Advances in the Management of Ph-positive ALL

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H&O What percentage of acute lymphocytic leukemia is Philadelphia chromosome–positive?

DH Philadelphia chromosome (Ph)–positive acute lymphocytic leukemia (ALL) accounts for approximately 25% of all adult ALL. The incidence of this subtype of ALL increases with age; according to data from the United States and Europe, over 50% of elderly patients with B-lineage ALL have Ph-positive disease.

H&O Historically, what have been the survival outcomes for this disease subtype?

DH Historically, Ph-positive disease was the subtype of ALL with the poorest prognosis. Patients with Ph-positive disease had a survival rate of 10% or less when treated with chemotherapy alone. By comparison, the cure rate among other ALL subgroups is approximately 40%, with some studies indicating even higher survival rates.

Ph-positive ALL has also been associated with a worse prognosis in children, although the survival rates are somewhat better than in adults—approximately 30%. However, the frequency of this subtype among children is very low, 3–4%.

H&O What were the initial attempts made to improve outcomes among patients with Ph-positive ALL?

DH Because the results with chemotherapy were so poor, the first step was to introduce stem cell transplantation. In most clinical trials, patients with Ph-positive ALL would receive stem cell transplantation after induction therapy. First the tumor load was reduced and patients achieved a so-called complete remission. The survival rate seen with this approach was approximately 40%.

These outcomes, achieved with allogeneic stem cell transplantation, were of course much better than what had been seen previously. In Europe, unrelated donors were also acceptable, and with this approach, approximately 70–80% of nonelderly Ph-positive ALL patients were undergoing transplantation.

Transplantation is possible only for younger patients. Elderly patients are not candidates for this approach. Considering that most patients with Ph-positive disease are elderly, an additional strategy was clearly needed.

H&O What was the next step?

DH After the successful use of a Bcr/Abl kinase inhibitor in the treatment of chronic myeloid leukemia, this treatment principle was transferred to the setting of Ph-positive ALL. The same fusion proteins, P190 and P210, are present in ALL, and so it was thought that the Bcr/Abl tyrosine kinase inhibitor imatinib (Gleevec, Novartis) would be effective in the treatment of adults with Ph-positive ALL.

H&O Could you describe the findings of studies evaluating imatinib in this setting?

DH Intensive chemotherapy plus imatinib achieves excellent results in the treatment of Ph-positive ALL. The hematologic complete response rate after chemotherapy induction was 60–70%; with the addition of imatinib,

this rate increased to 90% or higher. These findings were reported by several independent study groups. Another encouraging finding was that the improved complete response rate correlated with a dramatic decrease in the number of deaths during induction therapy.

This success has been the greatest change in adult ALL; what for decades was a poor prognostic factor has now become a positive prognostic factor.

H&O What was the next step after these initial findings?

DH The next step was to determine whether this strategy achieved not only a hematologic remission but also a molecular remission, with no malignant cells detectable by polymerase chain reaction, which can be used to detect the presence of the Bcr/Abl fusion protein. In all of the studies of imatinib in the treatment of Ph-positive ALL, the molecular remission rate was increased to approximately 50%.

Considering the benefit observed with stem cell transplantation, clinicians have been hesitant to exclude this treatment from the therapeutic strategy. Thus, patients are now receiving imatinib plus chemotherapy followed by stem cell transplantation. One of the major questions that now needs to be addressed is: if patients achieve a molecular remission, will they remain in remission if they forego transplantation? This question is currently being studied. One group has omitted stem cell transplantation from the treatment approach and has reported good results; however, this study was small and omitting transplantation cannot yet be considered evidence-based medicine.

H&O Have elderly patients, who are not candidates for transplantation, benefited from the use of imatinib?

DH The German ALL Study Group conducted a trial in which elderly patients received either conventional induction chemotherapy or 4 weeks of imatinib monotherapy. Patients who received imatinib achieved a complete response rate of 90%, compared with 50% among patients receiving chemotherapy. There were no deaths during induction with imatinib and patients required little or no hospitalization leading to improved quality of life; in addition, the side effects are much less toxic than those seen with chemotherapy.

However, elderly patients who respond to imatinib still show a higher rate of relapse, and investigators are exploring ways to preserve the initial success. A new European study is being planned to try to improve the outcomes among elderly patients after successful induction therapy.

H&O Are there other treatment approaches currently being considered for Ph-positive ALL?

DH Imatinib is also being studied in the pediatric setting. In addition, following the success of imatinib, new tyrosine kinase inhibitors are being developed. Dasatinib (Sprycel, Bristol-Myers Squibb) is being evaluating among patients with Ph-positive ALL who have become resistant to imatinib.

The resistance pattern in Ph-positive ALL is similar to that seen in CML; however, the rate of mutations at the time of diagnosis is apparently higher in Ph-positive ALL. In addition, the absolute rate of mutations seems to be higher at the time of relapse in the elderly Ph-positive ALL population.

H&O Why do some adults with Ph-positive ALL respond to therapy and others not?

DH Ph-positive ALL patients relapse as a result of the development of mutations. Among elderly patients, 70–80% of patients develop mutations that are resistant to imatinib. Some of these mutations are preexistent; patients have the clone that is already resistant to imatinib, or to other drugs, and clearly these patients will relapse.

Most likely, the future treatment of Ph-positive ALL will require not only measuring hematologic and molecular remission rates but also understanding how resistance develops and how it can be avoided.

Suggested Reading

Jabbour E, Cortes J, Kantarjian HM, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia and acute lymphocytic leukemia after BCR-ABL kinase mutation-related imatinib failure. *Blood*. 2006;108:1421-1423.

Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood*. 2004;103:4396-4407.

Hoelzer D, Goekbuget N, Ottmann OG. Targeted therapies in the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. *Semin Hematol*. 2002;39(4 suppl 3):32-37.

Wassmann B, Pfeifer H, Goekbuget N, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ALL). *Blood*. 2006;108:1469-1477.