Could you give some background on acute myeloid leukemia (AML)?

AML is the most common acute leukemia in adults. The median age of diagnosis is late 60s to early 70s, and there is some male-to-female predominance. There are approximately 13,000 new cases a year and 10,000 deaths a year. Unfortunately, most patients with AML still die of the disease.

Environmental factors, genetic abnormalities, and other benign hematologic diseases have been associated with increased risk for AML. We also know that AML risk is associated with previous chemotherapy and radiation exposure, so as people live longer with other types of cancers, it is possible that we will see an increase in AML cases.

How does AML prognosis compare with other hematologic malignancies?

A recent survey by Sant and colleagues was published in the Lancet Oncology describing hematologic malignancies in Europe from 1997 to 2008, as well as incidence and outcomes. Compared with others, AML carries a poor prognosis and has one of the lowest survival rates. Looking at prognosis divided by age, we see that although there have been small advances among the younger patients, the older patients with AML continue to have a poor prognosis.

Although it is technically true that all of the hematologic malignancies showed statistical improvements in overall survival, in AML this improvement was only from 12.8% to 14.2%, highlighting the fact that statistical significance is not necessarily clinical significance.

What is the current frontline treatment for AML?

The mainstay of treatment in AML is still cytarabine, a chemotherapeutic agent. The first paper using cytarabine, published in 1968 in Blood, called it “useful.” Even 40 years later, it is probably the best drug that we have in AML.

In 1973, the first pilot study was performed using an infusion of cytarabine and daunorubicin, called “7+3 DNR 45” (ie, 7 days treatment with cytarabine plus 3 days with daunorubicin at 45 mg/m²). Using this regimen produced a complete response rate of 56% in AML, which still makes it the regimen to beat.

There have since been modifications to classic 7+3 over the years, but few significant improvements. In 2009, Fernandez and colleagues published a randomized comparison of daunorubicin dosage at 45 mg/m² vs 90 mg/m², and found that 90 mg/m² is better. From this study, we better understand how to use our best therapy, 7+3, and this has resulted in a survival benefit for selected, younger AML patients.
Clinical trials have shown that it is effective in AML when used on its own, but a regimen that shows improved efficacy over cytarabine has not been determined.

There is also CPX-351, a formulation that holds cytarabine and daunorubicin in a fixed 5-to-1 molar ratio. Recent trials of CPX-351—published in Blood in 2014 by Lancet and colleagues—showed a benefit in overall survival for a very difficult-to-treat population of secondary AML patients. A randomized trial of CPX-351 versus 7+3 is ongoing.

**H&O** Have there been any improvements in treatments using low-dose cytarabine?

**GR** The current, standard low-intensity regimen using 10 or 14 days of low-dose, subcutaneous cytarabine (LDAC) has been used for older, frail AML patients for more than 30 years. An ongoing, multi-arm trial in United Kingdom is serially randomizing an assortment of novel compounds against standard LDAC. Several agents have already been tried, including vosaroxin, clofarabine, gemtuzumab, tipifarnib, and arsenic trioxide. These agents looked promising in combination with LDAC in single-arm studies, but failed to significantly improve survival in the randomized trial.

The good news is that there continue to be novel agents on the horizon that can be combined with and/or compared with LDAC. Potential competitors include volasertib, a polo-like kinase 1 (PLK-1) inhibitor; SGN-33, a novel antibody-drug conjugate; and SGI-110, a second-generation hypomethylator. Decitabine has also been compared with LDAC by Kantarjian and colleagues, and the data were sufficient to convince the European Medicines Agency, but not the US Food and Drug Administration, that decitabine is an effective low-intensity treatment for AML. Several studies have found that 10-day decitabine is especially effective, with response rates of 40% to 47%. There are also many ongoing trials of combinations of decitabine and azacitidine in AML that have solid scientific rationale behind using the combination. These data are anxiously awaited.

**H&O** Are there any new treatments for relapsed AML?

**GR** Unfortunately, we do not have any breakthroughs for relapsed AML. Elacytarabine, which is a liposomal formulation of cytarabine, failed to show a benefit in a trial with relapsed patients that we published in 2014 in the Journal of Clinical Oncology. This study was interesting, because it used investigator’s choice as the control regimen, and it resoundingly showed that all the regimens chosen for relapsed disease are equally ineffective.

Vosaroxin, a topoisomerase inhibitor, did not meet its endpoint in a recent trial (NCT01191801) studying...
relapsed disease, but it still is associated with a high complete response rate. Therefore, this drug may be useful in the future, when we determine how to use it optimally.

**H&O What are the new targets for mechanism-based therapies?**

**GR** Multiple mutations have been characterized in AML, including mutations affecting proliferation (e.g., receptor tyrosine kinases and signal transduction proteins), differentiation, apoptosis, epigenetic regulation, and the spliceosome. We have found aberrant histone modifications, dysregulated DNA methylation, and metabolic alterations. There are also quiescent leukemic stem cells that are not chemotherapy-sensitive. Although the mechanisms of the disease are much better understood than before, all of these alterations combine to create a complicated mechanism of action. But overall, we are investigating epigenetics, targeted therapies, and personalized medicine. Hopefully, we will soon be on the way to improved therapeutic options.

**H&O Are there any promising treatment strategies other than chemotherapy?**

**GR** Mutation-targeted strategies, FMS-like receptor tyrosine kinase-3 (Flt3) inhibitors, and isocitrate dehydrogenase (IDH) 1 and 2 inhibitors all are extremely promising. One question is whether these can improve upon previous therapies. Another major concern is whether we are putting selective pressure on 1 clone and thereby creating more mutations that are resistant to therapy.

To avoid this problem, it is possible to target the machinery instead of the mutation. One interesting example is bromodomain inhibition, which reduces the transcription of genes associated with cancer cell proliferation and survival. This strategy is of particular interest because it is a way to slow propagation of AML cells without focusing only on a single isolated mutation.

Immunotherapy is also a promising novel treatment area, especially adoptive cell transfer (ACT). ACT uses the patient’s own T cells, which are modified to express chimeric antigen receptors (CARs) that target a specific antigen on the tumor cells. This is a promising new therapy that could potentially be useful in AML.

**Suggested Readings**


