Optimizing Frontline Therapy in Ph+ ALL: The Role of Ponatinib and Beyond

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The treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) has witnessed major progress over the past two decades. The routine integration of BCR::ABL1 tyrosine kinase inhibitors (TKIs) into frontline regimens represented the first major breakthrough in the treatment of this disease. Several TKIs are available for the treatment of Ph+ ALL, including imatinib (first-generation TKI), dasatinib, nilotinib and bosutinib (second-generation TKIs), and ponatinib (third-generation TKI). Of note, ponatinib is active against the gatekeeper T315I *ABL1* kinase domain mutation, which is the dominant mechanism of relapse in patients with Ph+ ALL treated with first- or second-generation TKIs, providing a strong rationale for its use in the frontline setting. The randomized PhALLCON study showed superior measurable residual disease (MRD) remission rates and event-free survival with chemotherapy plus ponatinib versus chemotherapy plus imatinib, without significant differences in toxicity, leading to ponatinib being widely adopted as a standard of care in newly diagnosed Ph+ ALL. While there are not yet randomized data comparing ponatinib-based regimens with second-generation TKIs, several retrospective analyses have suggested superior outcomes with ponatinib. Overall, retrospective and prospective data suggest that the use of more potent TKIs such as ponatinib in the frontline setting leads to deeper and more durable responses, less reliance of allogeneic stem cell transplantation (SCT) in first remission, and better long-term survival.

While historically all fit patients with Ph+ ALL were recommended to receive intensive chemotherapy and allogeneic SCT, chemotherapy-free and SCT-free regimens are now being explored. For example, long-term survival >80% has been observed with the combination of dasatinib and blinatumomab in adults with newly diagnosed Ph+ ALL. The combination of ponatinib and blinatumomab is also highly effective, leading to high rates of deep response and promising survival rates, without need for SCT for most patients. While highly effective, these chemotherapy-free regimens are associated with a higher relative risk of central nervous system (CNS) relapses, and novel strategies to prevent these relapses are being explored. Strategies to further optimize these regimens currently being explored. These include: the use of more doses of intrathecal chemotherapy, integration of high-dose chemotherapy for patients at higher risk of relapse (e.g. those with hyperleukocytosis at presentation), and CD19 chimeric antigen receptor (CAR) T-cell consolidation.

The evolution of therapy for Ph+ ALL is particularly remarkable considering that Ph+ ALL was once considered to be one of the most aggressive forms of leukemia, necessitating treatment with intensive chemotherapy and consolidative allogeneic SCT. However, now chemotherapy-free regimens may perhaps be even more effective than traditional approaches using an intensive chemotherapy backbone.