ADVANCES IN LLM

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

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Survival After Relapse in Childhood Acute Lymphoblastic Leukemia

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H&O Could you discuss the prognostic factors in childhood acute lymphoblastic leukemia (ALL)?

NS One of the most important prognostic factors in childhood ALL is the age of presentation. Patients who present between the ages of 1 and 10 years have the best prognosis, whereas infants tend to have a very poor prognosis. Improvements are being observed within the adolescent age group. The other main prognostic factor is the level of the patient's white blood count upon presentation. Patients with lower white blood counts, particularly less than 10,000/mm^3 in B precursor ALL, do much better than those with markedly elevated white blood counts, such as those around 100,000/mm^3. In many protocols, a white blood count of 50,000/mm^3 or more is considered a risk factor for relapse and will change the patient's risk stratification.

Cytogenetics can also play a role in prognosis, particularly if a patient's leukemia cells are t(9;22) Philadelphia chromosome–positive (Ph+). In the past, this subtype represented a very aggressive form of leukemia. Fortunately, that has changed somewhat with the development of tyrosine kinase inhibitors, such as imatinib mesylate (Gleevec, Novartis), which selectively inhibits the tyrosine kinase activity of the BCR-ABL oncoprotein resulting from the t(9;22) translocation. These patients are doing better when these medications have been combined with chemotherapy. With the use of imatinib, event-free survival (EFS) at 3 years was greater than twice the historical control for this group of patients.

Additionally, other cytogenetic abnormalities like hypodiploidy (<44 chromosomes) and rearrangements of the *MLL* gene (11q23) indicate poor prognosis. When one of these gene rearrangements or cytogenetic markers is found, one should consider stem cell transplant earlier in the course rather than later. Immunophenotype of the leukemia cells is important since patients with T-cell ALL who experience a relapse have a very poor prognosis.

H&O Why is survival after relapse poor, and what factors affect survival?

NS Currently, it is not known why survival after relapse is poor, except that relapsed leukemia tends to be more resistant and harder to get in remission. These patients can go back into remission, but they may not stay in remission for very long. We do know there are some contributing factors, particularly the length of time since the patient was diagnosed with leukemia or the length of time since completion of therapy. The Children's Oncology Group (COG) has classified 3 stages of relapse. Early relapse occurs less than 18 months from diagnosis. Intermediate relapse occurs 18 to 36 months after diagnosis. Late relapse occurs at least 36 months past diagnosis. It is better for the patient whose leukemia relapses if the

relapse occurs late rather than during therapy or right after completion of therapy.

The other factor that has a huge impact on survival is where the disease recurs. Relapse in the bone marrow carries a poorer prognosis than relapse in extramedullary sites (such as the central nervous system or testes), or even combined bone marrow relapses. In contrast, if the disease recurs in the central nervous system, the patient can be treated with additional chemotherapy and radiation that was not included in the initial treatment, which is beneficial.

It is not known why patients relapse. It may be because the leukemia cells develop drug resistance, but that is unlikely the only cause. Recent studies directed by Dr. Charles Mullighan have compared patients' cells at the time of relapse with cells obtained at the time of diagnosis. Several mutations acquired at relapse were detected in subclones at diagnosis. This finding suggests that the genetic alterations may confer resistance to therapy and that they are present throughout the course of treatment and then start to grow.

H&O What is the strongest predictor of relapse? What is the weakest? (Are there any diagnostic features specific to patients who relapse?)

NS Cytogenetics are important factors in patients who relapse. A patient who is Ph+ but goes into remission and then relapses has a very aggressive leukemia. Once immunophenotype T-cell patients relapse, it is difficult for them to get back into remission or to be cured. In some studies, males are less likely than females to achieve remission. If a patient had central nervous system involvement at the time of their diagnosis, treatment following a relapse may be influenced by what their body can tolerate based on previous treatment.

H&O What are the treatment options for relapsed ALL?

NS There are no standard treatment options. There are a few prospective clinical trials available for patients who have relapsed, some of which incorporate new agents. Logically, one might think it would be better to treat a relapsed patient with different chemotherapy agents than the ones initially used. However, unlike certain other leukemias, patients with ALL will oftentimes respond to some of the same chemotherapy agents that they received during their initial treatment. That is especially true in the setting of a late relapse, when more than 3 years have passed since the patient last received chemotherapy. However, the problem is that these patients will not necessarily stay in remission. Additionally, there are some new agents—clofarabine (Clolar, Genzyme) is one—that have been approved for treating ALL in patients who have relapsed. We are looking at trying to use new agents or different types of agents that work by different mechanisms from what the patient previously received to overcome the resistant clone.

Once a patient is in remission, stem cell transplantation might be considered, depending on a patient's risk factors and how quickly remission was achieved. Transplant is indicated in patients with high-risk features, such as early and very early bone marrow relapses and T-cell ALL. Several studies have shown that minimal residual disease (MRD) after the achievement of a second remission is of prognostic significance. High levels of MRD at the end of induction and at later time points have correlated with an extremely high risk of subsequent relapse.

H&O What have recent studies found in regard to survival outcomes after relapse?

NS Colleagues from the COG conducted an analysis of the Children's Cancer Group (CCG) 1961 study for the treatment of higher-risk ALL, and the results were surprising. Many investigators had thought that relapsed patients who received less aggressive upfront therapy initially would have a higher rate of salvage from their relapse than patients treated with the more intense therapy. They found that high-risk patients had the same outcome, whether they received the standard intensity therapy or the more intense therapy. That finding makes us question whether it is feasible to achieve further clinically meaningful treatment intensification, given the likelihood of escalating treatment-related morbidity and mortality in the process. Similar findings have been reported among standard-risk patients in studies such as CCG 1952. There has been only one recent study in which results differed slightly. Investigators found that relapsed patients treated in the CCG 1922 study who had received intravenous 6-mercaptopurine (6-MP) had a poorer outcome than patients who had received oral 6-MP. The patients who received the oral dosage had a higher rate of remission. Therefore, in the case of CCG 1922, relapsed patients were less salvageable if they had received intravenous 6-MP during their initial therapy.

H&O What are some areas of research?

NS It is important to look at new agents or new types of chemotherapy that work by different mechanisms. One agent that is currently of significant interest is blinatumomab (MT103). This antibody works by recruiting

cytotoxic T cells into close proximity of the CD19-positive cells. Instead of simply using chemotherapy to kill the cells, this approach activates a particular component of the immune system to help kill the cells. The current hypothesis is that leukemia cells that are resistant to standard chemotherapy may be more susceptible to this approach.

There is also the Aurora A kinase inhibitor, MLN 8237. Aurora A kinase plays a role in making sure the cells proceed through mitosis. This inhibitor kills the leukemia cells in a different way from antileukemic agents. An additional approach could involve an anti–Bcl-2 inhibitor. We are anxious to test some of these newer agents in patients to see if we can improve outcome or be more successful in salvaging leukemia patients who relapse.

Suggested Readings

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