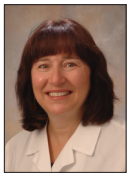
ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Novel Drug Targets in Acute Leukemia



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H&O What is the current standard of care for acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL)?

WS For both malignancies, treatment depends on the biology of the disease and the patient's age and performance status. Typically, we use combination chemotherapy plus postremission therapy, which may include additional chemotherapy and hematopoietic stem cell transplantation (HSCT).

If the patient is eligible for HSCT, this is our approach for any intermediate- or high-risk patients with AML. However, HSCT does not cure everyone and is not available for everyone. For older adults ineligible for HSCT, we do not have an optimal therapy. We cure fewer than 10% of adults older than 65 years with AML because standard chemotherapy followed by therapy after remission is not effective in that population, and many of those patients are not candidates for allogeneic HSCT. We have dramatically improved outcomes for certain subsets of patients with AML, particularly those with acute promyelocytic leukemia, but hope to improve treatment for the large remaining majority of patients by adding targeted therapy based on the molecular biology of the disease. However, we still have a very long way to go to improve survival rates for all patients with AML.

In ALL, the majority of patients receive combination chemotherapy, and this disease is highly curable in children. In young adults, ALL is becoming a more curable disease, but in older adults, it is still a challenge. However, we have some very exciting new antibodies and targeted therapies that may quickly change the way that we treat ALL.

One example is in the formerly highest-risk group of patients with Philadelphia chromosome–positive ALL. In this group, adding a targeted agent to frontline chemotherapy has vastly improved survival, and now, new antibodies can be added for other subtypes of ALL that will probably make a big difference and cure more patients.

H&O What are some promising new therapeutic areas for AML and ALL?

WS Molecularly targeted therapies are becoming more promising as we learn about the genes that are involved in the pathogenesis and development of AML. There are also new and broader applications for allogeneic HSCT and new opportunities for HSCT in more patients with different types of alternative donors. In ALL, there are new immunotherapies, including monoclonal antibodies and chimeric antigen receptor (CAR) T cells. There also are new targeted molecular agents that are active in certain subsets of AML and ALL, including kinase inhibitors, epigenetic modifiers, and exportin inhibitors. The biggest unmet need is in the adult population, particularly the older adult population with AML. We have some interesting leads, but no great answers at this moment.

H&O Could you describe these immunotherapies?

WS Several monoclonal antibodies have been tested for B-cell lineage ALL, including blinatumomab (Blincyto, Amgen), which was approved by the US Food and Drug Administration (FDA) in 2014. Another, inotuzumab

ozogamicin, is close to approval, and many more are still in the pipeline. These antibodies have high response rates in relapsed B-cell lineage ALL and are now being studied as frontline therapy in adults with ALL. These are very exciting new agents. Another exciting development in B-cell ALL is the use of CAR T cells, in which T cells are engineered and genetically modified to recognize B cells and kill them. The use of CAR T cells is technically challenging because of the side effects, but the response rates are extraordinarily high, even in patients with very advanced-stage disease.

Similar strategies are being developed for AML, but they are in earlier phases of testing. However, they may provide similar treatment options for these patients in the future.

H&O Are immune checkpoint inhibitors being investigated for acute leukemia?

WS Immune checkpoint inhibitors are very exciting in cancer in general, but the early trials in acute leukemia are just beginning. One trial being led by the University of Chicago (NCI 9706) is testing the addition of nivolumab (Opdivo, Bristol-Myers Squibb), a programmed cell death 1 antibody, in patients with AML who are in remission but at high risk of relapse. The goal of this study is to determine whether this agent can prolong remission and prevent relapse of disease.

H&O Are any new kinase inhibitors being examined for acute leukemia?

WS A large subset of patients with AML have a mutation in the kinase FLT3, and a number of FLT3 kinase inhibitors have been tested. A large international randomized trial has been completed and is being analyzed to determine whether the FLT3 inhibitor midostaurin improves survival when added to frontline therapy for AML. An abstract presented by Röllig and colleagues at the 2014 annual American Society of Hematology (ASH) meeting used sorafenib (Nexavar, Bayer/Onyx) in frontline therapy for AML with and without FLT3 mutations. Results from this study suggest that this treatment can benefit patients. Several new-generation kinase inhibitors that target FLT3 have activity in the relapse setting, and many will soon be tested in the frontline setting. For AML, FLT3 inhibitors likely have the most relevance and may prove very useful.

As mentioned earlier, kinase inhibitors specifically for patients with Philadelphia chromosome–positive ALL have definitely improved survival. Specifically, the ABL kinase inhibitors are added to chemotherapy and allow physicians to reduce the intensity of chemotherapy and still prolong survival.

Philadelphia chromosome–like or BRC-ABL1–like ALL, which occurs in 25% to 30% of young adults with ALL, is another subset of ALL. These patients have a multiplicity of different kinases that are activated, many of which can be targeted with kinase inhibitors that are already approved for other malignancies. Though these studies are still in early clinical trials, the inhibitors could be used in the frontline setting to improve survival for this high-risk group of patients. Many other kinase inhibitors are being investigated, but I think that these are the major categories for ALL and AML.

H&O Could you describe any epigenetic modifiers being investigated?

WS Study of epigenetic modifiers is a large area of research in the myeloid malignancies, and new modifiers are being tested, primarily in AML. This is a very large category that includes DNA-demethylating agents, DNA-hypomethylating agents, histone deacetylase inhibitors, and other modifiers involved in methylation and metabolism. Some of these agents are now being tested in the relapse setting with some interesting activity.

Researchers also are investigating indirect epigenetic modifiers. For example, isocitrate dehydrogenase is an epigenetic modifier and a metabolic enzyme that is deregulated in certain forms of AML. Drugs that inhibit isocitrate dehydrogenase are being tested in the frontline setting and seem to have a tremendously active profile in AML.

H&O Could you describe the exportin inhibitors being used for acute leukemia?

WS Exportins are involved in the transport of proteins from the nucleus to the cytoplasm. Exportin inhibitors are being tested in patients with relapsed AML. By blocking transport from the nucleus, these drugs cause toxic proteins to build up in the nucleus and eventually lead to cell death.

H&O Are there any other interesting novel drug targets?

WS Another important research area is investigating the leukemia stem cell. I think that we could benefit greatly from determining how the leukemia stem cell survives and progresses from a preleukemic cell into a leukemic cell, and how to prevent that from happening. Acute leukemias are "sneaky" diseases; we can identify the bulk leukemia population, and we can often eradicate that bulk population. However, the underlying preleukemia stem cell still remains and can "morph" again to become leukemia, which causes relapse. Often the relapse is not genetically the same as the initial bulk leukemia population but is derived from potentially the same preleukemic cell. If we could understand the leukemia stem cell better and prevent

it from surviving during chemotherapy and/or prevent it from becoming a full-blown leukemia cell, targeting these processes could prove beneficial. I think this will take a lot more work, but we currently have a lot of the molecular tools available to study those cell populations better.

H&O What is your view on the future of therapy for acute leukemia?

WS I think that the immunotherapies and some of the molecularly targeted agents are particularly exciting. New immunotherapies that are effective in other malignancies should be studied in the acute leukemias, which are rare but merit a close look with these new agents. We also must determine whether the exciting new findings on immunotherapies in ALL will also apply to AML. We have not dramatically improved outcomes for the majority of patients with AML in the last 2 decades. We have had some huge successes for some subsets of patients and interesting observations in others, but the older adults with AML still need more effective therapies. Hopefully, some of these immunotherapies will help.

I think we still need to improve our use of allogeneic HSCT for AML, because it remains the treatment of choice for a large percentage of patients but is associated with tremendous liability. Many patients are unable to undergo HSCT because they have no donor, though I think this is being addressed and alternative donors can now be found for most patients. However, HSCT is still associated with a very high treated-related toxicity and with a relatively high relapse rate. One possible way to reduce this is through modifications after SCT. My biggest hope, of course, is that we can find frontline therapies that will obviate the need for allogeneic SCT, but that is not available yet. SCT remains a very important part of our treatment armamentarium.

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