As leukemia options grow, drugs jockey to be first-line therapies

In June 2008, Beth Galliart was diagnosed with chronic myeloid leukemia. At the time, her doctors put her on Gleevec (imatinib), a small-molecule drug available since 2001 that is often touted as the poster child of personalized medicine. Marketed by Switzerland's Novartis, Gleevec specifically targets the tyrosine kinase enzyme that is overactive in the white blood cells of people with leukemia. For close to nine months, the drug worked wonders for Galliart, and her blood counts returned to normal levels. But she soon started to feel tired again. A blood test confirmed that her cancer had returned.

Galliart's doctors made a decision in March 2009 to switch her to Sprycel (dasatinib), a comparable tyrosine kinase inhibitor (TKI) from New York's Bristol-Myers Squibb. She ended up taking that drug for only three days, though: her doctors took her off the drug when they received the results of a genetic test revealing that her cancer cells had evolved the T315I mutation in the tyrosine kinase BCR-ABL, making it impervious to all approved TKIs for the disease, including Gleevec and Sprycel. Galliart, an executive assistant at an investment firm in Silicon Valley, California, prepared herself for a risky bone marrow transplant. Her family prepared for the possibility that she might die.

Distant cousins from Kansas came to visit and say their final goodbyes. They and Galliart were picking strawberries one day in May 2009 when her phone rang. It was a clinical study coordinator from the University of California–San Francisco (UCSF) on the line. A managing partner from Galliart's firm knew a UCSF doctor who was running a phase 1 clinical trial with an experimental agent called ponatinib. On the basis of preclinical work, this drug was thought to inhibit the mutated forms of the BCR-ABL protein that are responsible for people's resistance to most TKIs—including the T315I mutation.

Galliart quickly enrolled in the study. A month later, she received her first dose of the drug.

Although she did suffer intense bone pain for three days after first receiving ponatinib—"It was sort of like a bomb was going off in my whole body," recalls Galliart, who turns 48 this month—her cancerous blood cells have not come back since. She is now training for a half-marathon and regularly rides and jumps horses.

Fortunately, Galliart's positive experience with ponatinib is not unique. In a phase 2 trial of 449 people with CML or the similar acute lymphoblastic leukemia (ALL) who were intolerant to other TKIs or who had a confirmed T315I mutation, around half responded favorably to the drug. The results were presented last month at the American Society for Hematology meeting in Atlanta. Phase 1 trial results involving 81 participants, including Galliart, were published in late November in the *New England Journal of Medicine* (**367**, 2075–2088, 2012). Ponatinib was approved by the US Food and Drug Administration (FDA) on 14 December. It will be marketed by Ariad Pharmaceuticals of Cambridge, Massachusetts, as Iclusig.

"This drug has the potential to be a best-in-class agent that may be completely invulnerable to single-kinase-domain mutations," says Neil Shah, the UCSF hematologist who treated Galliart. "I'm hopeful that it really will remove single-kinase-mutation–mediated resistance out of the picture."

Give me five!

Iclusig is the fifth TKI available in the US—after Gleevec, Tasigna (nilotinib; also from Novartis), Sprycel and Bosulif (bosutinib)—for people with CML or Philadelphia chromosome–positive ALL. (The FDA approved Bosulif from New York's Pfizer in September 2012 for leukemia patients who have failed on other therapies.) Looking ahead, "I don't see any quantum leaps in tyrosine kinase inhibitors after ponatinib," says Shah. "It would be great to have another one for people who can't tolerate ponatinib for one reason or another yet happen to have, for instance, a T315I mutation. But aside from that, it's hard to see that there's a pressing need for another BCR-ABL tyrosine kinase inhibitor."

As such, attention is now shifting away from the drug pipeline and toward questions of clinical best practice. Like Bosulif, Iclusig is initially available only for people with resistant or intolerant disease. But, with an eye to gaining broader approval, Ariad launched a 528-person, phase 3 trial last July that is testing Iclusig head to head with Gleevec in people newly diagnosed with CML.

"The optimal first-line treatment for a patient with newly diagnosed chronic-phase CML is highly contentious at the moment," says John Goldman, a hematologist at Imperial College London who has studied many of the TKIs, including Iclusig. "There is no real agreement and a lot of strongly held opinions."

When used as first-line treatments, Tasigna, Sprycel and Bosulif have all produced better response rates than Gleevec (*N. Engl. J. Med.* **362**, 2251–2259 and 2260–2270, 2010; *J. Clin. Oncol.* **30**, 3486–3492, 2012). Because of this, some physicians speculate that patients given the newer TKIs as a first option will respond so well to the drugs that they'll be able to discontinue therapy. "I use second-generation TKIs because you get better responses, faster responses, deeper responses—and all these things are important," says Jorge Cortes, a leukemia specialist at the MD Anderson Cancer Center in Houston who has led trials involving all the TKIs.

Michelle Arani

CML, hold your horses: Beth Galliart.

But, as of yet, there's no long-term evidence that using these newer agents up front or waiting until a patient fails on Gleevec before administering them has any effect on survival outcomes. Thus, some doctors advocate allowing price to dictate the drug decision-making process. "The huge gorilla in the room is that imatinib is going to become generic," notes Charles Schiffer, a hematologist-oncologist at Wayne State University School of Medicine's Karmanos Cancer Institute in Detroit. Novartis's patent on the drug, which accounted for an estimated $4.7 billion in global sales last year, will expire in 2015 in the US, 2016 in the major EU countries and 2014 in Japan. "So, the issue is whether cost will or should be the driver, and many of us think it should and will be."

Regardless of how the drugs are administered, patients ultimately stand to gain from all these therapeutic options for CML, notes Hildy Dillon, senior vice president of patient services for the Leukemia & Lymphoma Society, a research and advocacy organization based in White Plains, New York. "There are more tools in the pocket of the clinician for a disease that, superficially, has become a manageable cancer but still has complications," she says. "What's exciting is that there are new drugs that can help with the complications."

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