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614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Olverembatinib (HQP1351) Combined with Chemotherapy Is an Effective and Safe Treatment in Patients with Philadelphia Chromosome-Positive (Ph +) Acute Lymphoblastic Leukemia (ALL) and Chronic Myeloid Leukemia in Lymphoid Blast Phase (CML-LBP) That Failed TKI-Based Regimens

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Background The prognosis of relapsed or refractory (R/R) Philadelphia Chromosome-Positive (Ph+) acute lymphoblastic leukemia (ALL) and TKI-resistant chronic myeloid leukemia in lymphoid blast phase (CML-LBP) remains poor, with lower rates of complete remission (CR) and shorter durations of response. Olverembatinib is a novel third-generation tyrosine kinase inhibitor (TKI) that has been demonstrated to effectively target a wide range of BCR::ABL1 kinase mutations, especially T315I, in patients with CML in the chronic or accelerated phase resistant to either imatinib or second-generation TKIs. However, data on olverembatinib-based regimens in R/R Ph+ ALL and CML-LBP are limited. Here, we report the efficacy and safety of olverembatinib, combined with chemotherapy, in patients with Ph+ ALL or CML-LBP that failed prior TKI-based therapies.
Methods A retrospective study was conducted in adults with Ph + ALL or CML-LBP who failed imatinib- or second-generation TKI-based chemotherapy and subsequently received olverembatinib-based chemotherapy. Per NCCN 2023 guidelines: refractory disease was defined as CR not achieved at the end of induction; relapsed disease, reappearance of blasts in the blood or bone marrow (> 5%) or any extramedullary site after CR; molecular resistance, persistent or rising BCR::ABL1 transcript (> 1-log)
by real-time quantitative polymerase chain reaction (RT-qPCR); and complete molecular response (CMR), BCR::ABL1 transcript < 0.01% by RT-qPCR. The primary endpoints of this study were CR rates in R/R patients and CMR rates in molecular-resistant patients.
Results From February 2022 to May 2023, 31 patients were included in this study, including 24 (77%) with TKI-based chemotherapy-failed Ph + ALL; 7 (23%) with TKI-resistant CML-LBP; 15 (48%) with R/R disease; and 16 (52%) with molecular-resistant disease. A total of 17 (57%) patients were male, and the median (range; IQR) age was 46 (20-72; 30-64) years. Among 30 patients screened for BCR::ABL1 kinase domain mutations before administration of olverembatinib, 6 (19%) had no mutations; 15 (48%) had T315I; and 9 (29%) had other mutations, including E255K (n = 2), G250E(n = 2), D241E (n = 1), Y253H (n = 1), F317L (n = 1), F359C(n = 1), and Y253Fplus M351T (n = 1).
The 15 R/R patients (11, Ph + ALL; 4, CML-BP) received olverembatinib 30 or 40 mg on alternate days combined with VP (vindesine 4 mg once per week for 4 weeks and prednisone 1 mg/kg for 3 weeks and tapered at the fourth). A total of 13 (86%) patients achieved CR after 4-week induction therapy. At a median (IQR) follow-up of 8 (4-13) months, 5 patients received allogeneic transplantation in CR, and were alive in CMR. A total of 8 patients received olverembatinib-based consolidation chemotherapy of either VP (n = 4) or hyper-CVAD (n = 4) after achieving CR. Six patients relapsed, of whom 4 died, and 1 remained in CMR. The 1-year relapse-free survival (RFS) and 1-year survival rates were 52% (95% CI, 21-83) and 68% (95% CI, 37-98), respectively.

Among the 16 patients with molecular resistance to TKI-based chemotherapy (imatinib [n = 4]; dasatinib [n = 9]; flumatinib [n = 3]), 2 received olverembatinib monotherapy, 7 olverembatinib plus VP, and 7 hyper-CVAD, of whom 8 received subsequent allogeneic transplantation. At a median (IQR) follow-up of 9 (5-11) months, 1 of the patients receiving olverembatinib monotherapy progressed to hematologic relapse and was switched to CAR T-cell therapy; the other patient did not achieve CMR and underwent transplantation. Of the 14 patients receiving olverembatinib plus chemotherapy, 7 (50%) achieved CMR and 3 (21.4%) progressed to relapse, of whom 1 had hematological relapse and 2 developed central nervous system leukemia (CNSL) with bone marrow remission. A total of 7 patients received allogeneic transplantation, of whom 3 achieved and 4 did not achieve CMR before transplantation. After transplantation, all the 7 patients were in CMR except one who developed CNSL. The 1-year RFS and survival rates were 67% (95% CI, 42-91) and 93% (95% CI, 79-100), respectively.
Among all patients, hematologic adverse events were readily manageable. Treatment-related nonhematologic severe adverse events were observed in 3 patients, including (each) stable angina pectoris, severe pneumonia, and fatal Klebsiella sepsis.
Conclusions Olverembatinib-based chemotherapy is effective and safe in patients with R/R and molecular resistant Ph $^{+}$ ALL or CML-LBP.

Disclosures No relevant conflicts of interest to declare.

OffLabel Disclosure: Olverembatinib is a novel third-generation tyrosine kinase inhibitor approved for the treatment of chronic phase or accelerated phase chronic myeloid leukemia harbouring T315I mutation. In this study, olverembatinib in combination with chemotherapy was given to adults with Philadelphia Chromosomeâ€"Positive Acute Lymphoblastic Leukemia and Chronic Myeloid Leukemia in Lymphoid Blast Phase who failed imatinib- or second-generation TKI-based chemotherapy.

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