functional status might be as or more important,” Hurria said.

A treatment plan must rest on honesty, even when prognosis is bad. Wenger said that patients often have estimates of prognosis that differ markedly from those of their doctors.

“They think their disease is curable when it is not. This misunderstanding leads to decisions not consistent with what patients would want if they understood the current status of their disease.”

What such patients often would want is assurance of palliative care and support.

Starting Forward

The IOM report aimed its recommendations at both large and small organizations.

“It has been heartening to interact with so many large organizations and institutions that have the ability to make change that are using the IOM report as a road map, including the Oncology Nursing Society and the American Society of Clinical Oncology,” McCabe said. “But the report has a message for everyone.”

For small practices, she suggests focusing first on communication skills, which can be incorporated into continuing education and professional development, and corralling existing resources, including online end-of-life care tools. Examples include Centering Communication in Palliative Care (http://www.clinicalcc.com), Oncotalk (http://depts.washington.edu/oncotalk/), and Cancer Prognostic Resources (http://www.cancercalculators.org).

Another measure, Ganz said, is to “organize ourselves so that it’s not just the oncologist shouldering the burden of quality cancer care.” In a commentary on the report (Oncol. Nurs. Forum 2013;40:603–9), McCabe, Ferrell, and a colleague contend that oncology nursing is essential to patient-centered care. Classic hallmarks of oncology nursing are educating patients, supporting them and their families in decision making, and supplying (or referring patients for) psychosocial support and palliative/hospice care.

“Shared medical records would be tremendously useful, with the care plan updated regularly,” Wenger said. Also, incorporating oncology into medical homes would facilitate patient-centered cancer care.

“The underlying message of this report is that we don’t have a choice. Something has to change,” Wenger said. “Do we get to craft the way the future of cancer care is going to look, or will it be given to us?”

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Marshaling the Immune System to Eliminate Minimal Residual Disease in B-ALL

By Karyn Hede

New deep sequencing data is reinforcing the power of minimal residual disease (MRD) to predict relapse in patients with B-cell-lineage acute lymphoblastic leukemia (ALL). That precise predictive value underscores the need to eliminate every remnant of disease in patients. Now, targeted biological treatments offer evidence that attaining that goal is within reach.

Deep DNA sequencing of samples taken from children before and after allogeneic transplant shows the importance of eliminating all traces of disease. Patients with no detectable leukemia before transplant had a less than 5% chance of relapse, whereas patients with detectable MRD relapsed 57% of the time, according to data presented at the 2013 American Society of Hematology meeting. Michael Pulsipher, M.D., director of the pediatric blood and marrow transplant program at Primary Children’s Medical Center at the University of Utah, and colleagues also showed that the presence of any tumor in the first 90 days after stem cell transplant indicated high probability of relapse.

“Part of the problem with minimal residual disease is it’s not been clear, outside of transplantation, that we know what to do,” said Nelson Chao, M.D., M.B.A., professor of medicine and immunology and chief of cellular therapy at Duke University Medical Center, in Durham, N.C. The aggressive nature of ALL blasts — immature B-cells, —means that the relapsing leukemia progresses rapidly and is often doesn’t respond to chemotherapy agents.

In the short term, Chao said that these newer, precise sequencing technologies should make detecting MRD more accurate. They should also aid clinical decision making in ALL patients, particularly for deciding on the intensity of induction and consolidation chemotherapy treatment.

Longer term, a new generation of biological treatments is showing early, remarkable response in ALL patients, raising hopes that eliminating MRD is possible for many more patients. In both pediatric and adult patients with relapsed or treatment-resistant ALL, investigational therapies that guide the immune system to destroy B cells have achieved complete remission, eliminating all trace of blasts in some clinical trial patients.

The most publicized of these therapies, chimeric antigen receptor—modified T cells (CAR), is engineered by programming the patient’s own T cells to target the B-cell receptor CD19 for destruction. At least three approaches for this technique are in
clinical trials targeting B-cell–mediated blood cancers, and all have shown unexpected success with intransigent ALL.

“Relapsed ALL is severe and rapidly progressive. Who would have thought that would be the disease where the CD19 CAR therapy works the best? And yet that’s the case,” said Michel Sadelain, M.D., who is leading clinical trials of the technology in adult patients at Memorial Sloan–Kettering Cancer Center in New York. He and coinventors at Fred Hutchinson Cancer Research Center in Seattle, along with a group of investors, recently formed Juno Therapeutics, to commercialize the technology.

Sadelain and colleagues reported short-term results on the first 16 treated patients in the Feb. 19, 2014, *Science Translational Medicine*. More than 20 adult patients have been treated, after a short, highly publicized suspension of the trial in April when two patients died. One patient with underlying heart disease succumbed to a severe cytokine response, and the second died of complications, including seizures, owing to a neurologic response. The team then revised entry criteria to exclude patients with a history of heart disease.

No explanation for the neurological event is evident, Sadelain said. “All we can do is take note that it has happened. There is no good understanding of that phenomenon at this point.”

However, the complete response rate, reported at 88% for the first 16 patients, is important because relapsed adult patients don’t respond to chemotherapy and are generally not eligible for a stem cell transplant. Achieving complete remission made several of the patients eligible for stem cell transplant. Of these, three have received transplants. Long-term response is not yet known; most patients have been treated within the last year, Sadelain said.

Even in trials conducted by other major CAR research teams—those developed by the University of Pennsylvania and licensed to Novartis and those developed at the National Cancer Institute and licensed to Kite Pharmaceuticals—published results have involved only a few patients. Even with little published data, the U.S. Food and Drug Administration issued “breakthrough therapy” status in July 2014 to the Novartis CAR therapy, which should expedite its development and regulatory review.

“CAR T-cell therapy has at least 2–3 years of testing in a multi-institutional setting for us to have the data to say with confidence that it lasts more than a year or two, and then we could say that we could potentially not do a transplant,” Pulsipher said. Until then, he added, its best potential use is to get patients into complete remission before transplant.

CAR treatment’s individualized nature seems to fulfill the promise of personalized medicine, yet questions of safety, cost, and generalizability remain. For most physicians treating ALL, the more attractive approach may be to use bispecific T-cell engagers (BiTES), which first bind to CD19 on B cells and then to CD3 on nearby T cells. The effect is to activate T cells, directing the immune system to destroy the now-targeted B cells. The advantage for practitioners is that BiTES are not patient specific.

“If you could get CARs off the shelf as an adjunct to chemotherapy, that would be the most interesting,” said Chao. “But giving a drug is a lot easier and a lot less cumbersome. So I think that could be the tradeoff. BiTES [may have] a much cleaner and easier path than a cellular therapy like CARs.”

Early results with blinatumomab BiTE therapy have been promising in relapsed ALL patients. In a July 2014 study in *Haematologica*, investigators at Germany’s University of Tübingen administered blinatumomab on a compassionate-use basis to nine pediatric patients who had relapsed after stem-cell transplant. Four achieved complete remission after the first treatment cycle, and two achieved complete remission after a second cycle. Four patients received a second transplant and after more than 1 year, 30% experienced event-free survival. Like the patients at Memorial Sloan–Kettering, toxic effects included seizures and cytokine release syndrome. A phase III trial randomizing pediatric patients in first relapse to standard chemotherapy or blinatumomab to induce remission before stem cell transplant is now under way.

Another promising approach, inotuzumab ozogamicin (IO), is a CD22 monoclonal antibody bound to a toxin, calicheamicin. Like CD19, CD22 occurs in B cells of 90% of ALL patients. At the American Society of Hematology meeting, researchers presented interim results from newly diagnosed adult ALL patients treated at the University of Texas M. D. Anderson Cancer Center in Houston. Not only was combining IO with lower-intensity chemotherapy safe; results were better than typical chemotherapy results: 93% achieved complete response. All these patients achieved MRD-negative status and 83% were still disease-free after 1 year. Investigators speculated that IO could become the new standard for frontline treatment of older ALL patients.

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