First-line combination of dasatinib and Peg-IFNα2b in chronic phase CML

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First-line combination of pegylated interferon α2a (Peg-IFNα2a) and first generation TKI imatinib has been reported to significantly increase the rate of deep molecular response over imatinib alone in chronic phase CML patients (SPIRIT and NordCML002 trials).[1,2] We now also know that second generation TKIs, such as dasatinib, induce faster and deeper molecular response when compared to imatinib (DASISION).[3] A phase II trial using second generation nilotinib and Peg-IFNα2a has recently reported high rates of deep molecular response (with MR4.5 being 17% at month 12).[4] Thus, researchers were eager to see if an optimal combination of dasatinib and Peg-IFNα2b might increase the proportion of patients who reach deep molecular response, which is the prerequisite for treatment free remission. At the annual meeting of the American Society of Hematology (ASH) in December 2015, two research groups presented the results of their studies evaluating the efficacy and safety of this combination in the first line treatment of CP-CML patients.

Results of the multicentre phase II study conducted by the French Intergroup of CML (Fi-LMC) were presented by *Roy et al*. In this trial, 81 newly diagnosed Ph+ CP-CML patients aged between 18 and 65 years were enrolled and started dasatinib therapy (100 mg qd). At 3 months, patients were eligible to add Peg-IFNα2b to dasatinib if met the following criteria: absolute neutrophil count (ANC) ≥ 1,5 x 10^9/L, platelets ≥ 100 x 10^9/L and lymphocytes ≤ 4 x 10^9/L. Those who did not, were to continue dasatinib alone. The primary endpoint was the cumulative rate of molecular response 4.5log at 12 months. Secondary endpoints included cytogenetic and molecular responses at several time points and safety.[5]

Of the 81 patients enrolled, 79 were included in the final analysis (1 died in CML-related haemorrhage, 1 patient was excluded due to a screening failure [masked Ph]). The median age in the study was 48 years, 56% were male and respectively 44%, 39% and 17% had a low, intermediate and high Sokal score. Based on the above mentioned criteria, 61 patients were eligible to combine dasatinib with Peg-IFNα2b at the dose of 30 μg/week after 3 months.[5]

In August 2015, all patients completed the 12-month follow-up time. At that time 79% of patients who had started combined treatment were still receiving both drugs (N=48), 9 patients were receiving dasatinib alone and 3 discontinued both drugs. Among those who were not eligible to receive combined treatment, but only received dasatinib, 72% were still on therapy at 12 months.

In patients with combined treatment, haematological adverse events (AEs) from month 3 to 12 included neutropenia (altogether 84%, of which Gr 3 was 30% and Gr 4 was 2%), anemia (11%, all Gr 1/2) and thrombocytopenia (6%, all Gr 1/2). Non-hematological AEs were essentially of low grade (only 5 Gr 3/4 events occurred). The most common AEs were general symptoms (21%), gastro-intestinal disorders (14%), nervous system related symptoms (10%), skin lesions (9%), infections (9%) and musculo-skeletal pain (8%).[5]

In the intention-to-treat analysis of patients receiving combined therapy (N=61), $MR^{4.5}$ rates were 10%, 15% and 31% at month 6, 9 and 12, respectively (*Figure 1*). As for the whole population (N=79), the $MR^{4.5}$ rate was found to be 25% at 12 months. The primary endpoint, consisting of the cumulative incidence of $MR^{4.5}$ by 12 months, was 36% in the Peg-IFNα2b eligible patients.[5]

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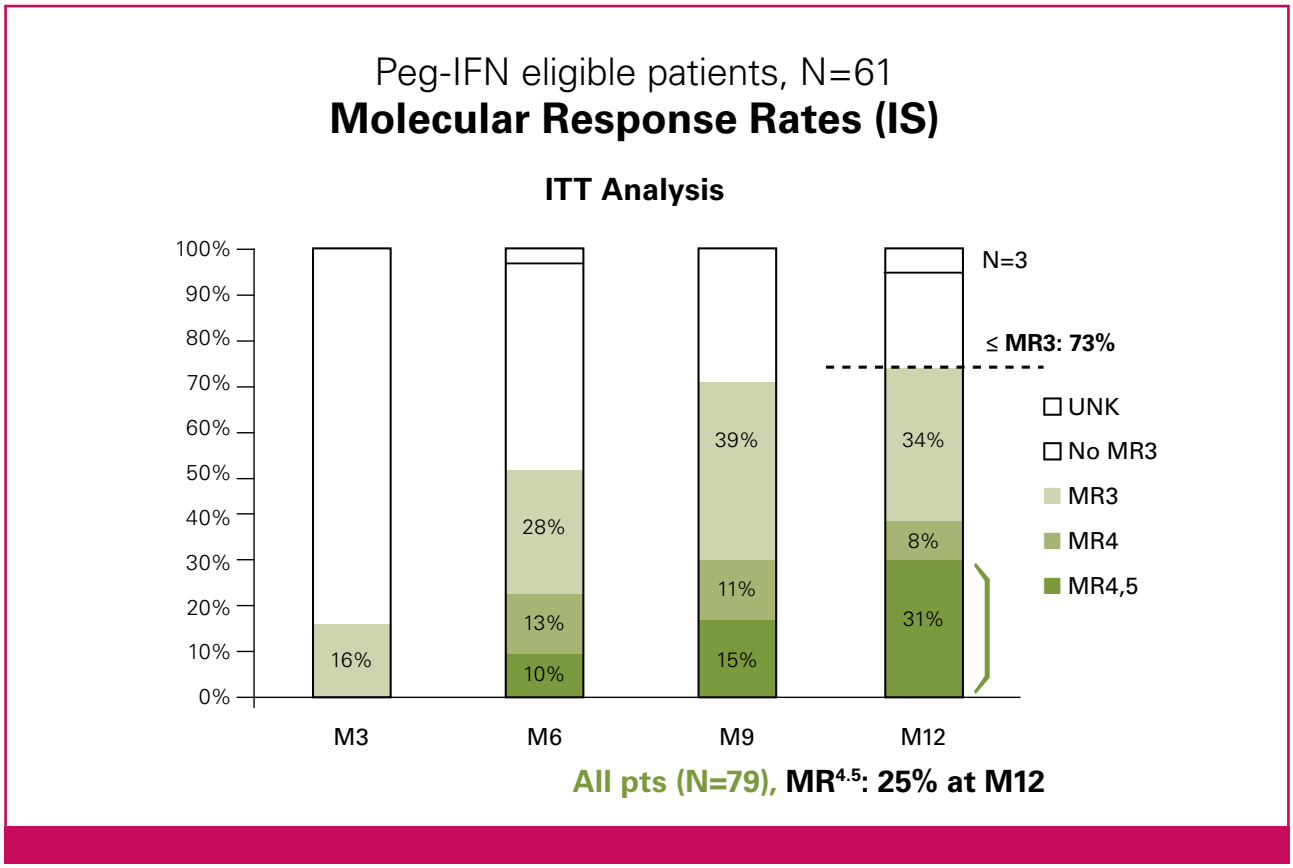

Figure 1. Molecular response rates with combined dasatinib plus Peg-IFNα2b therapy.[5]

The second trial (NordCML007), presented by *Hjorth-Hansen et al.*, also evaluated the efficacy and the safety of a dasatinib – Peg-IFNα2b combination, but had a different study design. In total, 40 newly diagnosed CP-CML patients were enrolled and treated with dasatinib (100 mg qd) for three months, and thereafter added 15 μg/week Peg-IFNα2b from month 3 to 6, followed by 25 μg/week till month 15. Of note, this IFN dose is lower than the dose used in SPIRIT and NordCML002. The rationale for this was that a lower dose could benefit the patient adherence. The primary endpoint of the trial was the rate of major molecular response (MMR) at month 12, while secondary objectives included cytogenetic and molecular response rates at certain time points, and safety. The study population was in average 48 years old and 25% of patients had a high Sokal risk.[6]

During the study, combined treatment was well tolerated with expected dasatinib and Peg IFNα2b related side effects. As for hematologic AEs, Gr 3/4 anemia, neutropenia and thrombocytopenia occurred in 1, 8 and 10 patients, respectively. Most common non-hematological AEs were gastrointestinal disorders, skin reactions, infections, depression/anxiety, flu-like symptoms and musculoskeletal pain, with altogether 8 Gr 3/4 events. Pleural effusion was reported in one case only.[6]

One patient discontinued dasatinib at 3 months due to headaches at. Two patients were not eligible to start IFN, one of them later moved away and stopped dasatinib as well. There was one more patient who discontinued dasatinib due to poor efficacy at 9 months. Earlier this patient had to stop Peg IFNα2b as well, due to haematological AEs. All in all: 3 patients stopped dasatinib and 6 discontinued Peg IFNα2b (both true for one patient). The reasons for discontinuing IFN included arrhythmia, anaphylaxis, flu-like symptoms and haematological toxicity. At month 12, 82% of patients (38/31) were still on combined therapy. Throughout the study, 47% of patients needed dasatinib dose interruptions, or reductions and in 52% of patients the dose needed to be adapted for Peg IFNα2b. This resulted in a mean dose of 91 mg/day for dasatinib and 18 μg/week for Peg-IFNα2b. Despite the fact that only 35% of patients could take the assigned dosing perfectly, response rates reached high levels.[6]

The early response at 3 months was very similar to what was reported in the dasatinib arm of the DASISION

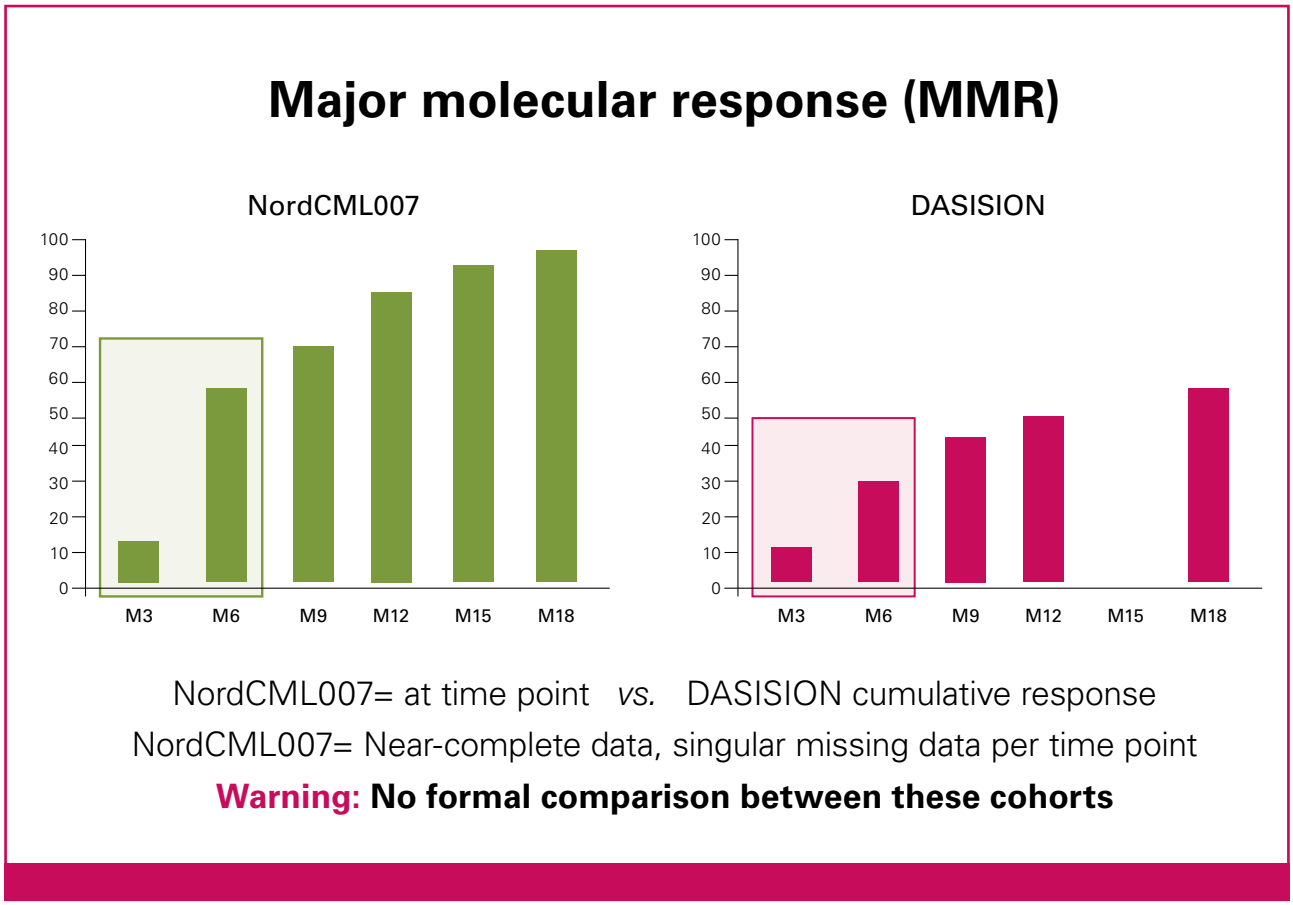

Figure 2. MMR at certain time points in the NordCML007 and DASISION trials.[6]

study, with an MMR rate of 10%. However, in the present trial, a remarkable increase was observed in the MMR rate at month 6, which was also reflected by the observation of deep responses (*Figure 2*). The primary endpoint, MMR at 12 months, was 82% as compared to 46% in the DASISION trial. During the trial, no progression was observed. At month 6, only 11% of patients had >35% Ph+MF or >10% BCR-ABL levels. At month 12, one patient failed CCyR and two more patients failed to reach a BCR-ABL transcript level below 1%.[6]

Conclusions

The results of the two presented trials were very concordant. Combined dasatinib and Peg IFNα2b therapy resulted in a high proportion of deep molecular response and meanwhile demonstrated a manageable (not negligible, though) toxicity profile in CP-CML patients. No new types of AEs were observed, and the rate of pleural effusions was reassuringly low. It is worth noting that around 80% of the patients were still on therapy at 12 months, and almost one third reached an MR[4.5]. These are promising results in an attempt to further increase the rate of treatment free remission, and warrant a randomized comparison of dasatinib with or without Peg IFNα2b.

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