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Abstract:
Ponatinib is a potent oral tyrosine kinase inhibitor of unmutated and mutated BCR-ABL, including BCR-ABL with the tyrosine kinase inhibitor-refractory threonine-to-isoleucine mutation at position 315 (T315I). We conducted a phase 2 trial of ponatinib in patients with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL). We enrolled 449 heavily pretreated patients who had CML or Ph-positive ALL with resistance to or unacceptable side effects from dasatinib or nilotinib or who had the BCR-ABL T315I mutation. Ponatinib was administered at an initial dose of 45 mg once daily. The median follow-up was 15 months. Among 267 patients with chronic-phase CML, 56% had a major cytogenetic response (51% of patients with resistance to or unacceptable side effects from dasatinib or nilotinib and 70% of patients with the T315I mutation), 46% had a complete cytogenetic response (40% and 66% in the two subgroups, respectively), and 34% had a major molecular response (27% and 56% in the two subgroups, respectively). Responses were observed regardless of the baseline BCR-ABL kinase domain mutation status and were durable; the estimated rate of a sustained major cytogenetic response of at least 12 months was 91%. No single BCR-ABL mutation conferring resistance to ponatinib was detected. Among 83 patients with accelerated-phase CML, 55% had a major hematologic response and 39% had a major cytogenetic response. Among 62 patients with blast-phase CML, 31% had a major hematologic response and 23% had a major cytogenetic response. Among 32 patients with Ph-positive ALL, 41% had a major hematologic response and 47% had a major cytogenetic response. Common adverse events were thrombocytopenia (in 37% of patients), rash (in 34%), dry skin (in 32%), and abdominal pain (in 22%). Serious arterial thrombotic events were observed in 9% of patients; these events were considered to be treatment-related in 3%. A total of 12% of patients discontinued treatment because of an adverse event. Ponatinib had significant antileukemic activity across categories of disease stage and mutation status. (Funded by Ariad Pharmaceuticals and others; PACE ClinicalTrials.gov number, NCT01207440 .).