Radotinib in the treatment of chronic phase chronic myeloid leukemia patients

We read with interest the article by Kim *et al.*[1] in which the authors provided the efficacy and safety data of radotinib (IY5511HCL), an oral BCR-ABL1-specific 2nd generation tyrosine kinase inhibitor (TKI), in 77 patients with chronic phase-chronic myeloid leukemia (CP-CML) in a multinational phase II trial. After a median duration of radotinib exposure of approximately 12 months and a median follow up of 23.4 months, the complete cytogenetic response (CCyR) rate was 47% by 12 months, and the overall and progression-free survival rates at 12 months were 96.1% and 86.3%, respectively. Thrombocytopenia, hepatotoxicity, hyperbilirubinemia and hyperglycemia were the most common hematologic and non-hematologic adverse events (AEs). The authors implied that radotinib was effective and relatively well tolerated in patients with CP-CML, and CCyR rates were higher in patients without BCR-ABL1 mutations.[1]

Although most of the CP-CML patients do well under imatinib, some of them develop resistance, and BCR-ABL1 kinase domain mutations are detected in approximately 50% of patients with treatment failure and progression.[2] Second generation TKIs (dasatinib and nilotinib) are used in patients who have intolerance and resistance to imatinib.[3,4] In the study cohort, CCyR rate at 12 months was 47%, and the authors compared their results with dasatinib and nilotinib. They concluded that the efficacy of the study drug was comparable, and even favorable, to those observed with dasatinib[3] and nilotinib.[4] But these 2 studies which the authors mentioned have shorter follow-up durations than the present study, and when the other TKIs were used as a second-line treatment at longer follow-up periods the CCyR rates were similar to those of the present study: dasatinib 45%,[5] nilotinib 44%,[6] and bosutinib 41%[7]. As expected, the response rates were higher in imatinib intolerant cases than in those who were resistant,[1] which has already been shown in the second-line dasatinib and nilotinib trials.[5,6] The authors concluded that in 5 patients with a BCR-ABL1 mutation which was less sensitive to nilotinib or dasatinib, 2 had gained major CyR. But there seems to be a problem in terms of efficacy of radotinib in patients with a mutated clone (n=14) because only 3 of these patients have responded to the study drug. Moreover, during follow up, 6 additional patients were found to harbor new mutations, including T315I. This is a major challenge for clinicians given that nearly half the patients with imatinib resistance have BCR-ABL1 mutations.

Dasatinib and nilotinib are generally well tolerated but they do have AEs that appear in the short term or after a longer follow up.[8] Their familiarity with these AEs allows physicians caring for CML patients to recognize and manage them.[9] Radotinib was used at an initial dose of 2x400 mg/daily in the present study, and the most common grade 3-4 hematologic AE was thrombocytopenia, which was observed in 25% of the patients.[1] Grade 1-2 hepatotoxicity was present in more than 70% of the patients, and the percentages of grade 3-4 hyperbilirubinemia and hyperglycemia were 23.4% and 19.5%, respectively. During follow up, 71.4% of the patients had a dose interruption, and a dose reduction was needed in 53 (68.8%). These numbers are quite high, which might suggest that the starting dose of radotinib should be lower. Furthermore, 42.9% of the patients discontinued treatment before 12 months, of which 18 patients (23.4%) stopped therapy due to AEs and abnormal laboratory results. This is also a high number after a relatively short duration of follow up, and although the authors concluded that the AEs were generally transient and manageable, nearly one-fourth of the patients stopped treatment with the study drug due to AEs within 12 months of treatment.

In conclusion, although radotinib seems to be a promising alternative treatment, more data should be collected regarding its efficacy and safety, and prospective randomized trials with longer follow-up periods are needed to strengthen the efficacy and safety data of this 2nd generation TKI.

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