ASH 2017- personal report, impressions and summary

Written by Sharf Giora- CML Advocates Network

ASH 2017 is the 10 th ASH conference I am attending in a raw, and I am being asked many times why do I like this conference and travel such a long distance to attend it every year.

The main reason that I, as a patients representative, leave home and travel to ASH is to hear and learn about the last innovations in treatment of blood cancers, and bring these news to patients in my country and across the globe, to empower them with knowledge, and mainly hope. that research in the various diseases is ongoing and if they are in a need for a new treatment, maybe it is just around the corner.

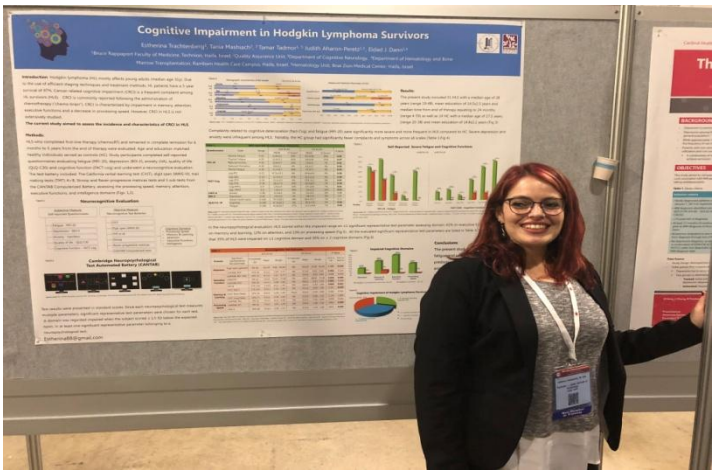
Giora and Nadav, a board member of Flute of Light at ASH 2017

The second reason why I go to ASH, which is not less important, is that this is the best place and opportunity to meet in a short time all the stakeholders that I am working with, like Drs and scientists from Israel and the globe, Pharma representatives from medical and patients relations, and other patients advocates, and to discuss with all of them how to continue and strengthen our collaboration.

The ASH meeting which takes place at the beginning of December each year, is the most important Hematology scientific meeting in the world, and it brings together about 30,000 Hematologists, researchers, clinical development leaders and also few dozen patients advocates. This is the place where the latest news about clinical trials results, and new treatments and directions are published for the first time. The conference is Huge and consists of thousands of sessions and presentations. It always impresses me to see the thousands

of Drs Running from one session to another in a very big conference center, where getting from one side to the other can take 15-20 minutes of walking. This year the conference took place in Southern part of the USA, Atlanta, but due to extremely stormy weather with 3 days of snow, the city was taken by surprise and the feeling was we are in Northern Canada. The airport was closed for a couple of days which prevented from some of the participants to arrive as planned.

The conference program is built from 3 main types of sessions. The first one is the Educational session in each disease area where the 3 main important topics are presented. The second are the oral presentations where 6 important abstracts are presented for 15 minutes each, on topics carefully chosen by the conference committee, and the last one is the Poster sessions where each day hundreds of researchers are presenting a poster on their work according to disease type.



Israeli researcher presenting their poster

One of my main takeaway massages from ASH was, not for the first time, that Medicine is not Math, and there are different opinions and approaches among the experts on various topics. There isn't always right or wrong. I saw it in the discussion about TFR, where some experts say that MR4 is enough to stop CML treatment and others claim that MR4.5 is required. Another example was after Dr Delphine Rea presented their observational study on reducing Nilotinib dose and changing to once daily regiment, (discussed below), and other experts were very much against this concept claiming it is even dangerous for patients. We as patient's representative can only stand and listen to all sides and try to understand the logic behind, before we make up our mind.

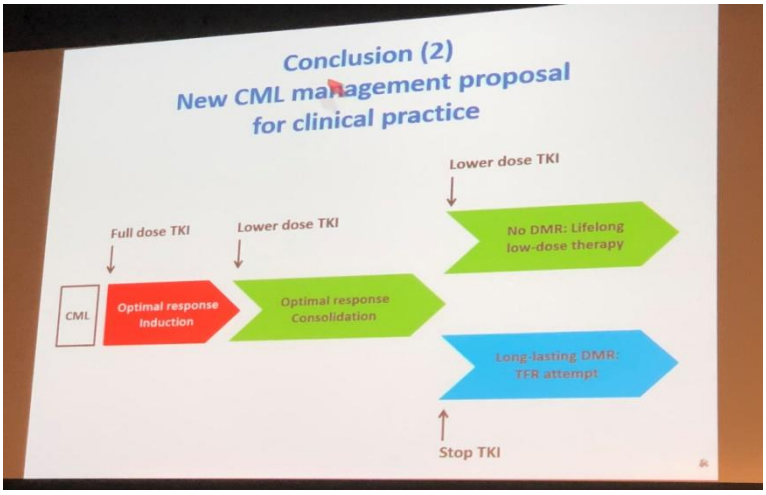
Here are some of the most important CML topics and news I have gathered from presentations and posters at ASH 2017.

Nilo-Red real life observational study- Molecular responses of CML patients after being switched from twice daily NIlotinib to once daily reduced dose- presented by Dr Delphine Rea, France

The standard dose for newly diagnosed CML patients treated with Nilotinib is twice daily 300 Mg and in 2 ed line it is twice daily 400 mg. Dose reduction is recommended only for patients with significant side effects. Since patients taking Nilotinib need to fast 2 hours before and 1 hour after taking the drug, this makes it quite difficult for the patient to adhere to treatment. The goal of this observational study was to check if patients will maintain their MMR after switching to a more convenient reduced dose and only once daily regimen. The study was done in 2 centers in Paris and Bordeaux and included 82 patients who were switched to once daily, reduced dose of Nilotinib, mainly 450 Mg. The median follow up time for the whole cohort since dose reduction was 25 months (0-73). 71 patients have follow up of at least 12 months and none of them experienced disease progression. 2 patients lost MMR after 4 and 6 months and continued to take the reduced dose, and regained their MMR spontaneously. In most patients molecular responses continued to improve after the dose reduction and switch to once daily dosing. 15 patients stopped treatment of Nilotinib after the dose reduction, and after 19 months only 3 lost their MMR and restarted treatment.

Dr Rea concludes that switching CML patients who achieved optimal molecular responses on twice daily dosing, to a reduced dose once a day is feasible. The anti Leukemic efficacy of the reduced dose is maintained and molecular responses continue to improve for most patients. This study paves the way for additional studies aiming at more convenient regimen of Nilotinib for patients, and avoiding over treatment with 2 ed generation TKI.

At the end Dr Rea presented a new possible way to treat newly diagnosed CML patients. Start with full dose TKI to achieve optimal response induction. Then lower the TKI dose for optimal response consolidation. Patients who don’t achieve DMR continue for life low dose and those who achieve DMR attempt TFR.



New CML management proposal by Dr Delphine Rea

GS note- As I mentioned above this is only an observational study from real life and not a planned comparative clinical trial, and the data is not enough at this point to base dose lowering decisions. Patients must consult their Drs before taking any action in regards to changing treatment does.

PF-114 – new 3 ed generation TKI of BCR-ABL

Dr Jorge Cortes from MD Anderson presented data on a new compound in clinical trial, with similar activity and structure like Ponatinib. The compound was designed to avoid inhibition of numerous off-target Kinases and thus avoid life threatening side effects. In a Phase 1 trial 24 heavily pre-treated patients were recruited out of which 11 had the T315I mutation. The compound exhibits anti-leukemia activity in this difficult patients population including the ones with the T315I mutation. The side effects profile seems to be safe with only one patient developing grade 3 rash. Unlike Ponatinib, no cardiovascular events have been observed. A Phase 2 multi center international study is planned for 2018.

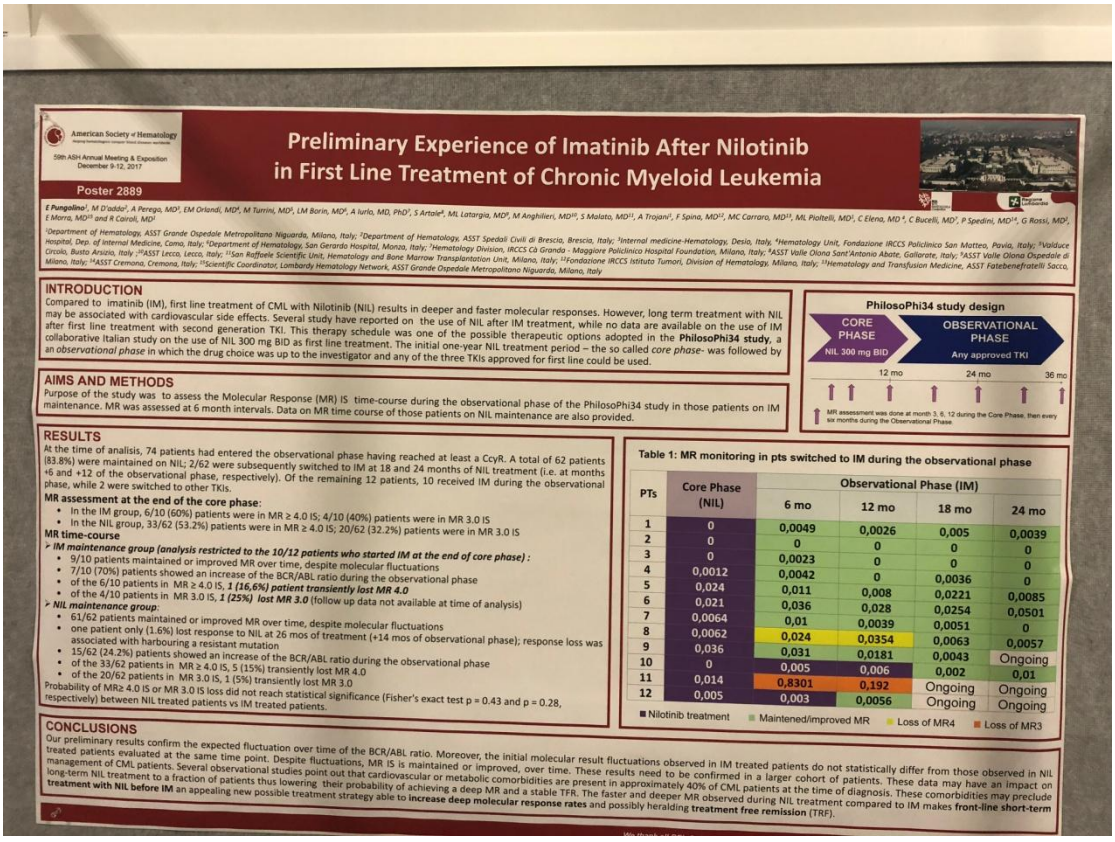
Bosutinib Vs Imatinib for newly Diagnosed CML – the BEFORE Trial- 18 months follow up- presented by Dr Carlo Gambacorti

Dr Gambacorti from Italy presented this 2 arms study- in one arm 246 patients received Bosutinib as first line treatment and in the comparative arm 241 patients received Imatinib. Bosutinib showed higher efficacy than Imatinib and after 18 months follow up, 57% of patients on Bosutinib achieved MMR compared to 48% on Imatinib. The better responses were also observed for MR4 and MR4.5. Achieving a PCR of lower than 10 % after 3 months from treatment initiation, is associated with better long term outcome. In this trial 75 % of the patients on Bosutinib achieved this goal compared to only 57% on Imatinib. Dr Gambacorti concludes that Bosutinib is a good first line treatment option for newly diagnosed CML patients.

GS comment- following this study the FDA has approved on 20.12.2017 Bosutinib as a first line treatment for newly diagnosed CML patients. We now have, at least in the US, 4 options for 1 st line treatment- Imatinib, Nilotinib, Dasatinib and Bosutinib.

Preliminary experience of Imatinib after Nilotinib in first line treatment of CML

This study of a French group was presented at the CML poster session on Sunday. The study included 74 patients who started Nilotinib as first line treatment and achieved a full Cytogenetic response. 10 patients were switched to Imatinib for comparison with the rest of the patients who were left on Nilotinib. The preliminary results indicate that there is no substantial difference in maintaining the response between the patients who stayed on Nilotinib and those switched to Imatinib, and in both groups the molecular response continued to improve. Since about 40% of newly diagnosed CML patients suffer from metabolic and cardiovascular co morbidities, a long term Nilotinib treatment might be an issue for them. The deeper and faster response achieved on Nilotinib as first line compared to Imatinib, makes the option of giving short term Nilotinib induction treatment, reaching a good molecular response and then switching to maintenance Imatinib treatment, an attractive option for this group of patients and will also allow a future possibility of stopping treatment.



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Preliminary Experience of Imatinib After Nilotinib in First Line Treatment of Chronic Myeloid Leukemia

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INTRODUCTION

Compared to imatinib (IM), first line treatment of CML with Nilotinib (NIL) results in deeper and faster molecular responses. However, long term treatment with NIL may be associated with cardiovascular side effects. Several study have reported on the use of NIL after IM treatment, while no data are available on the use of IM after first line treatment with second generation TKI. This therapy schedule was one of the possible therapeutic options adopted in the **PhilosoPhi34 study**, a collaborative Italian study on the use of NIL 300 mg BID as first line treatment. The initial one-year NIL treatment period – the so called *core phase*- was followed by an *observational phase* in which the drug choice was up to the investigator and any of the three TKIs approved for first line could be used.

AIMS AND METHODS

Purpose of the study was to assess the Molecular Response (MR) IS time-course during the observational phase of the PhilosoPhi34 study in those patients on IM maintenance. MR was assessed at 6 month intervals. Data on MR time course of those patients on NIL maintenance are also provided.

PhilosoPhi34 study design

MR assessment was done at month 3, 6, 12 during the Core Phase, then every six months during the Observational Phase

RESULTS

At the time of analisis, 74 patients had entered the observational phase having reached at least a CcyR. A total of 62 patients (83.8%) were maintained on NIL; 2/62 were subsequently switched to IM at 18 and 24 months of NIL treatment (i.e. at months +6 and +12 of the observational phase, respectively). Of the remaining 12 patients, 10 received IM during the observational phase, while 2 were switched to other TKIs.

MR assessment at the end of the core phase:

- In the IM group, 6/10 (60%) patients were in MR ≥ 4.0 IS; 4/10 (40%) patients were in MR 3.0 IS
- In the NIL group, 33/62 (53.2%) patients were in MR ≥ 4.0 IS; 20/62 (32.2%) patients were in MR 3.0 IS

MR time-course

- ***IM maintenance group (analysis restricted to the 10/12 patients who started IM at the end of core phase)*:**
  - 9/10 patients maintained or improved MR over time, despite molecular fluctuations
  - 7/10 (70%) patients showed an increase of the BCR/ABL ratio during the observational phase
  - of the 6/10 patients in MR ≥ 4.0 IS, ***1 (16,6%) patient transiently lost MR 4.0***
  - of the 4/10 patients in MR 3.0 IS, ***1 (25%) lost MR 3.0*** (follow up data not available at time of analysis)
- ***NIL maintenance group***:
  - 61/62 patients maintained or improved MR over time, despite molecular fluctuations
  - one patient only (1.6%) lost response to NIL at 26 mos of treatment (+14 mos of observational phase); response loss was associated with harbouring a resistant mutation
  - 15/62 (24.2%) patients showed an increase of the BCR/ABL ratio during the observational phase
  - of the 33/62 patients in MR ≥ 4.0 IS, 5 (15%) transiently lost MR 4.0
  - of the 20/62 patients in MR 3.0 IS, 1 (5%) transiently lost MR 3.0

Probability of MR≥ 4.0 IS or MR 3.0 IS loss did not reach statistical significance (Fisher's exact test p = 0.43 and p = 0.28, respectively) between NIL treated patients vs IM treated patients.

Table 1: MR monitoring in pts switched to IM during the observational phase

PTs	Core Phase (NIL)	Observational Phase (IM) 6 mo	12 mo	18 mo	24 mo
1	0	0,0049	0,0026	0,005	0,0039
2	0	0	0	0	0
3	0	0,0023	0	0	0
4	0,0012	0,0042	0	0,0036	0
5	0,024	0,011	0,008	0,0221	0,0085
6	0,021	0,036	0,028	0,0254	0,0501
7	0,0064	0,01	0,0039	0,0051	0
8	0,0062	0,024	0,0354	0,0063	0,0057
9	0,036	0,031	0,0181	0,0043	Ongoing
10	0	0,005	0,006	0,002	0,01
11	0,014	0,8301	0,192	Ongoing	Ongoing
12	0,005	0,003	0,0056	Ongoing	Ongoing

■ Nilotinib treatment ■ Maintened/improved MR ■ Loss of MR4 ■ Loss of MR3

CONCLUSIONS

Our preliminary results confirm the expected fluctuation over time of the BCR/ABL ratio. Moreover, the initial molecular result fluctuations observed in IM treated patients do not statistically differ from those observed in NIL treated patients evaluated at the same time point. Despite fluctuations, MR IS is maintained or improved, over time. These results need to be confirmed in a larger cohort of patients. These data may have an impact on management of CML patients. Several observational studies point out that cardiovascular or metabolic comorbidities are present in approximately 40% of CML patients at the time of diagnosis. These comorbidities may preclude long-term NIL treatment to a fraction of patients thus lowering their probability of achieving a deep MR and a stable TFR. The faster and deeper MR observed during NIL treatment compared to IM makes **front-line short-term treatment with NIL before IM** an appealing new possible treatment strategy able to **increase deep molecular response rates** and possibly heralding **treatment free remission** (TRF).