DRUG DEVELOPMENT

Target practice

Better designs for clinical trials and the use of combination therapies may improve leukaemia treatment.

BY ALLA KATSNELSON

Thirty-five years ago, as a fellow at the MD Anderson Cancer Center in Houston, Texas, Elihu Estey read dozens of protocols for clinical trials of drugs for acute myeloid leukaemia (AML). He was particularly drawn to their 'rationale' sections, which explain why the therapy is expected to work.

"They all sounded very compelling," says Estey, now a haematologist at the University of Washington in Seattle. "But of course, very few of them worked."

Since then, researchers have made significant advances in treating many types of leukaemia. However, AML — an aggressive blood cancer that causes white-blood-cell precursors called myeloid cells to proliferate uncontrollably — has remained a tough nut to crack.

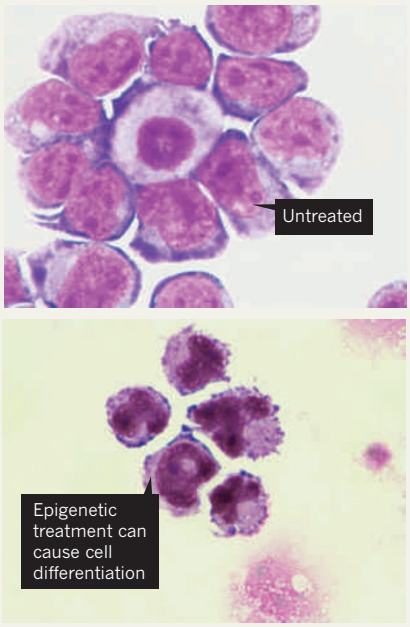
This is a big problem because AML accounts for about one-third of all leukaemia diagnoses. It is most common in people over 65 years of age, for whom the five-year survival rate is less than 10%; in younger adults the outcome is closer to 50%. And each person with AML — indeed, each cell in each person with AML — can carry a different combination of dozens of mutations (see 'Written in blood', page S4). This genetic diversity makes it difficult to design drugs, and to compare people in clinical trials.

The standard treatment for AML is a chemotherapy regimen developed in the 1970s. The least sick individuals might be eligible for blood-stem-cell transplantation. But that is a risky procedure with a mortality rate of 10–25% and long-lasting side effects. With the exception of an immune-based therapy currently in early-stage trials, no treatment on the horizon seems likely to alter this picture substantially. "There are no good drugs," says Estey.

The prognosis for other types of leukaemia is more promising. Acute lymphoblastic leukaemia (ALL), which accounts for 75% of cases of childhood leukaemia, has a 90% cure rate in children under 15, and some rare subtypes of adult leukaemias, such as hairy cell leukaemia and acute promyelocytic leukaemia, have a similarly positive outlook. Chronic lymphocytic leukaemia (CLL), which in most cases affects immune cells called B cells, responds to combinations of chemotherapy and treatment with monoclonal antibodies — immune molecules that bind to specific proteins — and has a survival rate of about 80% five years after diagnosis.

A CHANGE OF APPROACH

Epigenetic treatments are being developed for use in leukaemia cells.



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Perhaps the most dramatic change in outcome has been in chronic myeloid leukaemia (CML), with the 2001 approval of imatinib, marketed by Switzerland-based Novartis as Gleevec in the United States and Glivec elsewhere. The drug's introduction caused the five-year survival rate for CML to shoot up from 30% to around 90%. Imatinib also provided an early proof of concept for therapies targeted to a particular genetic abnormality — an approach that holds promise for a variety of other diseases.

Imatinib blocks the activity of a tyrosine kinase called BCR–ABL — an enzyme that promotes cell signalling and growth, and often triggers cancer when mutated. The *BCR–ABL* gene is produced when segments of chromosomes 9 and 22 swap places, fusing the *BCR* and *ABL* genes, which are usually separated on the different chromosomes. About 95% of people with CML carry this chromosomal change.

The drug turned out to be far from perfect: about a third of people with CML do not fully respond to it or eventually develop resistance. Four other drugs that inhibit BCR–ABL have since been approved in an effort to fill in the gaps (see 'Combined forces', page S7). One of these drugs, ponatinib (Iclusig), approved in December 2012, targets a particular mutation in *BCR–ABL* that makes cells resistant to imatinib and accounts for 20% of all *BCR–ABL* mutations.

The string of leukaemia drug approvals points to a growing awareness among scientists that no single drug is likely to be powerful enough to halt the disease on its own.

People with CML may need to switch from imatinib to other drug options as they develop resistance, says Hagop Kantarjian, an oncologist who chairs the leukaemia department at the MD Anderson Cancer Center. "Most patients can live their lives," he says, "provided they take their drugs and the drugs are changed up as needed."

Compared with CML, other types of leukaemia, such as AML and ALL, are genetically much more varied and, because they are acute, they mutate more rapidly over time. But targeted therapies such as imatinib can help when they are combined with other drugs, says oncologist Brian Druker, director of the Knight Cancer Institute at Oregon Health and Sciences University in Portland, Oregon, and one of three researchers responsible for developing imatinib. "By adding a targeted agent to standard chemotherapy, you can make a huge impact on the prognosis of an acute leukaemia."

BETTER TRIALS

Imatinib's dramatic success has helped to spur the development of drugs that inhibit other tyrosine kinase enzymes (see 'Recent leukaemia drugs'). One of the most promising targets is the enzyme FLT3, which is mutated in one-quarter of people with AML and increases the risk of relapse. A handful of FLT3 inhibitors are in trials. In a phase II clinical trial reported in December 2012, half of the people tested who carry a mutation in *FLT3* responded to quizartinib, as did a third who lack the mutation.

Although promising, results from trials of FLT3 inhibitors show that simply identifying a mutation does not guarantee treatment success. Researchers still do not know which of the commonly seen mutations within AML cells are important, or what impact they might have, says Alan Burnett, a haematologist and AML specialist at the Cardiff University Experimental Cancer Medical Centre, UK.

Some combinations of mutations seem to be associated with more favourable disease outcomes, for example, but no one knows why. And pharmaceutical companies may be reluctant to develop drugs that would target a specific combination of mutations in a small number of affected individuals, says Burnett.

To address some of these problems, researchers are exploring new ways of structuring clinical trials. Usually, novel drugs are not compared against each other at an early stage of clinical testing, and results are hard to compare because trials

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RECENT LEUKAEMIA DRUGS

Drugs approved since the start of 2012 and a sample of drugs in clinical trials.

Name	Marketed as	Manufacturer	Leukaemia type	Status	Mechanism of action
Ponatinib	Iclusig	Ariad Pharmaceuticals	CML, ALL	Approved in late 2012	Tyrosine kinase (BCR–ABL) inhibitor
Bosutinib	Bosulif	Pfizer	CML	Approved in late 2012	Tyrosine kinase (BCR–ABL, SRC) inhibitor
Midostaurin	(PKC412)	Novartis	AML	Phase III	Tyrosine kinase (multiple) inhibitor
Quizartinib	(AC220)	Ambit Bioscience	AML	Phase II	Tyrosine kinase (FLT3) inhibitor
EPZ5676	n/a	Epizyme	Acute leukaemia	Phase I	DOT1L inhibitor/epigenetics
Omacetaxine	Synribo	Teva	CML	Approved in late 2012	Protein translation inhibitor
Vosaroxin	n/a	Sunesis	AML	Phase III	DNA intercalator/topoisomerase II inhibitor
CART-19	n/a	University of Pennsylvania/Novartis	Diverse leukaemias	Phase I	Anti-CD19 chimaeric antigen receptor/ immunotherapy
Actimab-A	n/a	MSKCC/Actinium Pharmaceuticals	AML	Phase I/II	Anti-CD33, armed with radioactive isotope actinium-225
Obinutuzumab	(Ga101)	Roche	CLL	Phase III	Anti-CD20 monoclonal antibody

can be designed in different ways. To combat this, Estey and his colleagues have pitted four test drugs against each other in the earliest phase of clinical trials[1], with the idea of taking only the best into further development.

The approach has not gained much traction in the United States but has taken off elsewhere, with about 10 drugs evaluated in the past six years in the United Kingdom, along with efforts in Denmark and New Zealand. The idea is to identify "more efficient ways of finding drugs that make a difference", says Burnett, who leads the UK trials.

Druke, meanwhile, has helped to develop a screening system to test how well different people with leukaemia respond to a panel of 130 kinase inhibitors. The researchers use the data to predict which of the drugs might be most effective in each individual, and to help identify the driving molecular abnormality in the leukaemia[2]. In early 2013, Druker launched a study comparing people treated with standard therapy with those receiving drugs handpicked by his system. Experimental groups in a clinical trial generally receive the same treatment, but in this study their treatments differ, with individual molecular profiling used to select them.

ALTERED EXPRESSION

Other efforts to develop targeted drugs focus on epigenetic factors — enzymes that influence gene expression without altering the underlying genetic code (see 'Reversible tags', page S10). In the past few years, researchers have discovered that many epigenetic processes are dysregulated in leukaemia and other cancers. "With epigenetics you have a whole new class of enzymes that offer a different way to target cancer cells," says Scott Armstrong, a paediatric oncologist at the Memorial Sloan-Kettering Cancer Center in New York. "That gets people pretty excited both in terms of clinical prospects and financial prospects."

So far, however, the excitement has outpaced the achievement. Many epigenetics-based compounds work well in cultured leukaemia cells and animal models (see 'A change of approach'), but have been less successful in treating people. For example, the drugs 5-azacitidine (marketed as Vidaza) and decitabine (marketed as Dacogen) both interfere with DNA methylation — a brake system for gene expression. Both have gained widespread approval for the treatment of myelodysplastic syndrome, a non-aggressive cancer that progresses to AML in a third of patients.

But the benefit of these drugs is less clear in clinical trials for leukaemia. Unlike imatinib and other tyrosine kinase inhibitors, which target particular molecular markers, these epigenetic drugs may be less precise in their action, Armstrong says. The same problem afflicts another class of agents, known as histone deacetylase inhibitors, which modify DNA-associated proteins called histones, he says.

"Epigenetics gives you a whole new class of enzymes that offer a different way to target cancer cells."

Armstrong's team is focusing instead on a different epigenetic target: the DOT1L protein, which helps to regulate chromatin structure and gene expression. DOT1L seems to be required for cells carrying a mutation in a gene called *MLL* (also known as *KMT2A*) to become leukaemic[3]. That defect is present in about 5–10% of AML and ALL cases.

In September 2012, Armstrong and his colleagues, working with Epizyme, a biotech company based in Cambridge, Massachusetts, launched a clinical trial of a drug that blocks DOT1L in people with leukaemia carrying the mutant *MLL* gene. The drug, called EPZ-5676, "falls into the imatinib type of approach", Armstrong says, in that it targets a specific genetic abnormality.

As efforts to develop these sorts of small-molecule drugs have continued, a powerful immunological approach, in the works for three decades, seems to be making impressive strides. Called chimaeric antigen receptor (CAR) therapy, the two-step approach involves extracting T cells — immune cells that recognize pathogens and tumour tissue — from a person with leukaemia. The T cells are then armed with a receptor that allows them to kill the leukaemia and reintroduced.

This CAR therapy has brought about a complete or partial remission in 10 of 16 adults, and 6 of 8 children, who have received the treatment so far, says Carl June, an immunologist at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia who led the team that developed the therapy[4]. In August 2012, Novartis announced that it would license June's approach and fund his work to the tune of US$20 million.

In March 2013, researchers led by Renier Brentjens and Michel Sadelain at the Memorial Sloan-Kettering Cancer Center reported remission in five people who received a similar treatment[5]. June and Brentjens have now launched a trial to compare the two techniques and determine which elements of each work best. Researchers at the MD Anderson Cancer Center and at the Baylor College of Medicine in Houston, Texas, are also developing CAR therapies.

"The principle that these drugs can work has been established," says June. "Now it's a question of optimizing and also of cell manufacturing" (see 'Assembly line immunotherapy', page S17).

Others are more circumspect. "At the risk of seeming too cynical, I have heard about many things that, like CAR, seemed very promising but did not pan out," says Estey. "History would suggest that it alone will not be as successful as purported." ■

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1. Estey, E. H. & Thall, P. F. *Blood* **102,** 442–448 (2003).
2. Tyner, J. W. *et al. Cancer Res.* **73,** 285–296 (2013).
3. Deshpande, A. J. *et al. Blood* **121,** 2533–2541 (2013).
4. Kalos, M. *et al. Sci. Transl. Med.* **3,** 95ra73 (2011).
5. Brentjens, R. J. *et al. Sci. Transl. Med.* **5,** 177ra38 (2013).