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Should Ponatinib Be the Standard-of-Care Tyrosine Kinase Inhibitor in Ph+ ALL?

Elias Jabbour, MD
Professor of Medicine
Department of Leukemia
MD Anderson Cancer Center
Houston, Texas

H&O How common is Philadelphia chromosome–positive (Ph+) acute lymphocytic leukemia (ALL)?

EJ The Ph+ form of ALL is characterized by the presence of the t(9;22) translocation and rearrangement of *BCR::ABL1*. The Ph+ form is rare in pediatric patients with ALL and becomes more common with age, affecting up to half of those patients with ALL who are older than 60 to 65 years. As a result, approximately 30% of adults with ALL have the t(9;22) translocation and/or rearrangement of *BCR::ABL1*.

H&O What is the standard treatment for patients with Ph+ ALL?

EJ The historical standard of care for patients with Ph+ ALL was induction chemotherapy followed by an allogeneic stem cell transplant (allo-SCT). After tyrosine kinase inhibitors (TKIs) became available, the standard of care for induction therapy became chemotherapy plus the first-generation TKI imatinib or the second-generation TKI dasatinib (Sprycel, Bristol Myers Squibb), followed by allo-SCT. Maintenance therapy with a TKI was used after transplant.

Outcomes with imatinib and dasatinib are good but not optimal, for 2 reasons. The first is the acquisition of certain mutations, including the T315I mutation. Most patients in whom imatinib or dasatinib fails acquire this mutation, which explains why relapse occurs down the road. The second reason is that these agents do not induce deep molecular responses, which are needed for an optimal outcome.

Fortunately, the third-generation TKI ponatinib (Iclusig, Takeda) addresses these 2 shortcomings of earlier-generation TKIs.[1,2] First, it suppresses emergence of the T315I mutation. Second, it is a more potent agent than imatinib and dasatinib that produces deeper responses, which correlate with better outcomes. Our team designed a phase 2 study in 2010 that looked at chemotherapy with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD) plus ponatinib. The ponatinib dose was 45 mg/d during the 2 weeks of the induction cycle, and the drug was administered continuously at 45 mg/d for cycle 2 onward. After 2 deaths from vascular events, which are a known adverse event of ponatinib, we amended the study to keep the 45-mg/d dosage for the first 2 weeks but reduce it for cycle 2 onward to 30 mg/d at first and 15 mg/d after the achievement of a complete molecular response (CMR). We now have a median follow-up of more than 6 years for 86 patients.[3] The 6-year survival rate is 75% and the CMR rate is 85%, with 74% of these patients achieving a CMR within 3 months.

The study protocol stated that whoever had a donor option should receive a transplant, and 20% of the patients went on to transplant. In performing a landmark analysis at 6 months, the patients who did not receive a subsequent allo-SCT had better outcomes. In summary, we showed that ponatinib not only improves responses and outcomes but also may negate the role of transplant.

Later, a group of researchers in Europe began the phase 2 GIMEMA study, in which a corticosteroid and ponatinib at 45 mg/d were combined in 44 patients with Ph+ ALL who were unfit for intensive chemotherapy and transplant.[4] The study showed a complete hematologic response rate of 86% and a CMR rate of 41% at 24 weeks. Fatal treatment-emergent adverse events occurred in 5 patients, however, suggesting that the ponatinib dose should be reduced in this population. This is relevant to our finding that by adjusting the dose of ponatinib from 45 to 30 or even 15 mg/d, we can deliver safe regimens. We know that the adverse events seen in these studies were dose-dependent.

Furthermore, researchers from the Spanish PETHEMA group launched the phase 2 PONALFIL trial, in which 30 younger patients with Ph+ ALL received chemotherapy plus ponatinib at 30 mg/d.[5] A total of 26 of these patients went on to receive an allo-SCT. The overall survival rate at 3 years was 96%, which was reassuring.

In 2018, we launched the phase 3 PhALLCON trial.[6] In this trial, we randomly assigned 245 patients with Ph+ ALL in a 2:1 ratio to receive reduced-intensity chemotherapy plus either ponatinib at 30 mg/d or imatinib at 600 mg/day. The primary endpoint was measurable residual disease (MRD)–negative complete response (CR), which was defined as a 10^{-4} reduction of the baseline transcript plus a CR for 4 weeks. At a median follow-up of 18 to 20 months, twice as many patients in the ponatinib group as in the imatinib group met the primary endpoint: 35% vs 17%, respectively. This finding led to the March 2024 approval of ponatinib plus chemotherapy as frontline therapy in Ph+ ALL. As a result, ponatinib should now be considered the standard of care for patients with Ph+ ALL.

H&O What agents have been combined with ponatinib for use in Ph+ ALL?

EJ In 2014, at the same time we were investigating ponatinib, the immunotherapy agent blinatumomab (Blincyto, Amgen) was approved for use in Ph+ ALL after it was shown to be superior to chemotherapy. This finding led to the idea that we might be able to combine the 2 agents for a chemotherapy-free approach, which we are examining in a phase 2 study that has enrolled approximately 75 patients with Ph+ ALL.[7,8] The initial dose of ponatinib is 30 mg/d, which we reduce to 15 mg/d as soon as a CMR is obtained. Results from our first 60 patients have shown that at a median follow-up of 24 months, the CMR rate by reverse transcriptase–polymerase chain reaction (PCR) was 83% and the rate of MRD negativity was 98%. The estimated 3-year overall survival rate was 91%, and just 2 patients received a subsequent allo-SCT. What we have shown is that we can deliver a chemotherapy-free approach to most patients by using blinatumomab and ponatinib, which is revolutionary in the treatment of ALL.

ALL has gone from being one of the deadliest leukemias to one of the most curable. We have seen a dramatic increase in 5- to 10-year survival, which was less than 10% before allo-SCT was available, increased to 40% after the introduction of transplants, increased further to 50% to 70% with chemotherapy plus a TKI, and is now 90% without chemotherapy. This represents a major evolution.

We are exploring the use of the novel TKI olverembatinib in this setting, as well as a newer, subcutaneous formulation of blinatumomab.

H&O Could you discuss the problem of central nervous system (CNS) relapse?

EJ We used to give 8 rounds of intrathecal chemotherapy to patients with Ph+ ALL, which we later changed to 12 rounds of intrathecal chemotherapy. That change led to a significant decrease in the rate of CNS relapse. We fully omit chemotherapy in our chemotherapy-free regimen. Neither blinatumomab nor ponatinib crosses the blood-brain barrier; however, we have seen 4 CNS relapses so far in our study of blinatumomab and ponatinib. In response, we have amended our study to give 15 rounds of intrathecal chemotherapy. Patients with a high white blood cell count at diagnosis are at high risk and may benefit from systemic chemotherapy in addition to the 15 rounds of intrathecal chemotherapy.

H&O Could you discuss the use of MRD-negative CR as a study endpoint?

EJ A meta-analysis showed that MRD negativity correlates with improved long-term outcomes,[9] so the US Food and Drug Administration agreed to consider MRD-negative CR as an acceptable endpoint for drug approval in the PhALLCON trial. We are currently using MRD negativity as a major factor in our treatment

decision. Now, the question is how best to measure MRD. We used to measure MRD by using PCR to detect the *BCR::ABL1* transcript. However, this transcript is not eradicated in some patients because multilineage cells can harbor *BCR::ABL1*,[10,11] making the test nonspecific. Since then, we have moved to next-generation sequencing (NGS), which is both highly sensitive and highly specific. NGS can detect 1 cell among 1 million; it is also specific for lymphoblasts because it can track the receptor of immunoglobulin on a B cell. The disconcordance between PCR for *BCR::ABL1* and NGS for the ABL receptor is 25%; these are patients who do not have disease but whose PCR test result is positive. Their outcome is similar whether they are PCR-positive or PCR-negative as long as they are negative for MRD by NGS. As a result, we should base our treatment decisions—especially decisions about transplant—more on NGS than on PCR.

H&O What is the current role of transplant in our treatment algorithm for Ph+ ALL?

EJ If the patient has a CMR, I omit the allo-SCT. Allo-SCT should be offered when the patient is MRD-positive by NGS. We should continue to explore the role of chimeric antigen receptor T-cell therapy in the research setting, but in a standard-of-care setting, transplant should still be offered to patients who remain MRD-positive after every effort has been made to convert them to MRD-negative status before transplant. Transplants also should be offered to patients who have had lymphoblast crisis evolving from CML. TKIs should be used for at least 2 to 3 years after the transplant.

If we do not perform a transplant, the current protocol is lifetime administration of a TKI. We are currently exploring the idea of treatment discontinuation after patients have been in CMR for at least 4 to 5 years by NGS. This approach should be tested in a prospective trial.

H&O Could you discuss the safety of ponatinib?

EJ Ponatinib is associated with vascular events, mainly at higher doses. The PhALLCON trial showed that the rate of arterial and venous occlusive events was no higher in patients who received ponatinib with dose adjustment than in those who received imatinib therapy. Therefore, the key to succeed is to adjust the dose of ponatinib as soon as a deep molecular response is obtained. Of course, we still need to control any risk factors for vascular events, such as hypertension and dyslipidemia.

H&O What is next for the treatment of patients with Ph+ ALL?

EJ As good as ponatinib is, we still have room for improvement. That is why at MD Anderson we are exploring the use of the novel TKI olverembatinib in this setting,[12] as well as a newer, subcutaneous formulation of blinatumomab,[13] with the goal of ultimately being able to cure the patient and discontinue the TKI.

Disclosures

Dr Jabbour has received research grants from and consulted for Amgen, Adaptive Biotechnology, Ascentage Pharma, Bristol Myers Squibb, Pfizer, Takeda, Novartis, AbbVie, Genentech, Astex Pharmaceuticals, TargetRX, Terns Pharmaceuticals, and Johnson & Johnson.

References

1. Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol*. 2015;16(15):1547-1555.
2. Jabbour E, Short NJ, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. *Lancet Haematol*. 2018;5(12):e618-e627.
3. Kantarjian H, Short NJ, Jain N, et al. Frontline combination of ponatinib and hyper-CVAD in Philadelphia chromosome-positive acute lymphoblastic leukemia: 80-months follow-up results. *Am J Hematol*. 2023;98(3):493-501.
4. Martinelli G, Papayannidis C, Piciocchi A, et al. INCB84344-201: ponatinib and steroids in frontline therapy for unfit patients with Ph+ acute lymphoblastic leukemia. *Blood Adv*. 2022;6(6):1742-1753.
5. Ribera JM, García-Calduch O, Ribera J, et al. Ponatinib, chemotherapy, and transplant in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood Adv*. 2022;6(18):5395-5402.
6. Jabbour E, Kantarjian HM, Aldoss I, et al. Ponatinib vs imatinib in frontline Philadelphia chromosome-positive acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2024;331(21):1814-1823.
7. Kantarjian H, Short NJ, Haddad FG, et al. Results of the simultaneous combination of ponatinib and blinatumomab in Philadelphia chromosome-positive ALL [published online July 19, 2024]. *J Clin Oncol*. doi:10.1200/JCO.24.00272.
8. Jabbour E, Short NJ, Jain N, et al. Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: a US, single-centre, single-arm, phase 2 trial. *Lancet Haematol*. 2023;10(1):e24-e34.
9. Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. *JAMA Oncol*. 2017;3(7):e170580.
10. Short NJ, Jabbour E, Macaron W, et al. Ultrasensitive NGS MRD assessment in Ph+ ALL: prognostic impact and correlation with RT-PCR for BCR::ABL1. *Am J Hematol*. 2023;98(8):1196-1203.
11. Kim R, Chalandon Y, Rousselot P, et al. Significance of measurable residual disease in adult Philadelphia chromosome-positive ALL: a GRAAPH-2014 study. *J Clin Oncol*. 2024;42(26):3140-3150.
12. Jabbour E, Kantarjian HM, Koller PB, et al. Update of olverembatinib (HQP1351) overcoming ponatinib and/or asciminib resistance in patients (pts) with heavily pretreated/refractory chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) [ASH abstract 1798]. *Blood*. 2023;142(suppl 1).
13. Jabbour E, Zugmaier G, Agrawal V, et al. Single agent subcutaneous blinatumomab for advanced acute lymphoblastic leukemia. *Am J Hematol*. 2024;99(4):586-595.