

Imatinib: Not Just Kids' Stuff for Children with Ph+ ALL

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Is bigger better? Yes, when it comes to duration of imatinib in treatment of children with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), as discussed in yesterday's Plenary talk by Kirk Schultz, MD.

As the most common leukemia in children, ALL has an overall event-free survival (EFS) reaching as high as 80 percent. Starting in the 1960s, the change from single to multi-agent chemotherapy and the addition of CNS prophylaxis, using intrathecal chemotherapy and cranial irradiation, helped introduce the word "cure" to the world of ALL. Nevertheless, poor outcomes still predominate in very high-risk groups such as Ph+ ALL. In fact, Ph+ ALL has been associated with a four-year EFS of only 20 percent.

The tyrosine kinase inhibitor imatinib has proven to be a magic bullet to induce durable responses in patients with chronic myelogenous leukemia (CML). Its success in adult patients with Ph+ ALL has been less impressive, and incorporation of imatinib into ALL regimens remains an area of active clinical investigation. Dr. Schultz presented results from the Children's Oncology Group cooperative study in which the investigators addressed the hypothesis that response in Ph+ pediatric ALL is dependent on the duration of imatinib exposure.

Imatinib was combined with high-dose chemotherapy. The patients were enrolled after induction therapy and were treated with two separate consolidation blocks. After the second consolidation block, the patients either received an allogeneic stem cell transplant followed by maintenance, if an appropriate donor was available, or two blocks of reinduction and intensification chemotherapy followed by maintenance. Imatinib was administered for 21 days per block and differed among four cohorts by days of imatinib exposure, based on the number of blocks when imatinib was given. Only a fifth cohort received continuous dosing of imatinib daily through all blocks. For all cohorts, if patients underwent stem cell transplant, imatinib was withheld during conditioning and transplant, and was resumed four to six months post-transplant as maintenance. Among the five cohorts, the duration ranged from 42 to 280 continuous days of imatinib exposure prior to maintenance. For example, cohort 1 received 42 days of imatinib during 2 blocks of intensification, while cohort 5 received 280 continuous days of imatinib through 2 blocks of consolidation and 2 blocks of reinduction and intensification.

Dr. Schultz found that minimal residual disease was significantly lower in the patients who received imatinib during the consolidation blocks. Two-year EFS significantly increased from 41.2 percent in patients receiving the shortest duration of imatinib to 84.7 percent in those receiving a full 280 days of imatinib. Follow-up of these dramatic results should reveal if a longer duration of imatinib translates into long-term EFS and overall survival.