“We saw an opportunity to marry the kind of calculation we do to the kind of risk communication messages they do,” said NCI’s Feuer.

Accurate risk communication messages are based on several principles, Schwartz and Woloshin said. One is to put the number of deaths in numerical context—e.g., 3 of 100 people, or 3%—rather than the absolute number of people expected to die of a disease. Give the denominator, in other words, as well as the numerator.

Another is to avoid making statements of relative risk without giving actual figures. A 50% risk reduction sounds large but may not mean much if risk is reduced from 4% to 2%. But if risk is reduced from 60% to 30%, a 50% reduction can mean a lot.

A guiding principle is to put risks in accurate perspective. “We wanted to put risk in context,” Schwartz said, “by using denominators, by comparing each specific cancer to other cancers and other major causes of death, and by using standardized time frames and formats.”

The 10-year time frame is arbitrary but makes sense, they said, because it avoids the exaggerated risk that comes with time frames that are too long as well as those that are too short. “Over-a-lifetime risk distorts the picture, but so can too short a time frame,” Woloshin said. That can cause you to underestimate your risk.

The 10-year time frame also allows people time to do things such as make lifestyle changes or consider proven screening tests, they note on the website.

**Setting Priorities**

The charts present risk by age, sex, and race, but so far not by factors related to lifestyle or heredity. However, NCI plans to add smoking, the single most important risk factor for a variety of cancers and other causes of death.

In an earlier version of the charts (J. Natl. Cancer Inst. 2008;100:845–53), the Dartmouth authors included how smoking affects risk. Data and methods are now being updated using National Health Interview Surveys that include smoking status and follow-up data on mortality and cause of death.

As for family history, lifestyle, and other risk factors, finding comparable data sources may be more problematic.

“We see it as providing breadth, giving the broad landscape. It could help a person make decisions about priorities—diabetes, lung cancer, heart attack, for instance—before making decisions about lifestyle changes or screening.”

“We have to consider feasibility,” Schwartz said. “Right now we don’t have good data for all of them. But even with extra risk factors we might not know that much more.”

In any case, “Know Your Chances” is not designed to do exactly the same thing as other risk assessment tools, which may provide estimates for a single disease as a function of several risk factors. Instead, it could complement them, Feuer said. “We see it as providing breadth, giving the broad landscape. It could help a person make decisions about priorities—diabetes, lung cancer, heart attack, for instance—before making decisions about lifestyle changes or screening.”

“Both facts and values go into decision making,” Woloshin noted. “These charts give facts. The values are individual, how you process the facts. Research has shown people process the same facts differently.”

That finding suggests that the charts’ facts could be the basis for doctor-patient discussions of risks and what to do about them.

In fact, “the charts could be the first step in a huge educational process,” said Otis Brawley, M.D., chief medical officer of the American Cancer Society. He said physicians could use the charts to help patients avoid common pitfalls of exaggerating the chance of dying from one disease, such as prostate cancer, while minimizing the greater chance of dying from others. For instance, a 55-year-old white man has a 1 in 1,000 chance of dying from prostate cancer within 10 years, compared with 2 in 1,000 for high blood pressure, 3 in 1,000 for stroke, and 10 in 1,000 for lung cancer, according to the charts.

“One of the great problems we deal with in our society is that people don’t understand or they misperceive risk,” Brawley said. “These charts could reduce a lot of mental anguish and a lot of concern.”

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**Targeted Therapies Improve Outlook for Chronic Lymphocytic Leukemia**

By Vicki Brower

In a pilot trial of an autologous cell therapy for chronic lymphocytic leukemia (CLL), four of 14 patients achieved complete responses and four had partial responses, some of which are ongoing 4.5 years after treatment. University of Pennsylvania researchers recently reported mature data from the pilot trial of the treatment, CTL-019, begun in 2010, in which patients received an infusion of their own T cells that were genetically modified to express a chimeric antigen receptor (CAR) (Sci. Transl. Med. 2015;7:303;doi:10.1126/scitranslmed.aac5415; doi:10.1126/scitranslmed). CAR T cells target the CD19 protein found on the surface of B cells that characterize CLL.
“The durability of the remissions we have observed in this study are remarkable and give us great hope that these personalized cell therapies are going to be important options for patients whose cancers are no longer treatable by standard approaches,” said David L. Porter, M.D., principal investigator and Jodi Fisher Horowitz Professor in Leukemia Care Excellence at the University of Pennsylvania in Philadelphia. “The fact that some patients have no sign of disease 5 years after their cell infusion suggests that the cancer cells may have indeed been eradicated,” Porter said.

“One of the exciting things about the new cellular therapies is being able to even consider that possibility for cure without the need for lifelong treatment,” he said.

The most common leukemia in the West, CLL accounted for 119,390 leukemia patients in the U.S. in 2013 and 15,720 new cases in 2014. CLL may remain indolent in 30% of patients, but for most, new drugs are needed to improve side effects and increase long-term survival, especially for the elderly and those with high-risk disease. Stem cell transplantation is the only curative treatment for CLL, but CAR T-cell therapy and an array of new targeted drugs may be rapidly changing the long-term prognosis of CLL patients.

**Revolution in Treatments**

“There has been a revolution in CLL in the past 5 years, and treatment is now in the midst of a transformation,” said Anthony Mato, M.D., assistant professor of medicine at the University of Pennsylvania. “New drugs and cellular therapies which are providing better activity, good toxicity profiles, and options combining and omitting chemotherapy are rapidly proliferating,” he said. “For relapsed CLL, and patients with high-risk disease, we are seeing better survival with newer treatments and novel treatment combinations for what is a very complicated disease with respect to signaling pathways and redundancies,” Mato said. “While CLL lags behind chronic myelogenous leukemia with respect to our understanding of the disease, we are catching up,” he said.

Researchers are also gaining new knowledge about the development and progression of CLL, which will affect future treatment. In October 2015, new genomic research identified key driver mutations before and after treatment, and upon relapse, using samples from 538 CLL patients, including 278 on standard therapy (fludarabine, cyclophosphamide, and rituxan) (Nature 201;526, 525–530;doi:10.1038/nature15395). Dan A. Landau, M.D., Ph.D., is assistant professor of medicine, physiology, and biophysics at the Weill Cornell Medical College and a core member of the New York Genome Center. He and his colleagues discovered several new driver genes; gained a better understanding of pathways important to development of CLL, including MAP/ERK; and found a new pathway previously unknown and gained understanding of why patients relapse. “Our study also demonstrated that almost all CLL undergoes clonal evolution after relapse,” Landau said. “By using these samples, we could predict the course of evolution, which means that it should be possible to design treatments to prevent that from happening,” Landau said.

“The durability of the remissions we have observed in this study are remarkable and give us great hope that these personalized cell therapies are going to be important options for patients whose cancers are no longer treatable by standard approaches.”

Until recently, chemotherapy remained the backbone of CLL treatment, but that is rapidly changing. “Now, treatments are moving away from chemotherapy toward biological and targeted agents,” Porter said. Four recently approved targeted drugs that interfere with the B-cell receptor signaling pathway are in trials in different combinations, with and without chemotherapy, and a raft of triple combination treatments. New targets are also in development.

**B-Cell Signaling Pathways**

Since 2010, important evidence has been accumulating for the centrality of B-cell receptor signaling and antiapoptotic pathways in CLL. Small-molecule inhibitors of kinases involved in B-cell signaling are a booming area of research. One kinase in this signaling pathway is phosphoinositide 3-kinase delta (PI3Kδ). PI3Kδ is not only activated in cancerous B cells but also involved in many normal functions. However, scientists discovered that one isofom, PI3Kδδ, is relatively specific to hematopoietic cells. The first-in-class drug poziotinib is idelalisib, which was approved in the U.S. in 2014 for use with rituximab, a monoclonal antibody that targets the CD20 protein on B cells, in relapsed or refractory CLL.

In a landmark phase III trial, idelalisib and rituximab were compared with rituximab in 220 relapsed patients with clinically relevant medical issues (N. Engl. J. Med 2014;370:997–1007; doi:10.1056/NEJMoa1315226). The median progression-free survival (PFS) was 5.5 months in the placebo group and not reached in the idelalisib group. Overall survival (OS) at 12 months was 92% for the combination and 80% for rituximab.

At the June 2015 American Society of Clinical Oncology (ASCO) 2015 meeting, Jeffrey Alan Jones, M.D., M.P.H., assistant professor of medicine at Ohio State University in Columbus, discussed results of a phase III study of idelalisib in 261 patients with ofatumumab, a newer anti-CD20 antibody, versus ofatumumab alone in patients who relapsed (abstract 7023, http://meetinglibrary.asco.org/content/151048-156). Patients taking the combination had better PFS, 16.3 months vs. 8 months, and overall response rate, 75.3% vs. 18.4%. Those with high-risk disease had better median PFS with the combination, 13.7 months vs. 5.8 months. Side effects were similar in both cohorts and consistent with previous studies. “Early side effects, liver related, are generally reversible, but late side effects include colitis, which has led to problems with continuous dosing which need to be worked out,” said Steven Coutre, M.D., professor of medicine at the Stanford University Medical Center in Palo Alto, Calif., who was involved in trials for idelalisib.

Several other PI3Kδ inhibitors are also in development. Researchers discussed phase I results in 58 patients with a second-generation PI3Kδ inhibitor, TGR-1202, at ASCO in June (abstract
BCL-2 Inhibition: Restoring Cell Death

Another important regulator of CLL is the BCL-2 cell death protein. BCL-2 is overexpressed on CLL cells and interferes with apoptosis. Venetoclax, a small-molecule inhibitor of BCL-2, helps restore normal apoptosis of cancer cells. In a phase I study, response rates were high in patients with refractory or relapsed CLL, and safety was excellent, as reported at ASCO in 2014 (abstract 7015; http://meetinglibrary.asco.org/content/134145-144). The ORR was 77%, with a median duration of response 20.5 months, and 23% had complete responses.

Michael Weber, Ph.D., professor of microbiology, immunology, and cancer biology at the University of Virginia in Charlottesville, used patients’ circulating tumor cells to test combinations of ibritinib, the proteasome inhibitor carfilzomib, and venetoclax against ibritinib. Ibritinib and venetoclax induced apoptosis in 23% of samples, compared with 3.8% for ibritinib, 5.5% in ibritinib and carfilzomib, and 1.7% with carfilzomib (Leukemia 2014;28:407–10; doi:10.1038/leu.2013.249).

“Venetoclax and ibritinib target different pathways involved in promoting cancer cell survival and growth,” Weber said. “Cancer cells adapt and find new ways to reactivate a pathway to become resistant, but in this case, targeting a pathway outside the primary pathway was effective,” he said. One possible reason for the synergy is that venetoclax kills cells rapidly, and neutralizes a resistance mechanism generated by ibritinib, so that perhaps more cells are killed in the aggregate when the two drugs are combined, Weber said. Next, he will investigate whether second-generation, more specific BTK inhibitors might work better, or possibly worse, if BTK is not the only critical ibritinib target.

With combinations of newer drugs, turning CLL into a chronic, if not curable, disease for many more patients may be within reach, Weber said. “New treatments are being developed with amazing speed,” Jones said. Several new single and combination treatments are resulting in many durable and deep remissions on first-round therapy, or later, after relapse, he said. As a CLL investigator, Jones finds this development exciting. “We now have more colors on our palette,” he said. “It’s not entirely clear how it will play out, but there is great reason for optimism,” Jones said.

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Childhood Cancer Survivors: The Long Road Ahead

By Cathryn Delude

Fifty years ago, childhood cancers were largely fatal; today the survival rate tops 83%. But as the ranks of these survivors reaching adulthood and middle age pass 400,000, so do the late effects from their lifesaving treatments.

Childhood cancer survivors experience multiple and often severe health problems more typical of those decades older; they also die prematurely.

“Childhood cancer survivors may have a stroke at 35, a heart transplant at 40—something we would never expect at their age,” said Julia Rowland, Ph.D., director of the office of cancer survivorship at the National Cancer Institute.

After the recognition that childhood cancer treatments increase risk of morbidity and early mortality, two decades of solid research has linked those problems to delayed effects of the radiation, chemotherapies, and surgeries children received at a developmentally sensitive stage of life. In response, pediatric oncologists have tailored therapies to reduce the burden of late effects.

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