EDITORIAL

Chemotherapy-free Treatment — A New Era in Acute Lymphoblastic Leukemia?

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In this issue of the *Journal*, Foà et al.[1] report on an innovative approach to treat acute lymphoblastic leukemia (ALL) involving the replacement of chemotherapy with targeted therapies, including dexamethasone, the tyrosine kinase inhibitor dasatinib, and the bispecific anti-CD3 and anti-CD19 antibody blinatumomab. This new regimen is feasible, active, and safe, with very low treatment-related mortality and promising overall and disease-free survival outcomes.

This is a change in the treatment approach. The use of intensive multiagent chemotherapy in children with ALL has led to a long-term cure in more than 90% of patients. However, the treatment that has led to this remarkable cure can be associated with long-term sequelae.[2] Until recently, this aggressive chemotherapeutic approach has been used in patients with ALL in all age groups, with various levels of success depending on patient age. Among adolescents and young adults up to 40 years of age, a high cure rate of 70% has been achieved.[3] Among adults, survival at 5 years or more is 50%, but among elderly patients, intensive chemotherapy has led to survival of less than 30%.[4] The major hazard of treatment is myelotoxicity leading to infection, which causes death in the induction and consolidation phase in 1 to 3% of children with ALL, increasing to 10% or more in adolescents and young adults, to 10 to 20% in adults, and to a much higher percentage in elderly patients. Thus, the search for less toxic treatment is important. In this trial of a chemotherapy-free induction and consolidation strategy, Foà and colleagues achieved the goal of fewer toxic effects, with only one induction-related death in 63 adult patients. This finding clearly showed the feasibility and safety of this approach.

The trial involved patients with Philadelphia chromosome (Ph)–positive ALL, the poorest prognostic subtype of ALL. In the era before tyrosine kinase inhibitors, the incidence of a complete response was 60 to 70%, overall survival among patients who received chemotherapy was 10%, and overall survival among patients who underwent allogeneic hematopoietic stem-cell transplantation was 30%. With the first-generation tyrosine kinase inhibitor imatinib (Gleevec), the incidence of a complete response increased to 90% or higher, the incidence of *BCR-ABL*–negative disease increased from 5% to 50%, and 5-to-10-year overall survival increased from 50% to 70%.[4] After a complete response, half the patients underwent allogeneic stem-cell transplantation, with a treatment-related mortality of up to 20%. A remarkable finding in the trial conducted by Foà et al. is the very low nonrelapse mortality among patients who underwent transplantation during remission. In this group of 24 patients who had not received systemic chemotherapy before transplantation, only 1 patient died. Thus, damage from the toxicity of induction combination chemotherapy appears to place the patient at risk for toxic effects and death from subsequent stem-cell transplantation — a consequence that is avoided with targeted therapy.

In Ph-positive ALL, the majority of relapses are caused by the development of resistant mutations in the driving oncogene, particularly the *ABL1* mutation T315I. In a similar study[5] that involved low-intensity induction chemotherapy

and dasatinib as frontline therapy in elderly patients with Ph-positive ALL, the incidence of complete hematologic remission was also high (97%), but more than half the patients had a relapse. Three fourths of the 24 patients with a relapse had the T315I mutation. It has become clear that blinatumomab exerts its greatest beneficial effects in these patients. In a trial of blinatumomab in adults with ALL, approximately 80% of those with relapsed or refractory disease had a molecular remission, but the effect on overall survival was small.[6] In another trial involving patients with minimal residual disease (i.e., patients with complete hematologic remission who remained minimal residual disease–positive), a complete molecular response occurred in nearly 80%, with a significant improvement in outcome.[7] The most important finding was that blinatumomab eliminated the otherwise resistant *ABL1* mutations in the minimal residual disease–positive cells; this elimination was the major reason for the very low incidence of relapse.

In the phase 2 trial conducted by Foà and colleagues, chemotherapy-free induction and consolidation therapy with dasatinib and blinatumomab in patients with Ph-positive ALL was highly successful, with an overall survival of 95% and a disease-free survival of 88% at a median follow-up of 18 months. Several factors contributed to these outcomes, including the very low incidence of induction therapy–induced death, the high molecular response, the eradication of cells expressing *ABL1* mutations, and the low mortality after allogeneic transplantation. All these results were achieved with surprisingly few toxic effects.

This trial presents many questions. Will the excellent outcomes be preserved with longer follow-up? The answer is probably yes, given that the majority of relapses in ALL occur within the first 1.5 to 2.0 years after the initiation of treatment. Will there be a difference in long-term outcomes between patients who do not undergo transplantation and those who do? Will *ABL1* mutations, including T315I, emerge and will minimal residual disease recur with longer follow-up? Can this overall approach in Ph-positive ALL be used in patients with other subtypes of ALL, such as Ph-negative, B-lineage ALL or even T-cell ALL? If these promising trial results hold, chemotherapy-free induction without the immediate and long-term toxic effects of intensive chemotherapy regimens could also be used in adolescents and, finally, in children. These questions will need to be addressed with longer follow-up and large, prospective trials.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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