Advances in the Treatment of Hematologic Cancers

Hematologic malignancies, including various types of leukemia, myeloma, and lymphoma, will account for nearly 10% of newly diagnosed cancers in the United States this year. With the exception of acute lymphocytic leukemia (ALL) and Hodgkin’s lymphoma, these diseases tend to be associated with increasing age. The rising average age of the US population—the number of people older than 65 will double by 2050—makes this demographic an important factor in the development of new treatments. In addition to facing an increased risk of hematologic cancers, older patients may have reduced tolerance for the types of intensive therapy that have been the mainstay of treatment for the last 30 years. This highlights the importance of developing less toxic treatments. New advances are coming from two directions: targeted pathways and immune-based therapies. (Continued on page 3)

Estimated New Cancer Cases in the United States, 2014*

- Digestive System
- Breast
- Genital System
- Respiratory System
- Other
- Hematologic
- Leukemia
- Myeloma
- Lymphoma

* Data from the American Cancer Society, as reported in Siegel et al., CA Cancer J Clin 2014;64:9-29.
In the conclusion to his epic poem, “The Road Not Taken,” Robert Frost wrote:

Two roads diverged in a wood, and I –
I took the one less traveled by,
And that has made all the difference.

Cellular processes usually take paths that result in normal growth and function, but they can go down another path, and that can make the difference.

In this issue of CancerUpdate, we discuss progress in hematologic malignancy treatment and diagnosis. In the past year, two new agents have been approved for the treatment of lymphoid malignancy that have added powerful weapons to our armamentarium. By attacking key B-cell receptor pathways, these agents add to and in some cases may replace our traditional chemotherapy and antibody approaches.

We are using our knowledge of pathways to help prevent relapse, with an emphasis on acute myeloid leukemia (AML) posttransplant. By knowing which genes and pathways may be activated or mutated in a particular AML subtype, we may be able to detect residual disease or early relapse and, when needed, intervene. Two investigator-initiated trials being conducted at Baylor Sammons Cancer Center at Dallas are discussed. One utilizes a longitudinal approach to track specific cellular mutations before and after transplant to examine clonal evolution; the other focuses on using a sensitive assay for 2-HG to better follow patients with mutations in the isocitrate dehydrogenase pathway.

In a study underway in the laboratories of Baylor Institute for Immunology Research, driver genes in multiple myeloma are being examined to determine their role in myeloma development and progression.

When exciting work is happening, it is appropriate to blow one’s horn. Few in the world can blow a trumpet as well as Ryan Anthony, who is profiled in this issue. (I recommend a YouTube search for his rendition of “Penny Lane.”) Mr. Anthony, the principal trumpet for the Dallas Symphony Orchestra, is a myeloma survivor, having undergone a hematopoietic stem cell transplant a year ago. He has formed an organization, Cancer Blows, to raise funds for myeloma research. We salute Mr. Anthony and the path that he has chosen.

Alan M. Miller, MD, PhD
Chief of Oncology, Baylor Health Care System
Medical Director, Baylor Charles A. Sammons Cancer Center at Dallas
Targeted Pathways

In one of the biggest success stories in cancer treatment, the tyrosine kinase inhibitor (TKI) imatinib (Gleevec®, Novartis AG, Basel, Switzerland) has totally changed the treatment paradigm for chronic myeloid leukemia (CML). Imatinib specifically blocks the activity of the hallmark BCR-ABL fusion gene that characterizes CML. The US Food and Drug Administration (FDA) approved imatinib for the first-line treatment of CML in 2002. Since then, three additional TKIs—nilotinib, dasatinib, and bosutinib—have become commercially available for the treatment of CML. A fifth drug, ponatinib, was temporarily removed from the market in October 2013 because of concerns about side effects. Under a revised marketing label approved by the US FDA in December 2013, ponatinib is now approved for patients with CML who have failed to benefit from or are ineligible to take the four alternative therapies.

Now, investigators are looking more closely at the B-cell receptor (BCR) pathway to find potential therapeutic targets for B-cell cancers, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma, and indolent non-Hodgkin’s lymphoma. Because the cancer cells are more reliant on the BCR pathway for growth and survival, it is substantially upregulated in B-cell malignancies, and several targeted drugs have been designed to downregulate different components of the pathway.

Therapeutic Targets in the B-Cell Receptor Pathway
The phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) arm of the BCR pathway is involved in critical cellular functions, including growth control, metabolism, and apoptosis. Of the various classes of PI3K isoforms, only class 1A isoforms (p110alpha, beta, and delta) have been associated with tumorigenesis, with the delta and gamma isoforms primarily associated with hematopoietic cells, including B cells. The specificity of p110delta makes it a promising therapeutic target in B-cell cancers that are characterized by constitutively activated PI3K signaling, such as CLL. Idelalisib (Zydelig®, Gilead Sciences, Inc., Foster City, CA; also code-named GS-1101 or CAL-101) is an orally administered p110delta inhibitor that was approved by the FDA in July 2014 for the treatment of relapsed CLL, relapsed follicular B-cell non-Hodgkin’s lymphoma, and relapsed small lymphocytic lymphoma. Three phase 3 trials currently underway at Baylor Sammons Cancer Center are testing the efficacy of idelalisib in combination with rituximab for previously treated CLL or previously treated indolent non-Hodgkin’s lymphoma, or in combination with rituximab and bendamustine for previously treated CLL.

Another vital part of the BCR pathway, contributing to B-cell maturation, is Bruton’s tyrosine kinase (BTK). In CLL, BTK is upregulated at the transcript level and is constitutively active. Ibrutinib (Imbruvica®, Pharmacyclics, Inc., Sunnyvale, CA) is the first drug designed to specifically target BTK. It irreversibly binds BTK, inactivating its kinase activity and thereby inducing apoptosis and reducing proliferation. Ibrutinib was approved by the FDA in 2013 for the treatment of mantle cell lymphoma and in 2014 for the treatment of CLL. In July 2014, ibrutinib received a breakthrough therapy designation from the FDA for the treatment of patients with CLL who carry a deletion in the short arm of chromosome 17, which is associated with a poor response to standard treatment. This designation is intended to expedite the development and review of drugs for serious or life-threatening conditions.

According to M. Yair Levy, MD, medical director of Hematologic Malignancy Clinical Research at Baylor Charles A. Sammons Cancer Center, “Drugs targeting these pathways have shown surprising efficacy. For example, we have seen unprecedented activity using ibrutinib for the treatment of CLL, with a response rate of 73% in heavily pretreated patients. In addition to the high response in CLL, we are also seeing amazing results in mantle cell lymphoma. When this disease recurs, it can be very aggressive. Two to three years ago, we didn’t have any second-line therapy for mantle cell lymphoma. When bortezomib and lenalidomide came on line, they resulted in response rates of around 20%. With ibrutinib, we can get response rates three times as high, even in people who have already received bortezomib or lenalidomide.”

**Immune-Based Therapies**

As recently as 2 years ago, one of the most talked about agents for precision medicine in the treatment of hematologic cancers was the immunologic agent rituximab (Rituxan®, Genentech, South San Francisco, CA). Rituximab is a chimeric human/mouse monoclonal antibody that targets the CD20 antigen on the surface of B lymphocytes. It was approved by the FDA in 1997 for treatment of relapsed and refractory non-Hodgkin’s lymphoma. Although rituximab, alone or in combination with standard chemotherapy regimens, resulted in improved outcomes for some patients with B-cell malignancies, monoclonal antibodies against other tumor cell surface antigens have met with varying levels of success, with some being withdrawn from the market. Researchers are now looking at new technologic approaches to harness the patient’s own immune system to fight cancer.

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M. Yair Levy, MD
Bispecific T-Cell Engagers (BiTEs)

Although T cells have the capability of controlling tumor growth in cancer patients, tumor-specific T cell responses are difficult to elicit and sustain. BiTE technology is a novel approach for engaging T cells for cancer therapy. The technology involves the linking of two single-chain antibodies—one with specificity for a T cell antigen and one with specificity for a tumor cell antigen—by means of a linker sequence. This brings the T cell and tumor cell into close proximity, resulting in activation of the T cell to exert cytotoxic activity against the tumor cell. Blinatumomab (Amgen Inc., Thousand Oaks, CA) is a BiTE antibody that is bispecific for CD3 (T cell antigen) and CD19 (B cell antigen). It is currently being tested for the treatment of patients with relapsed non-Hodgkin’s lymphoma or acute lymphoblastic leukemia. In July 2014, blinatumomab received breakthrough therapy designation from the FDA, based on encouraging results from a phase 2 trial in adult patients with relapsed or refractory ALL.

Chimeric Antigen Receptor T Cells (CAR T Cells)

CAR T cells are T cells that are removed from a patient or donor and engineered to have altered antigen receptors (chimeric antigen receptors, or CARs) that specifically target cancer cells. The tumor-specific antigen receptors on the outside of the cells are linked to stimulatory molecules on the inside that provide the signals to fully activate the T cell to proliferate and attack cancer cells. Viral transfection is used to modify the T cell’s antigen receptors (for B-cell malignancies, CARs typically target CD19), after which the CAR T cells are cocultured with appropriate antigen-presenting cells, causing them to proliferate. The expanded population of CAR T cells is infused into the patient, where they continue to divide for several weeks. They appear to live longer than normal killer T cells and become serial killers of cancer cells. Some CAR T cells can become memory T cells, ready to attack if the cancer recurs. Numerous early phase clinical trials are currently testing CAR T cell technology for the treatment of leukemias, as well as assorted solid tumors.

First, regardless of the initial efficacy of a drug, a patient may stop responding. Dr. Levy commented: “Cancer is amazingly robust and clever. The pathways being targeted by some of these new agents have multiple redundancies, so a cancer cell can become independent of a particular pathway if necessary.”

For that reason, oncologists generally achieve better results by combining several treatment modalities. There are currently many studies, for example, combining ibrutinib or idelalisib with cytotoxic chemotherapy or with other targeted agents. Ideally, multiple points on a pathway could be blocked with different targeted agents, although with current pricing structures, the cost of such an approach could quickly become unsustainable.

Another core problem has to do with drug side effects. A common assumption is that targeted agents have no significant toxicities, but this is not always true. Nearly one-quarter of the patients receiving the multitargeted TKI ponatinib for CML or Philadelphia chromosome–positive ALL experienced arterial or venous thrombotic complications, causing the drug to be temporarily withdrawn from the market. As many as one-third of patients now taking imatinib are not compliant with treatment recommendations because of side effects (musculoskeletal problems, edema, a general sense of not feeling well). Balancing the potential for serious side effects against therapeutic benefit will continue to be a critical issue for oncologists selecting optimal treatments for their patients.

In this issue of CancerUpdate, we focus on new research directions in the treatment of hematologic cancers, with special emphasis on research programs being conducted at Baylor Sammons Cancer Center: the role of isocitrate dehydrogenase in acute myeloid leukemia; the regulation of driver genes in multiple myeloma; and the prevention of relapse after stem cell transplantation.

Designing Therapy for the Individual Patient

With several promising lines of new therapy becoming available, oncologists need to consider how best to incorporate these agents into treatment protocols for individual patients. As with the cytotoxic drugs that have gone before, several core problems must be addressed as new paradigms evolve.
Driver Genes, Regulatory Elements, and a New Look at Multiple Myeloma

Multiple myeloma (MM) is a malignancy of plasma cells that is characterized by bone destruction, renal failure, anemia, and hypercalcemia. MM is treatable, and the introduction of newer systemic therapies (bortezomib, thalidomide, lenalidomide), as well as advances in autologous and allogeneic stem cell transplantation have significantly improved patient outcomes over the last 10 years. Nonetheless, this disease is rarely curable, and the 5-year survival rate is still only about 45%. New treatment strategies are badly needed to improve this grim prognosis.

With funding from a grant awarded by Baylor Charles A. Sammons Cancer Center’s Research Grant Program, Yin Lin, PhD, assistant investigator at Baylor Institute for Immunology Research (BIIR), is initiating a pilot study that may suggest innovative treatment approaches for MM. He proposes to identify regulatory elements that control the expression of driver genes in MM.

What Are Driver Genes?

Tumor cells contain a large number of somatic mutations, most of which accumulate as a function of time and have nothing to do with the neoplastic process. Only a few confer a selective growth advantage, either directly or indirectly, to the tumor cell. These are the mutations that occur in “driver” genes.

About 140 driver genes have been identified across a variety of different cancer types. Most of these genes are related to cellular processes that involve cell fate (whether the cell is destined to divide or to differentiate), cell survival (allowing a cell to proliferate under limiting nutrient concentrations), or genome maintenance (how the cell handles mistakes in DNA replication or cell division).

Driver genes fall into two categories: Mut-driver genes and Epi-driver genes. Mut-driver genes are frequently mutated at gene loci, which results in gain or loss of function of their biochemical activities. Epi-driver genes are typically not mutated but are aberrantly expressed as a result of DNA methylation or chromatin modification. Using whole-genome and exome sequencing, researchers with the Multiple Myeloma Research Consortium (MMRC) have identified driver gene mutations associated with MM (see table below). Many of these genes are involved in protein homeostasis, RNA processing, histone methylation, and blood coagulation. In addition, members of the nuclear factor-kB signaling pathway have been implicated as driver genes. Dr. Lin will use selected genes identified in these studies for his new project.

Driver Genes Identified in Samples from Patients with Multiple Myeloma

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<tr>
<th>Mut-Driver Genes*</th>
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<td>BRAF</td>
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<td>PRDM1</td>
<td>XBP1</td>
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*Based on data originally published in Nature 471:467; Cancer Cell 25:91; Nature Communications 5:2997
The Regulation of Driver Genes:
What Will Be Investigated in This Project?

While the transcriptional profiles and genetic alterations that characterize MM have been studied in great detail, how regulatory elements control aberrant gene expression is not well understood. Dr. Lin proposes to study two kinds of regulatory elements, enhancers and long noncoding RNAs (lncRNAs). He will investigate the molecular mechanisms by which they control driver gene expression in MM.

Enhancers are short pieces of DNA that activate the expression of their target genes by binding to transcription factors. They are cis-acting and can be located up to 1 million base pairs away from the promoters of their target genes. The direct interaction between the enhancer and its target gene occurs through the physical looping of DNA. Genetic variation in the enhancer DNA is associated with many types of disease, and deletion of an enhancer can obliterate the function of the gene.

Dr. Lin commented: “A better understanding of enhancers may allow us to apply genome-based therapeutics to rewire the regulatory controls that are specific to MM so that it loses its selective growth advantage and immune resistance.”

In this pilot project, Dr. Lin will investigate enhancer repertoires that control aberrant driver gene expression during MM development and progression. He will also engineer sequence-specific nucleases to selectively delete the enhancers to determine the functional consequences of their loss.

LncRNAs (>200 bases) resemble messenger RNAs, but they do not serve as templates for protein synthesis. Rather, they appear to be important but poorly understood components in gene regulation. Recent studies suggest that lncRNAs can control transcription by acting as decoys to titrate away transcription factors, a scaffold for chromatin modifiers, and/or a guide to recruit chromatin modifiers to a specific genomic region. Dr. Lin will identify lncRNAs that are aberrantly expressed in MM and investigate their driver potential and molecular action.

About the Investigator

Dr. Lin’s background is in molecular immunology, with a focus on gene regulation. He completed graduate work in this area at the University of California, Los Angeles, and continued studies in the gene regulation of B-cell biology and hematopoietic malignancy as a postdoctoral fellow at the University of California, San Diego. Because he previously focused on animal studies, Dr. Lin was excited to come to Baylor Sammons Cancer Center and BIIR, where he has the opportunity to work with samples from human patients.

“The goal of our research is to better understand multiple myeloma, identify new targets for genome-based therapeutics, and provide alternative panels of molecular biomarkers,” said Dr. Lin. “We welcome the opportunity to collaborate with Baylor clinicians, other BIIR investigators, and outside collaborators to achieve this goal.”

Yin Lin, PhD

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Yin Lin, PhD
Kreb’s Cycle: A Role for Metabolic Enzymes in Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is the most common form of leukemia in adults, with approximately 18,860 new cases and 10,460 deaths expected to occur this year. It is largely a disease of older people, with more than half of patients 65 years or older at the time of diagnosis. Treatment for AML typically begins with the administration of cytarabine and anthracycline induction chemotherapy to achieve remission, followed by multiple rounds of consolidation chemotherapy and possibly by stem cell transplant.

AML is a heterogeneous malignancy, with distinct disease subtypes characterized by recurrent chromosomal translocations and somatic mutations. These subtypes are associated with different levels of risk. For example, monosomal karyotypes (-5, 5q-, -7, 7q-) are related to poor risk, while some specific translocations [t(16;16), t(8;21), t(15;17)] are associated with better risk. In addition to cytogenetics, molecular markers, including FMS-like tyrosine kinase 3 (FLT3), c-KIT, nucleophosmin (NPM1), and CEBPA, can help in defining prognostic groups.

Even with this growing body of knowledge about the effects of chromosomal and somatic abnormalities on disease risk, the prediction of relapse in a specific patient remains uncertain. The current best approach is to be able to determine as early as possible if a patient has had a relapse or if there was subclinical residual disease after the completion of treatment. This will help us understand the effectiveness of the original treatment and make more informed decisions about post-remission strategies.

Isocitrate Dehydrogenase

For a number of years, researchers have been using next-generation sequencing techniques to identify new mutations that might be useful as prognostic biomarkers or as therapeutic targets for the treatment of AML. This led to the discovery that mutations in isocitrate dehydrogenase (IDH), a metabolic enzyme, could be found in 10% to 20% of patients with AML, conferring a poor prognosis.

IDH is a critical enzyme in the Kreb’s cycle, a series of chemical reactions used by aerobic organisms to generate energy, provide precursors for certain amino acids, and produce NADH. It is present in two isoforms: IDH1 is cytosolic, and IDH2 is mitochondrial. As homodimers, the IDH enzymes convert isocitrate into α-ketoglutarate (α-KG). In addition to being an intermediate in the Kreb’s cycle, α-KG also affects a variety of dioxygenases, including several that influence the epigenetic environment of the cell.

Mutations in IDH genes prevent oxidative decarboxylation of isocitrate to α-KG, affecting the overall energy landscape of the cell. In addition, the IDH mutations result in a new function, the conversion of α-KG to D-2-hydroxyglutarate (D-2-HG), which acts as a competitive inhibitor of dioxygenases. This leads to alterations in the epigenetic programming of the cell, blocking differentiation and potentially contributing to the development of AML and some solid tumors. In support of this, researchers have demonstrated that AMLs with mutated IDH1/2 show global hypermethylation and a specific hypermethylation signature.

Optical Isomers of 2-HG

The measurement of total 2-HG is straightforward, but small changes are difficult to detect against the background of normal variation, making it problematic for the use of disease monitoring. However, 2-HG is present as a mixture of two optical isomers. Optical isomers are molecules with the same sequence of atoms and bonds but with a different three-dimensional shape such that they form nonsuperimposable mirror images of each other. (The human hand is an illustrative example.) They are functionally defined by the direction in which a plane of polarized light rotates when it passes through a solution of one of the isomers: D for dextrorotatory and
Potential Metabolic Effects of Mutations in Isocitrate Dehydrogenase (IDH), a Critical Enzyme in the Kreb’s Cycle.

Citrate

Isocitrate

Wild-type homodimer

Mutant heterodimer

IDH1

IDH1

IDH1

IDH1

Alpha-Ketoglutarate

D-2-Hydroxy-glutamate

Succinyl CoA

Co-substrate for dioxygenases and other enzymes

Disrupted metabolism, competitive inhibition of dioxygenases, alterations in epigenetic programming of the cell

L for levorotatory. Although optical isomers share the same physical properties (e.g., melting points, boiling points, etc.), their biological properties can be very different. A striking example is seen in the ethambutol drugs, where the D-isomer is used for the treatment of tuberculosis, while the L-isomer is a toxic agent that can cause blindness.

Alan Miller, MD, PhD, chief of oncology, Baylor Health Care System and medical director, Baylor Charles A. Sammons Cancer Center, and Lawrence Sweetman, PhD, assistant director, Center for Metabolomics, Institute of Metabolic Disease, Baylor Research Institute are undertaking a pilot project to measure both optical isomers of 2-HG in patients with IDH mutation–positive AML. According to Dr. Miller: “If we can detect small variations in 2-HG, we may be able to determine earlier if a patient has had a relapse or whether there is minimal residual disease after treatment. We plan to study the ratio of the two isomers, as subtle changes in this ratio may be more sensitive than absolute concentrations to the presence of subclinical amounts of disease.”

The study will use plasma obtained from serial blood samples (prior to treatment, after treatment, after recurrence) of AML patients. A specially designed two-dimensional gas chromatography column will be used to separate and accurately quantify both optical isomers by mass spectrometry with stable isotopically labeled internal standards. Both the D- and L-isomers will be measured, as well as the ratio between the two, to see if levels are correlated with the presence of the IDH1/2 mutation, if they are altered when the tumor burden is decreased, and if there is a correlation with treatment outcome. Dr. Sweetman said: “There is an enormous literature implicating 2-HG in the development of these cancers, but we haven’t yet had the measurements we need to get a clear picture of what’s going on. The accurate measurement of the D- and L-isomers of 2-HG will help us to determine its real role in AML.”

“If we can detect small variations in 2-HG, we may be able to determine earlier if a patient has had a relapse or whether there is minimal residual disease after treatment. We plan to study the ratio of the two isomers, as subtle changes in this ratio may be more sensitive than absolute concentrations to the presence of subclinical amounts of disease.”

Alan Miller, MD, PhD
Ryan Anthony: Blowing Away Cancer

Ryan Anthony has had a professional life that many musicians can only dream of: playing with internationally known groups, including the Canadian Brass, before coming to Dallas as principal trumpet for the Dallas Symphony Orchestra. But none of this prepared him for the journey he began in 2012, when he was diagnosed with multiple myeloma.

“Trumpet playing is what brought me to the doctor,” said Ryan. “I was getting chest and back pains while I was playing, and just not feeling well.” Although some of his symptoms suggested myeloma, every test came back negative, and he was told not to worry because he was too young for this type of cancer. But then came more testing and the bad news: not only did he have multiple myeloma, he also had a very severe form, with a poor prognosis. He started treatment that day at Baylor Sammons Cancer Center at Dallas, and was recommended for an autologous stem cell transplant.
Ryan and his wife Niki talked with six different cancer centers, looking for the one where they felt he could get the best treatment. Ultimately, they chose to stay at Baylor Sammons. “It was by far the best option for us,” said Ryan. “We believed in the doctors, the infrastructure, how they treated my disease. And it made a huge difference that I could be at home with my family and friends during the treatment.”

One of the things that surprised Ryan is that he didn’t have to put his life on hold because of his treatment. During induction therapy, he continued to work full-time, performing in three to four concerts every week. He currently receives maintenance therapy every 2 weeks and continues to perform every weekend, including the days of his treatment.

Now, 2 years later, Ryan is in complete remission, and he wants to give back. “During my treatment,” he said, “trumpet players all over the world called me and asked, ‘What can we do?’ It occurred to me that we could come together to make a difference as musicians, performing in a concert that I wanted to call ‘Cancer Blows.’ Major names in the industry have chosen to participate and to stand with me to make a statement about multiple myeloma. We will celebrate where we are now compared with 20 years ago and look at what still needs to be done.”

Cancer Blows™ will be a once-in-a-lifetime musical event featuring at least 20 of the most famous trumpet players in the world. A special concert and after-party will be held at Meyerson Symphony Center in Dallas, Texas, on March 4, 2015.

All proceeds from the Cancer Blows concert and after party will be directed through The Ryan Anthony Foundation and will benefit Baylor Health Care System Foundation and Multiple Myeloma Research Foundation to fund education and research in multiple myeloma and other blood cancers.

Mark your calendars now for this extraordinary event. Further information will appear in the next issue of CancerUpdate.
At the Blood and Marrow Transplantation (BMT) Program at Baylor University Medical Center at Dallas, quality of life after the transplantation is a major endpoint. According to Edward Agura, MD, medical director of the BMT Program at Baylor Dallas, “While issues such as infection and graft-versus-host disease can affect quality of life, the number one cause of patients not living a normal life after transplantation is relapse of their disease.”

Recent advances in the areas of molecular genetics and immunology have led to innovative new approaches for the prevention of relapse.

Preventing Relapse After Stem Cell Transplantation

Stem cell transplantation using bone marrow-derived stem cells is a critical part of the treatment approach for most patients with hematologic cancers. It has increased longevity and improved quality of life even in patients with difficult-to-treat diseases like multiple myeloma, but its greatest success has been in the treatment of leukemia. From the publication of the first patient series in the late 1970s, transplantation has changed the treatment paradigm for patients with leukemia, offering the hope of a cure for diseases that had been considered treatable but incurable. With the continuing development of stem cell transplantation technology, more patients are becoming eligible for transplantations, more donor cells are available, and outcomes are improving.

Genetic Approaches

The last decade has seen the rapid development of precision medicine approaches for the treatment of hematologic malignancies. These approaches are based on the identification of specific genetic defects that affect the prognosis of a disease and the development of targeted agents that attack the mutated gene or its products. For example, the FLT3 (FMS-like tyrosine kinase-3) gene encodes a receptor tyrosine kinase involved in hematopoiesis. Activating mutations of FLT3 are one of the most frequent lesions found in acute myeloid leukemia (AML), where they are associated with an increased risk of relapse and reduced overall survival compared with FLT3 mutation–negative AML. In a study currently underway at Baylor Charles A. Sammons Cancer Center at Dallas,
patients with FLT3 mutation-positive AML who have received an allogeneic stem cell transplantation are being treated with midostaurin, a drug that inhibits the activity of FLT3, to determine if it will affect relapse after transplantation. The drug will be given after transplantation for up to a year.

Drugs are now also being tested that specifically inhibit the mutated isocitrate dehydrogenase (IDH) protein. (See related story on p. 8.) IDH is a critical component of the energy-producing Kreb’s cycle, and mutations in it are associated with poor prognosis and increased risk of relapse in AML. AG-221, a drug that targets the IDH2 isotype found in mitochondria, is currently showing promising results in phase I trials.

In pursuing this strategy, an important question is whether the genetic abnormalities found in relapsed cancer are the same as those that characterized the initial disease. Dr. Agura commented: “We think that cancer comes back because we didn’t succeed in eliminating all of it. But we are finding that the relapsed cancer is not quite the same as the original disease. It differs genetically. Not by much—maybe 1 to 5 new alterations in the cancer cell—but it does appear to change over time.” Dr. Agura and colleagues are now involved in a longitudinal study looking at the genetic defects in leukemia cells before and after transplantation and after relapse. They want to assess differences in the relapsed cancer compared with the primary disease and determine if there might be a new genetic mutation for which a targeted treatment is available.

Historically, no test was available to determine if the patient was truly in remission or if microscopic deposits of subclinical disease were still present. By the time a relapse was morphologically detectable, many months could have passed. The rapidly growing roster of genetic mutations associated with specific cancers provides tools for the detection of minimal residual disease (MRD). Any mutation that differentiates the cancer cells from normal cells (e.g., IDH, FLT3 in AML) may be used to detect MRD. In proof of this concept, an early study in patients with AML using a real-time polymerase chain reaction (PCR) assay was able to detect FLT3 positivity after previous PCR-negativity up to 3 months before cytomorphological relapse became apparent. In another study, a pending relapse was detectable by persistent PCR positivity for FLT3. Ideally, the more mutations that are available, the more likely it is that MRD will be detected. With current technology, panels of 50 or more genes that are frequently mutated in AML are possible.

Dr. Agura said, “We’re at a point where we can marry genetic detection and personalization with new breakthrough drugs that work differently. This may lead to a new paradigm for both treating and preventing hematologic disease.”

**Immunologic Approaches**

One of the factors that determines if and when a relapse will occur is the strength of the immune system in fighting the cancer cells. In particular, cytokine-induced activated T cells (killer cells) can be cytolytic against leukemia cells. Unfortunately, full recovery of a functional immune system can be slow after stem cell transplantation. In order to enhance the formation of killer cells, allogeneic T cells can be activated ex vivo and administered as a vaccine to the patient, or T cell function can be enhanced in vivo using immunomodulatory approaches with exogenous cytokines.

Another approach is to genetically modify the patient’s immune cells to recognize a specific cancer. In this approach, the patient’s T cells are genetically engineered to produce special cell surface receptors (called CARs, or chimeric antigen receptors) that recognize a specific antigen on tumor cells (e.g., CD19, a normal B-cell antigen which is expressed on lymphoma and CLL cells), and then are returned to the patient either after transplantation or without a transplantation. A pharmacologic modification of this approach involves a new class of monoclonal antibodies called bispecific T-cell engagers (BiTEs) that combine a CD3 binding site for T cells and a second binding site for the targeted cancer cells. By linking these two cells together, the T cell is activated to initiate cytotoxic activity against the cancer cell. (See related article on p. 1.)

Many of these approaches are already being tested in clinical trials, and more are in the developmental pipeline. Dr. Agura commented: “Important advances have occurred in the field of stem cell transplantation over the last 15 years, and more will come as ongoing clinical trials reach maturity. Nonetheless, significant limitations remain, and too many patients will experience a recurrence of their disease. This makes prevention of relapse one of the most important and most exciting areas of research today in the field of transplantation.”
Site-Specific Tumor Conferences at Baylor Charles A. Sammons Cancer Center at Dallas

At Baylor Sammons Cancer Center at Dallas, a key element at the heart of our approach to patient care and education is the site-specific tumor conference program. Rather than focusing solely on recommendations for patient care, the site-specific conferences also aim at educating the medical professionals attending the conference.

Unlike tumor boards, continuing medical education credit is available for physicians who attend. Because several patients with the same diagnosis are presented at each conference, attendees are provided with an in-depth view from specialists, accompanied by lively discussion. Below please find the schedules for tumor conferences at Baylor Charles A. Sammons Center at Dallas.

Conference Schedules

Baylor Dallas

<table>
<thead>
<tr>
<th>Conference</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone and Soft Tissue</td>
<td>1st Tuesday</td>
</tr>
<tr>
<td>Breast</td>
<td>Thursdays</td>
</tr>
<tr>
<td>Chest</td>
<td>1st, 2nd, and 4th Wednesdays</td>
</tr>
<tr>
<td>Colorectal Multidisciplinary Tumor (MDT)</td>
<td>Thursdays</td>
</tr>
<tr>
<td>Endocrine</td>
<td>3rd Tuesday</td>
</tr>
<tr>
<td>GI</td>
<td>Alternating with Colorectal MDT</td>
</tr>
<tr>
<td>Gynecology</td>
<td>Wednesdays</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>2nd and 4th Tuesdays</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conference</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and Neck Journal Club</td>
<td>5th Tuesday</td>
</tr>
<tr>
<td>Hematopoietic Diseases</td>
<td>Wednesdays</td>
</tr>
<tr>
<td>Liver</td>
<td>2nd and 4th Tuesdays</td>
</tr>
<tr>
<td>Neuro-oncology</td>
<td>2nd and 4th Wednesdays</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1st and 3rd Fridays</td>
</tr>
<tr>
<td>Skin</td>
<td>1st and 3rd Wednesdays</td>
</tr>
<tr>
<td>Skull Base</td>
<td>1st Wednesday</td>
</tr>
<tr>
<td>Urology</td>
<td>2nd (MDT) and 3rd Wednesdays</td>
</tr>
</tbody>
</table>

Baylor Dallas

The site-specific tumor conferences are on the 10th floor conference center in the outpatient cancer center. The exceptions to this are the liver and pancreas tumor conferences, which are held in the transplant large conference room on the 9th floor of the outpatient cancer center, as well as the gynecology tumor conference, which is in room 8 of the lower level of Truett, and the skull base tumor conference, which is in the Radiology resident classroom.

For more information about site-specific tumor conferences at Baylor Charles A. Sammons Cancer Center at Dallas, please call 214.820.4073.
## New Clinical Trials at Baylor Charles A. Sammons Cancer Center at Dallas

<table>
<thead>
<tr>
<th>Site</th>
<th>Study ID</th>
<th>Location</th>
<th>Principal investigator</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>13076</td>
<td>Texas Oncology–Dallas</td>
<td>Joyce A. O’Shaughnessy, MD</td>
<td>A phase II randomized, double-blind placebo controlled, study of letrozole with or without BYL719 or buparlisib, for the neoadjuvant treatment of postmenopausal women with hormone receptor-positive HER2-negative breast cancer (CBYL719A2201)</td>
</tr>
<tr>
<td></td>
<td>12152</td>
<td>Texas Oncology–Dallas</td>
<td>Joyce A. O’Shaughnessy, MD</td>
<td>A randomized, placebo-controlled, double blind, phase 3 study evaluating safety and efficacy of the addition of veliparib plus carboplatin versus the addition of carboplatin to standard neoadjuvant chemotherapy versus standard neoadjuvant chemotherapy in subjects with early stage triple negative breast cancer (TNBC): M14-011</td>
</tr>
<tr>
<td></td>
<td>13117</td>
<td>Texas Oncology–Dallas</td>
<td>Cynthia R. C. Osborne, MD</td>
<td>H-33692: Scalp Cooling Alopecia Prevention Trial (SCALP)</td>
</tr>
<tr>
<td></td>
<td>11025</td>
<td>Texas Oncology–Dallas</td>
<td>Joyce A. O’Shaughnessy, MD</td>
<td>(USO 11025/ Novartis CBKM120ZUS39T) Phase II multicenter single-arm study of BKM120 plus capecitabine for triple negative breast cancer (TNBC) patients with brain metastases</td>
</tr>
<tr>
<td></td>
<td>13225</td>
<td>Texas Oncology–Dallas</td>
<td>Joyce A. O’Shaughnessy, MD</td>
<td>A randomized, double-blind, phase 2 Study of ruxolitinib or placebo in combination with capecitabine in subjects with advanced or metastatic HER2-negative breast cancer (INCB 18424-268)</td>
</tr>
<tr>
<td></td>
<td>13026</td>
<td>Texas Oncology–Dallas</td>
<td>Joyce A. O’Shaughnessy, MD</td>
<td>(USO 13026) Evaluation of miracle mouthwash (MMW) plus hydrocortisone and prednisolone mouth rinse as prophylaxis for everolimus-associated stomatitis</td>
</tr>
<tr>
<td></td>
<td>13074</td>
<td>Texas Oncology–Dallas</td>
<td>Carlos H. Roberto Becerra, MD</td>
<td>A phase Ib/II, multicenter, study of the combination of LEE011 and BYL719 with letrozole in adult patients with advanced ER+ breast cancer (CLEE011X2107)</td>
</tr>
<tr>
<td></td>
<td>13122</td>
<td>Texas Oncology–Dallas</td>
<td>Carlos H. Roberto Becerra, MD</td>
<td>A phase 1b study of LY2835219 in combination with endocrine therapies for patients with hormone receptor positive, HER2 negative metastatic breast cancer (I3Y-MC-JPBH)</td>
</tr>
</tbody>
</table>
### Online Access to Clinical Trials

Physicians and patients can now access information about open clinical trials in oncology at Baylor Sammons Cancer Center with these steps:

- Go to BaylorHealth.edu/Sammons.
- Click on “Research” on the left-hand menu, then click on “Clinical Trials” in the drop-down menu.
- Select a condition (e.g., “Cancer”) and then select a specific disease (e.g., “Breast Cancer”)

For additional details or questions about the studies, please contact the Office of Clinical Oncology Research Coordination at 214.818.8472, 817.698.8472 or via e-mail at cancer.trials@baylorhealth.edu.

<table>
<thead>
<tr>
<th>Site</th>
<th>Study ID</th>
<th>Location</th>
<th>Principal investigator</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>13057</td>
<td>Texas Oncology–Dallas</td>
<td>Carlos H. Roberto Becerra, MD</td>
<td>A phase II clinical study of BBI608 in adult patients with advanced colorectal cancer (BBI608-224)</td>
</tr>
<tr>
<td>GU</td>
<td>T01402</td>
<td>Texas Oncology–Dallas</td>
<td>Thomas E. Hutson, DO</td>
<td>A041-04: A phase II randomized double-blind study of dalantercept in combination with axitinib compared to axitinib alone in patients with advanced renal cell carcinoma</td>
</tr>
<tr>
<td>Hematology</td>
<td>013-128</td>
<td>Baylor Dallas</td>
<td>Moshe Levy, MD</td>
<td>Single arm open-label Phase 2 study evaluating dasatinib therapy discontinuation in patients with chronic phase chronic myeloid leukemia (CP-CML) with stable complete molecular response (CMR)</td>
</tr>
<tr>
<td></td>
<td>013-282</td>
<td>Baylor Dallas</td>
<td>Moshe Levy, MD</td>
<td>A phase II Simon two-stage study of the addition of pracinostat to a hypomethylating agent (HMA) in patients with myelodysplastic syndrome (MDS) who have failed to respond or maintain a response to the HMA alone</td>
</tr>
<tr>
<td></td>
<td>013-308</td>
<td>Baylor Dallas</td>
<td>Joseph W. Fay, MD</td>
<td>An open-label, multicenter, phase 1b study of JNJ-54767414 (HuMaxCD38) (Anti-CD38 monoclonal antibody) in combination with backbone regimens for the treatment of subjects with multiple myeloma</td>
</tr>
<tr>
<td></td>
<td>014-025</td>
<td>Baylor Dallas</td>
<td>Moshe Levy, MD</td>
<td>A phase I/II study of low dose cytarabine and lintuzumab-Ac225 in older patients with untreated acute myeloid leukemia</td>
</tr>
<tr>
<td></td>
<td>014-036</td>
<td>Baylor Dallas</td>
<td>Estil A. Vance, MD</td>
<td>A randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 study of the safety, tolerability, and efficacy of CMX001 for the prevention of cytomegalovirus (CMV) infection in CMV-seropositive (R+) hematopoietic stem cell transplant recipients</td>
</tr>
<tr>
<td>Site</td>
<td>Study ID</td>
<td>Location</td>
<td>Principal investigator</td>
<td>Title</td>
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</tr>
<tr>
<td>Hematology</td>
<td>014-070</td>
<td>Baylor Dallas</td>
<td>Houston Holmes, MD</td>
<td>A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously untreated chronic lymphocytic leukemia</td>
</tr>
<tr>
<td></td>
<td>014-095</td>
<td>Baylor Dallas</td>
<td>Moshe Levy, MD</td>
<td>A multicenter open-label, randomized phase 1b/2, study of the Bruton’s tyrosine kinase (BTK) inhibitor, ibrutinib, in combination with lenalidomide, with and without rituximab in subjects with relapsed or refractory diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>T01305</td>
<td>Texas Oncology–Dallas</td>
<td>Luis A. Pineiro, MD</td>
<td>An observational, non-inerventional, multi-center, multi-national study of patients with atypical hemolytic-uremic syndrome (AHUS registry)</td>
</tr>
<tr>
<td>Liver/</td>
<td>13195</td>
<td>Texas Oncology–Dallas</td>
<td>Carlos H. Roberto Becerra, MD</td>
<td>A phase I/Ii study of CX-4945 in combination with gemcitabine plus cisplatin in the frontline treatment of patients with cholangiocarcinoma (S4-13-001)</td>
</tr>
<tr>
<td>Bile Duct</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>13232</td>
<td>Texas Oncology–Dallas</td>
<td>Kartik Konduri, MD</td>
<td>Randomized, double-blind, multicenter, phase 3 study comparing veliparib plus carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel in previously untreated advanced or metastatic squamous non-small cell lung cancer (NSCLC): M11-091</td>
</tr>
<tr>
<td></td>
<td>13179</td>
<td>Texas Oncology–Dallas</td>
<td>Kartik Konduri, MD</td>
<td>A phase IIIb/IV safety trial of nivolumab (BMS-936558) in subjects with advanced or metastatic non-small cell lung cancer who have progressed during or after receiving at least one prior systemic regimen (CA209153)</td>
</tr>
<tr>
<td></td>
<td>13213</td>
<td>Texas Oncology–Dallas</td>
<td>Kartik Konduri, MD</td>
<td>(9090-14) A randomized, phase 3 study of ganetespib in combination with docetaxel versus docetaxel alone in patients with advanced non-small-cell lung adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>13217</td>
<td>Texas Oncology–Dallas</td>
<td>Kartik Konduri, MD</td>
<td>TIGER-2: A phase 2, open-label, multicenter, safety and efficacy study of oral CO-1686 as 2nd line EGFR–directed TKI in patients with mutant EGFR non-small cell lung cancer (NSCLC) with the T790M resistance mutation (CO-1686-019)</td>
</tr>
</tbody>
</table>

(Continued on page 20)


### Clinical Trials (Continued from page 17)

<table>
<thead>
<tr>
<th>Site</th>
<th>Study ID</th>
<th>Location</th>
<th>Principal investigator</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>14034</td>
<td>Texas Oncology–Dallas</td>
<td>Kartik Konduri, MD</td>
<td>(ABI-007-NSCL-005) Safety and efficacy of nab®-paclitaxel (Abraxane®) in combination with carboplatin as first line treatment in elderly subjects with advanced non-small cell lung cancer (NSCLC): A Phase IV, randomized, open-label, multicenter study (Abound.70+)</td>
</tr>
<tr>
<td>Neuro-oncology</td>
<td>014-046</td>
<td>Baylor Dallas</td>
<td>Isaac Melguizo-Gavilanes, MD</td>
<td>A phase 1 study of memantine in combination with temozolomide in patients receiving concurrent chemoradiation for newly diagnosed glioblastoma multiforme</td>
</tr>
<tr>
<td></td>
<td>014-051</td>
<td>Baylor Dallas</td>
<td>Karen Fink, MD, PhD</td>
<td>A retrospective and prospective longitudinal brain data collection study for multidisciplinary tumor conferences</td>
</tr>
<tr>
<td></td>
<td>014-080</td>
<td>Baylor Dallas</td>
<td>Karen Fink, MD, PhD</td>
<td>A phase 1/2 study of SL-701, a subcutaneously injected multivalent glioma-associated antigen vaccine, in adult patients with recurrent glioblastoma</td>
</tr>
<tr>
<td>Pancreas</td>
<td>13084</td>
<td>Texas Oncology–Dallas</td>
<td>Carlos H. Roberto Becerra, MD</td>
<td>A pilot study examining the utility of transrenal quantitative KRAS testing in disease monitoring in patients with metastatic pancreatic cancer (TROV-006)</td>
</tr>
<tr>
<td>Solid Tumor</td>
<td>14048</td>
<td>Texas Oncology–Dallas</td>
<td>Carlos H. Roberto Becerra, MD</td>
<td>A phase 1 clinical study of BBI503 in adult patients with advanced solid tumors (BBI503-101)</td>
</tr>
</tbody>
</table>