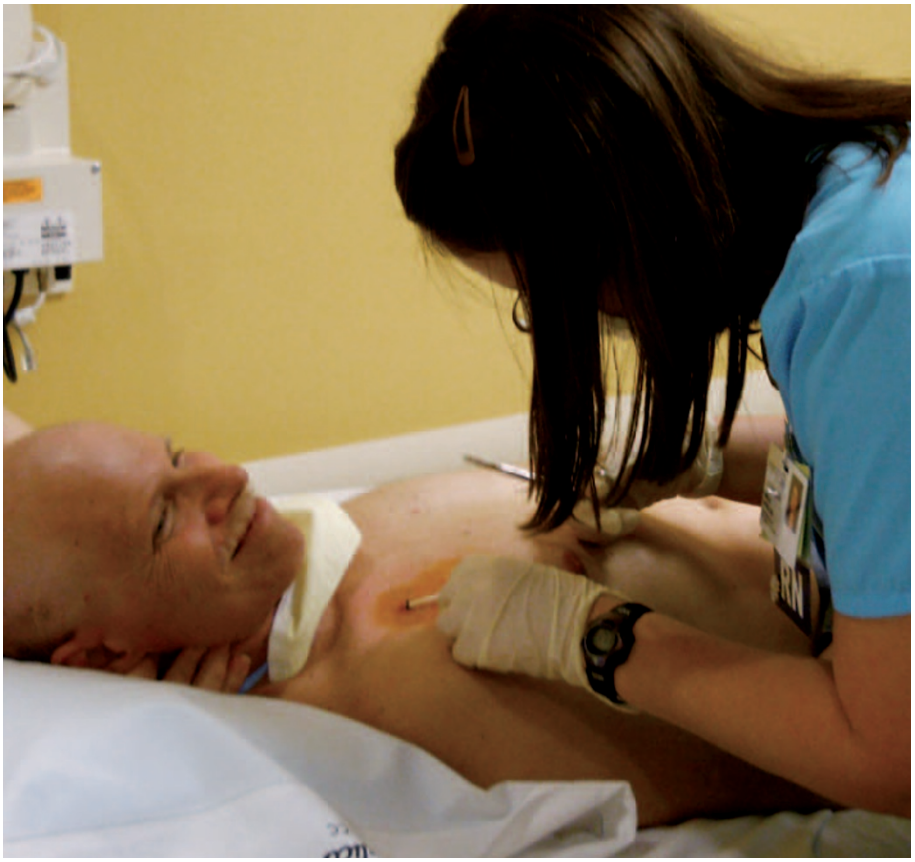

PAT KILLINGSWORTH

Pat Killingsworth prepares to receive an infusion of his own previously collected stem cells.

STEM CELLS

# Transplants on trial

*Stem-cell transplants are an important tool for treating myeloma. But with improved drug alternatives, doctors disagree about the best time to give the treatment.*

BY ELIE DOLGIN

Pat Killingsworth was 51 when he learned that he had multiple myeloma. His oncologist, Steven Zeldenrust of the Mayo Clinic in Rochester, Minnesota, immediately gave him the latest combination of drugs: lenalidomide, a derivative of the immunomodulatory agent thalidomide that hit the market in 2004, and an older chemotherapy agent called dexamethasone. Four months later, the clinic harvested and banked millions of Killingsworth's blood stem cells in case he later needed a more extreme chemotherapy treatment that would destroy his bone marrow along with his cancer.

For almost three years, Killingsworth showed no signs of the disease, and his stem cells simply sat in the freezer. But in late 2010, the cancer started to creep back. Blood tests revealed rising levels of monoclonal protein — a hallmark of multiple myeloma — and X-rays exposed several lesions in the bones around his hips, sternum, ribs and head. "At that point, I said: 'It's time to get serious'," recalls Killingsworth, now semi-retired and living in Florida. "We need to transplant." This summer, he spent 16 days at the H. Lee Moffitt Cancer Center in Tampa, Florida, where he received high doses of chemotherapy with the drug melphalan to wipe out the myeloma cells, followed by a transfusion of his own banked stem cells to replace diseased or damaged bone marrow.

For weeks, he felt too nauseous to eat much or sleep through the night. But at least the stem-cell harvest itself was not much of an ordeal — doctors used to collect bone-marrow stem cells from people surgically under anaesthesia, but they now take stem cells from the blood in the same way that blood banks collect platelets. Unfortunately, the therapy didn't work, and Killingsworth's cancer levels spiked after the procedure — a rare event seen in about 2–3% of cases. "I was looking forward to years of drug-free normal living," says Killingsworth. "I did everything right, it just didn't take." In October 2011, he started a triple-drug regimen of lenalidomide, dexamethasone and the protease inhibitor bortezomib.

## DIVIDED OPINION

For Killingsworth — author of the 2009 book *Living with Myeloma* and a patient's advocate for Millennium Pharmaceuticals in Cambridge, Massachusetts — waiting until he relapsed before undergoing the arduous stem-cell transplant with its concomitant high-dose chemotherapy was the right decision.

"I could have gotten it right away, but there's still no research evidence that doing so makes any difference," he says. "My cancer had over four years to become therapy-resistant, so I suppose you could argue that something like that could have happened, but you'd just be guessing." But myeloma specialists are still debating when to go ahead with such 'autologous' stem-cell transplants, so-called because they involve giving patients their own blood stem cells.

Treating people with multiple myeloma is the most common reason for autotransplants, with more than 10,000 operations performed annually in the United States alone. For younger myeloma patients — generally those under 65, although some medical centres also perform the therapy on older, medically fit individuals — transplants provide the best hope of stopping the cancer in its tracks. Some residual myeloma cells sometimes survive in the banked stem cells, so researchers are investigating whether they can use disease-free cells from healthy donors instead. But the high rates of tissue rejection associated with donor transplants have made autotransplants the standard for the field.

Even so, opinion is divided on the best treatment. Some myeloma specialists favour an aggressive treatment tactic, in which transplants are administered soon after diagnosis, when the disease is thought to be at its most vulnerable. Others opt for a milder protocol that reserves the hard-hitting transplant option — with its attendant risks of infection, bleeding and anaemia — as a last line of defence if less toxic therapies fail.

Investigations that compared early and late transplants indicated that both approaches extend people's lifespan by a comparable amount, normally one to two years on average[1,2]. But those studies were done before newer and more potent drugs, such as lenalidomide or the protease inhibitor bortezomib, were routinely

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used (see 'More shots on target', page S40).

"Novel agents have really changed the way we think about transplant," says Kenneth Anderson, medical director of the Dana-Farber Cancer Institute's Kraft Family Blood Center in Boston, Massachusetts. "The question now is: if you have such a high extent and frequency of response to novel agents, does a transplant add value or not?"

## TIMING THE TRANSPLANT

Some of the first trial data attempting to answer this question were presented in the summer of 2011 at the Congress of the European Hematology Association in London. In a study of 402 newly diagnosed patients, Antonio Palumbo, head of the myeloma unit at the University of Torino in Italy, found that 73% of people who underwent two rounds of high-dose chemotherapy and stem-cell transplantation were disease-free two years after treatment, compared with just 54% of those who received lenalidomide and conventional chemotherapy but no transplants. "Data are showing that transplant should be performed at diagnosis," says Palumbo, although he admits that long-term data are needed to see if there is any comparable effect on overall survival.

Two similar trials of 1,000 patients each are planned in the United States and Europe to compare the efficacy of stem-cell transplants with new drugs and to determine whether delaying transplants, as Killingsworth did, makes any difference to patient outcomes. Those results won't be known for many years, however. In the meantime, researchers who study multiple myeloma remain divided about when, if and how to use transplantation therapy. "The burning question is: do we need to give transplants to patients up front or [should] we use new treatments?" says Philippe Moreau, a haemotologist at the University Hospital of Nantes in France. "The novel agents are really changing the scenario."

Mayo Clinic haematologist Vincent Rajkumar argues that much of the debate boils down to a fundamental difference of opinion over the end goal of myeloma treatment. "What's happening in myeloma is really a clash of philosophies about whether this disease is curable or not," he says.

Those who believe it can be cured generally come in all guns blazing in the hopes of hitting the cancer hard and early, before secondary mutations kick in or tumours adapt to their microenvironments, which would make treatment even more difficult. They tend to use stem-cell transplants within months of diagnosis, sometimes in two back-to-back procedures, while simultaneously applying all the available therapeutic options.

According to Michele Cavo, a haematologist at the University of Bologna in Italy, this is the approach favoured by most doctors in Europe. "European physicians," he says, "prefer not to postpone transplant until the time of relapse." The aggressive tactic has some supporters in the United States too, notably Bart Barlogie, director of the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences. "When you give everything up front you can have superior success," Barlogie says.

## TOTAL THERAPY

Since 1990, Barlogie has advanced a provocatively titled treatment called 'total therapy', which involves a battery of chemotherapy drugs for a few months before giving patients two rounds of stem-cell transplantation. Using his procedure, he says, "we actually have been able to cure people with myeloma". Of the 231 people who received the first version of the therapy more than two decades ago — and so did not receive the recently approved drugs — around 50 are still alive, half of whom have never seen their cancer recur[3].

Over the years, Barlogie and his colleagues have updated their protocols to incorporate newer drugs, and have even found a gene signature in myeloma cells that can reliably identify who will respond well to the therapy and who will not. By focusing on only those myeloma patients expected to respond, the Arkansas team reported last year that almost 90% of the recipients of the latest incarnation of total therapy — which incorporates lenalidomide, thalidomide and dexamethasone — showed no signs of myeloma for at least four years after treatment. By using mathematical models that incorporate long-term data from previous versions of total therapy, the researchers estimate that about half of all patients will have beaten the cancer for good[4].

***Researchers remain divided about when, if and how to use transplants.***

"We believe this is a paradigm-shifting reality," says Arkansas molecular biologist John Shaughnessy, who with Barlogie founded a molecular diagnostics company called Myeloma Health (now a subsidiary of New York-based Signal Genetics) to commercialize the genomic profile test. "Total therapy has revealed that cure is a possibility," Shaughnessy says.

But not everyone shares this view. Survival curves in similar blood cancers, such as leukaemia and lymphoma, level out over time — the hallmark of a cure in the cancer field. This doesn't happen in patients undergoing treatment for multiple myeloma. So Rajkumar argues that some myeloma researchers are "widening the goalposts" by interpreting the word 'cure' to mean achieving in some patients a state of 'sustained complete response', defined as a long-term absence of a series of molecular markers.

For those who believe that a cure is the goal of therapy, sustained complete response is a necessary first step, and high rates of complete response generally require intensive treatment. This leads many physicians to use more aggressive therapies, including early or repeat transplants, which can produce serious side effects such as blood clots and nerve damage.

But many doctors don't accept this definition of 'cure'. And some are quick to point out that such cures have been achieved in some patients with multiple myeloma treated with protocols that are far less aggressive than total therapy. Many doctors are therefore unwilling to risk their patients' quality of life for an unproven cure, especially those who are responding well to more moderate therapies.

## PATIENT CHOICE

Jean-Paul Fermand, a haematologist at the Hôpital Saint-Louis in Paris, sees another problem with the aggressive approach: the evolution of multidrug resistance. "If you use all the tools that you have at your disposal, there are risks of toxicity and of the tumour cells acquiring resistance against different classes of therapeutic agents," he says. "And then if a relapse occurs, you have no therapeutic options and the patient will die."

For this reason, clinical trials aside, many doctors use a sequential approach instead of total therapy, and emphasize the balance between treatment efficacy and the patient's quality of life. They often use the least toxic regimens first and let patients decide for themselves when to perform the transplant. "I can't look you in the eye and say I know what's going to make you live longer because those trials haven't been done," Rajkumar says. "So we're willing to allow a lot of patient autonomy in making that call."

Some doctors go even further, only using stem-cell transplants when nothing else seems to work. "I don't think transplants are worthwhile," says James Berenson, medical and scientific director of the Institute for Myeloma and Bone Cancer Research in West Hollywood, California. "You have to think long and hard about what you're doing to the patient and how [a stem-cell transplant] affects their long-term outcome."

For Dennis Dinger, a retired ceramics engineer in Clemson, South Carolina, who was diagnosed with myeloma a week after turning 60, the long-lasting side effects of stem-cell transplant are a reality of everyday life. Dinger started a protocol akin to total therapy in 2008 at St Francis Hospital in Greenville but had only one stem-cell transplant before heart problems and nerve damage cut his therapy short. Even so, Dinger, now 63 and the author of the 2010 book *My Bout with Multiple Myeloma*, has no regrets. "I can live with my fingers and toes not feeling right, and I wasn't all that active anyway, so the fact that my heart is not the equivalent of a marathon runner's is not a big deal to me," he says. "But the fact that the cancer is gone — that's the big deal."

Another big deal will come when doctors agree on guidelines for best practice. But like so much else relating to stem-cell transplants, the question is: will the consensus come sooner or later? ■

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