for long. However, this is by no means an official recommendation on the safety or feasibility of dose reductions – further larger studies are needed to prove the safety of reducing TKIs dosing. (Clark/Copland, Abstract 938)

**Second TKI discontinuation in CML Patients that failed first discontinuation and subsequently Regained Deep Molecular Response after TKI Re-Challenge**

While several studies have demonstrated that TKIs could be safely discontinued in those patients previously treated with imatinib (STIM, TWISTER, EUROSKI) and more recently with nilotinib and dasatinib (STOP 2G-TKI). However, the question remains whether the ~50% of patients that failed to stop treatment can make a second attempt to discontinue.

68 patients were included in this study. All patients were treated initially with imatinib and 16% of patients switched to nilotinib (6/11) or to dasatinib (5/11) for intolerance/resistance reasons prior to the first TKI discontinuation. The median time on TKI prior to the first discontinuation was 63 months, the median duration of first deep molecular response was 35 months. All patients in this study failed stopping treatment (in median after 2.5 months) and restarted treatment in median for 31 months (range: 9-72 months) before the second attempt of discontinuation. 30 of 68 patients (44%) patients remained treatment-free after a median follow-up of 21.5 months (1-106). Interestingly, the longer time it took the patients to get into Deep molecular response in the first attempt to stop was associated with a significantly lower chance to stop successfully in the 2nd discontinuation.
The investigators conclude that TKIs could safely and successfully be discontinued a second time in CML patients despite a failure of the first stop attempt, so no “chance lost forever”.

Summary

Seeing the significant number of stop trials presented at ASH, but also seeing the number of unanswered questions in terms of prognostic factors, long-term monitoring, it is obvious that CML experts do not yet agree on general recommendations on the right procedure and standards to stop TKIs treatment for CML patients. However, given there not many ongoing stop studies today that are still recruiting patients, while stopping outside of trials is becoming clinical practice by many doctors, there is a clear need for such guidelines. On one hand, stopping alongside the strict protocols of current trials seems to be safe, as we have yet seen any reports of progressions of patients who stopped and then lost their molecular response. On the other hand, EURO-SKI shows that relapses can occur very late even after 3 years and more, requires a very careful, strict and continuous quality PCR monitoring.

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