

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## Advances in the Treatment of Philadelphia Chromosome–positive Acute Lymphoblastic Leukemia

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### **H&O** How is Philadelphia chromosome–positive acute lymphoblastic leukemia diagnosed?

**WS** The diagnosis of Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL) is made most quickly using reverse transcriptase polymerase chain reaction (RT-PCR). This assay looks for the fusion product of the chromosome translocation (ie, t[9;22]), which results in the *BCR-ABL* fusion gene. It is possible to detect the transcript, the BCR-ABL messenger RNA, using RT-PCR usually within 24–48 hours of receiving the sample. The diagnosis was classically made using cytogenetics, which requires a longer period of time to obtain results. Once it has been determined that the patient has either the BCR-ABL transcript or the Philadelphia chromosome by cytogenetics (or fluorescence in situ hybridization), the patient can be considered diagnosed with Ph+ ALL. This assessment should be part of the work-up of any new patient with precursor B phenotype ALL at the time of diagnosis. Ph+ ALL is more common in older patients, so the index of suspicion may be higher among the elderly, but all patients should undergo RT-PCR testing for the BCR-ABL transcript.

### **H&O** Historically, what was the prognosis for patients with Ph+ ALL?

**WS** The prognosis was traditionally poor for patients with Ph+ ALL. Virtually no adult patients (<5%) are

cured with standard chemotherapy. The median survival was 8–10 months in the absence of allogeneic stem cell transplantation, which is the only potentially curative therapy in this setting. In past series, the cure rate for this approach done in the first remission was reported at 30–50% or possibly higher; the patients in these series, however, tend to be young, well-selected patients. Because the disease is most common in patients over age 60, the curative potential of allogeneic stem cell transplantation has not been fully analyzed because relatively few elderly patients have undergone the procedure in a clinical-trial setting.

### **H&O** With the introduction of tyrosine kinase inhibitors, how has the prognosis changed?

**WS** In several studies, it has been documented that the addition of imatinib (Gleevec, Novartis), a tyrosine kinase inhibitor (TKI) of *BCR-ABL*, to frontline, induction therapy results in much higher rates of complete remission than conventional chemotherapy. In older adults with Ph+ ALL, imatinib has been administered alone or in combination with only low-dose steroids, and it has resulted in high rates of complete remission. These patients tend to be very ill at the time of presentation, so achieving complete remission with a well-tolerated therapy is remarkable. Moreover, the disease-free survival appears to be significantly longer with imatinib-based therapy than with standard chemotherapy. The Children's Oncology Group (COG) presented findings at the 2007 annual meeting of the American Society of Hematology (Study AALL0031) for the pediatric population with Ph+ ALL: it was demonstrated that when imatinib was administered at various points after induction therapy (but not as induction therapy), the earlier the agent was given and the higher the cumulative dose, the better the survival was. The pediatric patients went on to receive allogeneic stem cell transplantation from matched sibling donors when available, and the outcome with transplantation was better than historical controls (though with admittedly short follow-up). Interestingly, survival without transplantation appeared to be statistically equal to the survival seen with transplantation. Other series in adults, such as one from The University of Texas M. D. Anderson Cancer Center and others by researchers in Japan and Korea, show that patients achieve a higher rate of complete remission with

imatinib and that this agent can be used in postremission therapy. Furthermore, these patients, when transplanted, appear to have better survival than historical controls. It seems certain, therefore, that induction therapy with imatinib improves disease-free survival and possibly overall outcomes after allogeneic stem cell transplantation. Some studies have suggested that patients should continue with TKI-based therapy after transplantation, and studies, such as the COG Study AALL0031, have suggested that transplantation may be unnecessary for prolonged disease-free survival. However, the suggestion that transplantation can be avoided requires further evaluation. In my view, patients who are candidates for transplantation should still undergo the procedure.

Unfortunately, relapse remains a problem for patients who receive imatinib. The emergence of resistant clones is quite common in ALL as the cause of relapse. Central nervous system (CNS) relapses are common with imatinib, which does not penetrate the CNS. Aggressive CNS prophylaxis is therefore needed. In the pediatric population, relapse tends to occur much later than in the adult population. The disease-free survival is longer in children with Ph+ ALL, but overall outcomes remain to be determined.

### **H&O** Is research ongoing into agents that can be used in patients who relapse?

**WS** Yes. The next-generation TKIs, which overcome many of the mechanisms of resistance (eg, point mutations), are under investigation in frontline therapy. Dasatinib (Sprycel, Bristol-Myers Squibb) is a next-generation agent that can penetrate the CNS and overcome many of the point mutations, thereby further improving disease-free survival. CNS prophylaxis may still be needed, but if a more potent agent can be used up-front, the emergence of resistant clones may be avoided with prolonged therapy. Dasatinib has more than one target; in addition to *BCR-ABL*, it also targets Src tyrosine kinases. It is known that in ALL, there are multiple mechanisms of resistance and pathways of disease progression. If combination therapy with agents that target multiple kinases or monotherapy with a multityrosinase kinase inhibitor is used, perhaps even better outcomes will be achieved. This will be an avenue of research in the future. There are also other mechanisms of resistance that are being identified (eg, drug effector mechanisms), which may provide potential targets.

Researchers are also interested in understanding whether, in older adults, less chemotherapy could be used along with a more potent TKI. Furthermore, is it possible to treat older patients with lower-dose prolonged chemotherapy plus dasatinib in the absence of transplantation and achieve positive outcomes? Whether a TKI should be administered posttransplantation is another important research question, which some researchers are beginning to address.

### **H&O** In summary, is it fair to say that Ph+ ALL has gone from having a poor prognosis to having a relatively good prognosis?

**WS** The prognosis has improved for Ph+ ALL owing to therapy with targeted TKIs, which has improved outcomes. Of course, this disease is still quite serious, but the future is considerably brighter for ALL patients than it was prior to the introduction of TKIs. Great progress has been made, and I am optimistic for the future. Longer follow-up from the initial studies of imatinib in this setting is needed. It is understood that disease-free survival has been improved, but the effects on overall survival remain to be elucidated. Are patients cured? By prolonging the therapy with TKIs, is it possible to eradicate minimal residual disease and, then, eventually to cease therapy?

### **Suggested Readings**

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