Chronic Myeloid Leukemia Data at ASH 2021: A Podcast on Patient Unmet Needs and Later-Line Treatment Developments

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PODCAST TRANSCRIPT

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LA: Hi everyone and welcome to the Adis rapid plus podcast series. Today we will be focusing on chronic myeloid leukaemia and the key data presented at the ASH 2021 American Society of Hematology Conference. Joining us today is Dr. Massimo Breccia from the Department of Translational and Precision Medicine at the University of Rome. Thank you so much for

being here and for sharing your insights with us today. Massimo will be taking us through the top highlights of the CML (chronic myeloid leukemia) data from the ASH 2021 Conference, whilst also giving specific focus to patient unmet needs and later-line therapies for the disease.

LA: So, Massimo, there's a lot of important data this year but before we cover that, could you maybe talk us through what the main unmet needs are for patients living with CML?

MB: Thank you for your question. So unmet needs for CML patients who failed at least two lines of treatment are still a matter of discussion. Sequential use of tyrosine kinase inhibitors (TKIs) is associated with a decreased probability of response and worse overall survival. A second line of treatment with a second-generation TKI rescued about 45–50% of patients. We also have to consider that all available TKIs have off-target effects that can lead to long-term safety issues and about 20% of patients discontinued their treatment due to adverse events.

LA: Right so if sequential use of TKIs is associated with poorer treatment response, as you say, are there any factors contributing to these patients becoming clinically resistant to these TKIs?

MB: Yes, sequential treatment induces the emergence of new mutations (for example, T315I or compound mutations). The frequency

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of T315I mutation was reported ranging between 3% and 15%. And as you know, currently the unique available option is ponatinib and allogeneic stem cell transplant. This latter procedure has been suggested by international guidelines in patients with poor response to a frontline second-generation TKI followed by ponatinib, or the emergence of mutant clones poorly responsive to available TKIs, or in case of intolerance to multiple TKIs or with inadequate recovery of normal hematopoiesis [1].

LA: It's clear then that novel therapy options for clinically resistant patients are essential. So with this in mind, what new developments have actually been reported for third-line treatment in CML at ASH 2021?

MB: So asciminib, for example, is the first example of [an] allosteric TKI active on [the] myristic site of ABL. It has been recently approved by the FDA based on the results of the randomized ASCEMBL trial that tested the drug at the dose of 40 mg BID versus bosutinib at the starting dose of 500 mg in patients in third line.

The results of this trial were updated at 48 weeks of treatment at the last ASH meeting so the cumulative incidence of major molecular response (MMR) was still in favour of asciminib (33.2%) compared to bosutinib (18.6%); and the MR4 and MR4.5 rates were 14.0% and 9.6% with asciminib and 6.6% and 2.6% with bosutinib, respectively. The most common adverse events leading to treatment discontinuation included thrombocytopenia (3.2%) and neutropenia (2.6%) in the asciminib arm and indeed increased alanine aminotransferase (5.3%) and neutropenia (3.9%) in the bosutinib arm [2].

Also compassionate use of this drug was activated all over the world and first data presented at the ASH meeting. Thirty-nine patients from the Russian group received asciminib for at least 3 months were reported. The median age was 54 years and 23 were in chronic phase, with 59% of patients that were mutated and 31% were T315I mutated. More than 60% of these patients were heavily pre-treated with more than four lines of therapy and 44% received previously ponatinib. So 32% of them achieved a complete cytogenetic response and 34% an MMR. And patients who started

asciminib with a low residual disease burden achieved optimal responses [3].

LA: Were similar results found elsewhere with asciminib?

MB: Yes, also the Spanish experience was reported. Forty-nine patients received the drug for a median time of 11.6 months. The median age was 64 years and 48 were in chronic phase. Again, more than 30% were mutated and 20% were T315I mutated. More than 90% in this experience previously received more than three TKIs and 36% received ponatinib. More than 40% of these patients achieved and/or maintained a complete cytogenetic response and 21% MMR, with fatigue, joint pain and nausea that were the most common reported side effects [4].

LA: Well thank you for that. So, other TKIs are still in fairly early phases; could you maybe talk us through some of the data presented for these?

MB: Yeah, another TKI is vobociclib, a third-generation TKI with limited off-target effects, actually tested in a phase 1 study. Fifty-two patients were enrolled, 41 in a dose escalation and 11 in the dose expansion part. Thirty-one patients were resistant and 46% received more than four TKIs, with 22 patients pre-treated with ponatinib and 20 patients mutated at baseline. So 42 patients were evaluable for response and 24 patients achieved and/or maintained a complete cytogenetic response, while 15 patients achieved an MMR. Most common side effects included thrombocytopenia in 33% of patients, cough in 19%, anaemia and diarrhoea in 17%, with only ten patients that presented cardiovascular treatment-emergent adverse events [5] but only one seems to be related to the drug.

The Chinese group updated the results of another TKI, olverembatinib, previously known as HQP1351. A phase 1 study enrolled 101 patients, 86 in chronic phase and 15 in accelerated phase. Again, more than 80% of these patients received previously two lines of treatment and 62% harboured the T315I mutation. Overall, 66% of patients achieved a complete cytogenetic response, 53% an MMR. In the setting of T315I mutated patients, 78% achieved a complete cytogenetic response and 71% a major

molecular response. The most common side effects reported in the phase 1 study were thrombocytopenia in 77% of patients and skin hyperpigmentation in 86% [6].

Another two phase 2 studies were also updated for this drug: both enrolled T315I mutated patients but ponatinib-naïve. Of 41 patients in chronic phase, 32 of them completed 12 cycles and 56% of them achieved an MMR. Again, the most common side effects were thrombocytopenia in 70% of cases and skin hyperpigmentation in 56%. Twenty-three patients were enrolled in accelerated phase, 14 completed 12 cycles and 39% of patients achieved an MMR. Even in accelerated phase, thrombocytopenia and skin pigmentations were reported in 73% and 69% of patients, respectively. In advanced phases of disease were also reported metabolic side effects such as proteinuria, hypocalcaemia and hypertriglyceridemia in 56% of patients [7].

PF-114 is the other drug, a fourth-generation TKI based on the scaffold of ponatinib. The Russian group updated the results of a phase 1 dose-escalation study. The aim was to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity. Fifty-one patients were enrolled, 46 in chronic phase, 16 patients T315I mutated. Twenty-two percent of patients achieved a complete cytogenetic response and 15.6% a major molecular response. But the MTD was determined at 600 mg due to the occurrence of grade 3 skin psoriasis-like alterations. No cardiovascular side effects were reported nor ankle-brachial index deviations during the study [8].

LA: That's a brilliant overview of early phase but has anything been presented in perhaps later phases from other trials?

MB: Yeah, the final analysis of the phase 4 BYOND study was detailed. The study showed the management of bosutinib in patients beyond the second line of treatment at the starting dose of 500 mg/day and with the primary endpoint of a confirmed major cytogenetic response at 1 year. Of 163 patients enrolled, 48% still receive the treatment after a median follow-up of 47.8 months. About 26% of patients discontinued due to the adverse events and, in fact, the median dose intensity

was 300 mg/day with more than 70% of patients that required a dose reduction. The complete cytogenetic response rate, considering patients who achieved or maintained the response, was 81%. The major molecular response rate was 71.8% with an overall survival of 88%. Only two patients died [from] the disease [9].

LA: It's really interesting then to see the adverse event data being reported at all of these trials, especially considering their implications on things such as treatment discontinuation. In that respect, has dose optimisation been reported in any other major trials?

MB: Yes, dose optimization was reported for ponatinib in the OPTIC trial. Patients in chronic phase in third or subsequent lines of treatment were initially randomized to three different doses of ponatinib (45, 30 or 15 mg) but with a possible de-escalation to 15 mg, if started at an increased dose of 45 or 30 mg after the achievement of the primary endpoint (that is less than 1% *BCR/ABL1* ratio at 12 months). The starting dose of 45 mg and the subsequent de-escalation to 15 mg was associated to the maximum benefit in terms of efficacy not only in the setting of T315I mutated patients but also with other mutations or in patients who started with a lack of a complete hematologic response. During the last ASH meeting, a subanalysis of the OPTIC trial was presented with response rate according to the baseline *BCR/ABL1* level and mutation status. At baseline, 84.1% of patients had a very high disease burden (more than 10% *BCR-ABL1*^{IS} ratio); nearly 24% had a T315I mutation and 17.0% had a mutation different from T315I, with nearly 58% without mutations. Patients with T315I mutation had the highest primary endpoint (so 60% by 3 years) with the 45 mg compared with the other cohorts. Patients with more than 10% of ratio baseline achieved a clinical benefit if started with 45 mg/day [10].

And the efficacy outcomes were generally comparable or better in the OPTIC trial when compared with the previous PACE trial, including the achievement of less than 1% *BCR-ABL1*^{IS} response by 24 months. In the PACE trial, 52%; in the OPTIC trial, 56%; even according to the 2-year progression-free survival

Table 1 Differences among possible agents to use in third line

	Kinase activity	Site of action	Recommended dose	Activity on T315I mutation	IC ₅₀
Ponatinib	BCR/ABL1 PDGFR α VEGFR2 FGFR1 Src	ATP site	45 mg/day (with reduction to 15 mg after achieving < 1% BCR/ABL transcript)	Yes	0.37 nM
Asciminib	BCR/ABL1	Myristolic site	40 mg BID	Yes (but recommended dose of 200 mg BID)	0.25 nM
Vodobotinib	BCR/ABL1	ATP site	174 mg QD	No	7 nM
Olverembatinib	Pan-BCR/ABL1	ATP site	40 mg QD	Yes	0.34 nM

(68% in PACE vs 80% in the OPTIC trial) and 2-year overall survival (86% in the PACE trial; 91% in the OPTIC trial). So dose reductions due to the adverse events occurred in 82% of patients in the PACE and 46% in the OPTIC trial and a 60% reduction in relative risk for arterial occlusive events in OPTIC trial vs PACE trial was observed [11].

LA: So it's really encouraging then to see all of these developments for potential later-line CML treatments coming out. But what does this mean in terms of patient outcomes moving forwards? Are these adverse events you mentioned, for example, a cause for concern or are the options in general looking quite promising?

MB: Considering the subset of patients resistant or intolerant to several treatments, the results of these new agents seem promising, but I believe it is too early to define an algorithm of treatment, even according to the type of resistance and type of mutations (Table 1). Most of the drugs are very selective and the toxicity seems to be limited to few events with a reduced rate of grade 3/4. And until now off-target effects were not reported.

LA: That's a really fantastic summary of the key data that's come out of ASH 2021. Thank you so much, Massimo, for joining us again and I really hope this will be helpful and interesting for all of our listeners!

MB: Thank you, thank you very much.

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