Oncology's successes must not fail the heart

Anna Wagstaff

Targeted therapies seek to close down signalling pathways that allow tumours to prosper. But these pathways may also be vital to other clinical functions. With rising concern about collateral cardiac damage from cancer treatment comes a call for a new partnership between oncology and cardiology, to avoid problems and to treat them quickly and expertly if they do arise.

When in 1999 a patient arrived at Bern University Hospital with trastuzumab-associated severe heart failure, cardiologist Thomas Suter, now head of inpatient services, had nowhere to turn for advice. "We simply didn't know what to do with her. We went into the literature, and there was nothing there."

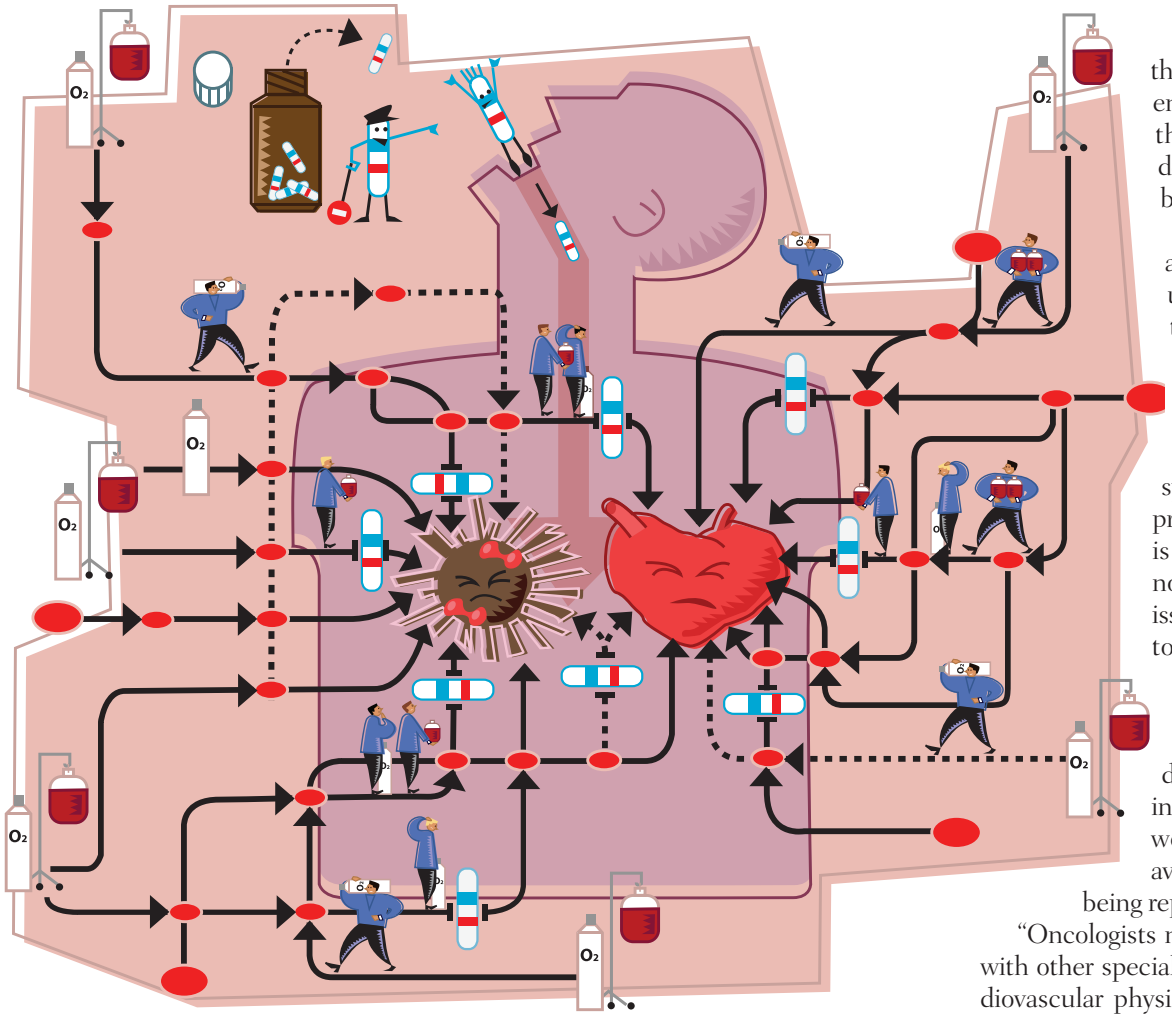
The patient, who had metastatic Her2+ breast cancer, had been participating in the first big trial of the targeted therapy, trastuzumab, that would reveal it as a powerful new weapon against a particularly nasty type of breast cancer, in part fulfilling the hopes of those who had followed its long path to development. Less expected, however, was the heart damage the drug appeared to be doing in some patients.

As the trial reached its conclusion, it transpired that Suter's patient was just one among an astonishing 27% of all participating women, treated concomitantly with an anthracycline, who developed symptomatic cardiac dysfunction. Research has since shown that the Her2 pathway that is implicated in the cancer also provides an essential lifeline for hearts that are under stress, which is why closing that pathway in patients treated with anthracyclines – highly cardiotoxic drugs – proved so problematic.

Happily, trastuzumab-associated damage proved largely reversible in the majority of the patients affected – though it will take many more years before the final word can be said about long-term effects.

Drawing on the lessons from that trial, adjuvant trial designs included strict protocols for monitoring heart function, and patients with heart problems were not allowed to enrol. The HERA trial, for instance, excluded any patient who, after completing chemotherapy and radiotherapy, had a left ventricular ejection fraction (LVEF) of less than 55%, as well as those with a history of documented congestive heart failure, coronary artery disease, uncontrolled hypertension, high-risk arrhythmias or clinically significant valvular disease. HERA, for which Suter provided expert cardiology input, also specified a minimum period between the last day a patient receives an anthracycline and the first day of the trastuzumab infusion.

As a result of these sorts of modifications, heart toxicity in the various adjuvant trials fell dramatically, with only 7% of patients on the HERA trial recording LVEF declines of greater than 10 percentage points (though it was as high as 17% in trials with more aggressive regimens). Today a great deal of effort is spent on bringing these rates down further – identifying who really benefits and who stands to lose more than they gain; looking for the best way to administer the drugs to minimise toxicity; and establishing the most appropriate way to



monitor and manage cardiac toxicities that cannot be eliminated.

For Suter's patient and many others, these precautions came too late. Suter is convinced that, even allowing for the benefits of hindsight, this problem should have been foreseen and avoided. "If we are really critical with ourselves, we would have known from animal data that were published in the early 1990s that if you inhibit this system [the Her2 signalling pathway] you will have significant cardiovascular side-effects. If the people who developed these drugs had looked at these data, this would have been known before the treatment entered the clinical scenario, and they would have set up the trial so we would not have been taken by surprise."

Tunnel vision

Suter warns that clinical and preclinical researchers can focus too narrowly on the anti-cancer activity of new targeted therapies without giving enough thought to what these therapies are doing to other essential biological functions.

"For people who are involved in setting up and conducting these trials, their major focus is the cancer. And rightly so. Signalling side-effects that affect other body systems are not their primary focus, and so it is as simple as people not thinking of these issues. It's embarrassing to admit, but I think that is the reality."

Suter is now calling for a more interdisciplinary approach in both awareness and working practices to avoid the same mistakes being repeated.

"Oncologists need to learn to work with other specialists, such as the cardiovascular physician, and vice versa. The cardiovascular physician should become aware of the problems some of these drugs cause and should be interested in looking into these side-effects and helping oncologists to deal with them and attempt to differentiate what is dangerous from what is not."

He cites as one example the cardio-oncology clinic that has been set up in his own hospital. "Two of us, a cardiologist and an oncologist, look at patients who have developed these side-effects. You need someone who looks at the

ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

"It's embarrassing to admit, but it is as simple as people not thinking of these issues"

"It's naïve to believe that, if you inhibit a pathway to kill a cancer cell, you won't kill other healthy cells"

efficacy of cancer treatment and someone who can advise the oncologist what to do when problems occur. This affects the choices of cancer treatment. If you have a patient at risk for certain diseases, you might not want to use anthracyclines any more, in particular when you plan to treat them in a second step with targeted therapies."

Be aware

He stresses, however, that calling in a cardiologist after a problem has occurred is not the answer. What is needed is a greater awareness of the potential for cardiac problems. Preclinical researchers need to do the appropriate tests in relevant models. Cardiac function and biomarkers need to be thoroughly investigated in phase I and phase II trials. Clinicians in everyday practice need to be looking out for signs of heart distress and taking appropriate action.

Cardiologists are already well aware of the long-term damage that some cancer treatments can inflict. "We still see many Hodgkin's patients who were treated in the 1980s and 1990s, usually with anthracyclines and radiation therapy – another insult. We frequently see them 10, 15, 20 years after their initial treatment, because that is when the heart problems become manifest. Once patients develop end-stage heart failure our options for helping them are quite limited. We do not have the resources to undertake cardiac transplantation for that unfortunate group who, on the one hand has been cured of their cancer, while on the other now succumb to the late effects of their cardiotoxic treatment."

A steady stream of new targeted therapies is entering the therapeutic armamentarium, many aimed at blocking multiple pathways and destined to be used in multidrug combinations, with little known about the full extent of signalling pathways being blocked and the consequences. Suter wants the medical community to do everything it can, not only to protect patients from acute toxicity while undergoing treatment, but also to ensure that, in 10 to 20 years, patients will not face similar problems to the Hodgkin's patients who are still arriving at his department today.

Why now?

As the Hodgkin's story shows, the problem of cardiac toxicity from anti-cancer treatments is not new. But Suter cites a number of developments that point to the need for a much stronger partnership between oncology and cardiology today.

Chief among them is the move towards targeted therapies, which are designed to block signalling pathways, many of which play a role in the normal functioning of a healthy body. "Targeted does not mean targeted to a cancer cell," he explains. "It means targeted to a certain signalling pathway. And some of these are important for the survival not just of the cancer cells. It's naïve to believe that, if you inhibit a certain signalling pathway in a cancer cell to kill that cell, you won't kill other healthy cells with the same inhibitory drug."

This is a particular worry when it comes to the heart, because hearts cannot repair themselves by growing new cells – which is why transplant can end up as the only option.

Also important to bear in mind, says Suter, is the variety of ways in which hearts can suffer damage. He lists as the five most important:

- Ischaemia – lack of oxygen in the heart
- Arrhythmias – disorders of the heart's regular rhythmic beating
- Cardiac pump dysfunction and heart failure – which impacts on the heart's ability to pump blood
- Hypertension – high blood pressure, which puts pressure on the heart
- Pulmonary embolism – blood clots blocking the pulmonary artery

Any drug that affects a signalling pathway that may be implicated in any of these forms of heart damage must be regarded as suspicious for cardiotoxicity.

Trastuzumab targets the Her2 receptor by inhibiting the ErbB-neuregulin system, which protects hearts suffering the sort of oxidative stress induced by anthracyclines. Angiogenesis inhibitors, however, have been found to threaten the heart in a very different way. A recent study of renal cell cancer patients treated outside of trials with sunitinib or sorafenib showed that 33.8% of patients suffered a cardiac event, with 18% of patients showing symptoms of cardiac distress. Here the damage appears to operate via the impact on HIF-1-related gene products, which are targeted by both drugs, and which are now believed to operate as physiologic mediators of heart muscle response to acute or chronic ischaemia, myocardial remodelling and peri-infarct vascularisation.

Angiogenesis inhibitors are also known to lead to high rates of hypertension, through inhibition of VEGF

receptor signalling – indeed there are some suggestions that the level of hypertension induced may be a predictor of tumour response. Luckily, this appears relatively easy to treat without interfering with the anti-tumour action of the drug.

The fact that so many signalling pathways are implicated in maintaining a healthy heart poses a particular challenge to one of the key strategies that has emerged to address the problem of drug resistance. Multikinase inhibitors such as sunitinib have been deliberately developed with a scattergun approach designed to close down not just the pathways that are the chief suspects in fuelling tumour vascularisation, but also all the back-up pathways that may offer an alternative signalling channel.

This may yet prove a winning strategy, but the price paid in cardiotoxicity is clear: 14% of patients on sunitinib suffered a decrease in LVEF of 10 percentage points or more, while only 5% did so on the more finely targeted sorafenib (*JCO* 26:5204–5212). Rates of hypertension provided by Pfizer and Bayer respectively in the sunitinib and sorafenib package inserts are 30% versus 17%, while a study by Chu et al. (*Lancet* 370:2011–2019) recorded cardiac ischaemia in 18% of patients on sunitinib, compared with a figure of 3% given on the sorafenib package insert (though these figures may not be directly comparable).

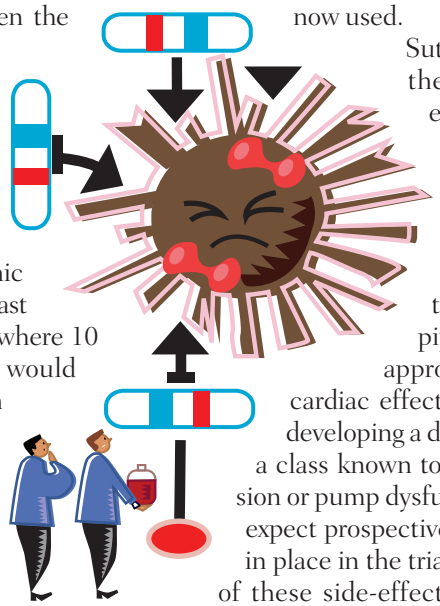
The move towards targeted paradigms of treatment is sufficient reason on its own to require much tighter coordination between oncology and cardiology.

Yet this, says Suter, is only half the story. The other half relates to the more gradual changes in cancer treatment that have taken place over decades.

The price of success

As therapies improve, and more cancer patients live longer, issues of quality of life and avoiding late effects become increasingly important. Suter points out that many of the effects of real concern occur five or 10 years after treatment.

The use of adjuvant treatments in early disease also demands a careful balance between the likelihood any given patient will benefit from the additional therapy against the possibility of harm. Even some advanced cancers are increasingly treated like chronic diseases. Suter cites breast cancer as an example, where 10 years ago a woman would receive a three-month course of chemotherapy following surgery. "Some of the treatments nowadays we use for five or 10 years, like anti-hormone treatment. Some of the new targeted drugs you use for one year – probably even longer in the future – so this is another paradigm change and another reason for more side-effects."



In short, the increasing concern over cardiac side-effects is itself largely a side-effect of a good-news story, but it is a concern nonetheless, and Suter believes patients will suffer if the oncology community does not wake-up to the implications. He is reasonably confident that, with trastuzumab at least, patients treated within trials are being followed-up – the HERA trial, for instance, requires cardiac monitoring for 10 years following the end of treatment. However, these trials screened out patients with cardiac disease, significant cardiovascular risk factors and pre-existing pump dysfunction. To his knowledge, no-one is collecting data on the cardiac side-effects among the wider population in which this drug is now used.

Suter worries too that the lessons of the early trastuzumab trials have not yet been fully learned, and drugs are still proceeding through the development pipeline without the appropriate testing for cardiac effects. "When you are developing a drug that belongs to a class known to induce hypertension or pump dysfunction, you would expect prospective monitoring to be in place in the trials to look for signs of these side-effects, but this is not always happening."

The Schmidinger study on sunitinib and sorafenib published in the *Journal of Clinical Oncology* last October (*JCO* 26:5204–5212) seems to justify these fears, concluding that clinical trials have largely underestimated the true level of cardiac damage caused by both drugs. The findings prompted an editorial (Lenihan, *JCO* 26:5154–5155) that pointed to the need to "revise the reporting of cardiovascular

The increasing concern over side-effects is itself largely a side-effect of a good-news story

Guidelines are still rare and uncertain, and none exist yet at an international level

toxicity in oncology clinical trials, especially to include an understandable and practical grading system for the clinical diagnosis of heart failure not based solely on investigator reporting of symptoms or serial changes in LVEF." It also called for the reporting of all "clinically important findings that have an effect on outcomes, and not just laboratory-based findings that serve as surrogate markers."

Suter himself is now flagging up potential heart problems that could arise with another angiogenesis inhibitor, bevacizumab, approved in the US for adjuvant treatment of breast cancer, "I am extremely worried about the combination of anti-VEGF and radiation therapy, because both affect endothelial cells."

The future is interdisciplinary

However, it is not possible to generalise, he says. And there is the problem. There is much that we don't know – and we can't know – until the effects of these therapies have been studied in humans for many years.

While there is much more in the literature than when Suter was working out how to treat trastuzumab-related heart failure in 1999, guidelines are still rare and uncertain, and none exist yet at an international level. "What we are looking at is a database of four to five years with some of the targeted therapies, and mainly this is just trastuzumab. We don't know what we are doing, for instance, with anti-VEGF drugs such as sunitinib, sorafenib and bevacizumab."

UK guidelines on cardiac management for patients on trastuzumab are set to be published in the *British Journal of Cancer* imminently. Canadian recommendations on risk factors, effects of various regimens, monitoring and management of patients being treated adjuvantly with trastuzumab were published in 2008 in *Current Oncology* (vol 15, pp24–35; see opposite).

Some early studies on the cardiotoxicity of lapatinib, a tyrosine kinase inhibitor that targets much the same pathway as trastuzumab, can be found (e.g. Moy and Goss, *The Oncologist*, 12:756–765). The Schmidinger piece in the *JCO* (vol. 26, pp 5204–5212) provides information on the cardiac management of 74 renal cancer patients on sunitinib or sorafenib, leading to some general conclusions about the importance of effective monitoring for very early signs of heart toxicity and the prompt delivery of appropriate interventions.

"There are no great recommendations," says Suter. "The problem is that we still don't have all the data. We are treating these patients and we see some cardiovascular side effects. What we would be really interested in is what happens to these patients five or 10 years down the road, and these data we don't have."

His advice is two-fold. Be aware and work closely with cardiologists. "In the clinical setting, in real life, we need physicians who are aware of the problem and who monitor their patients accordingly. If they see any signs of any problem, they need to take appropriate measures in terms of diagnosis and prevention and treatment."

Interdisciplinary working, he stresses, is only necessary in patients with risk factors, rather than for those who are young and have no significant cardiovascular risk factors. "You need to identify early on the patients who are at risk, and only for these should you have this interdisciplinary assessment. In breast cancer, a 30-year-old patient who is healthy otherwise, may not need this approach, but with a 75-year-old patient with long-term hypertension, pre-existing cardiac disease and now Her2 overexpressing breast cancer, it would be best to assess this patient in a cardio-oncology clinic before deciding on a treatment plan."

Given the difficulty many cancer services have in developing multidisciplinary approaches within the core oncology specialisms – pathology, surgery, radiotherapy, medical oncology, cancer nursing – it may seem a tall order to bring in cardiology as well. A failure to do so, however, will result in unnecessary deaths and suffering from cardiac problems among patients treated with these new therapies. Suter and his colleagues want to help now, rather than spending decades picking up the pieces.

The Canadian recommendations

There are few guidelines yet available on how to deal with cardiotoxicity associated with the new targeted cancer therapies. Here we publish an edited version of the recommendations on cardiac management during adjuvant trastuzumab therapy that were drawn up by the Canadian Trastuzumab Working Group, and published in *Current Oncology* (vol 15, pp 24–35).

Risk factors for cardiotoxicity

- Patients with existing heart failure or an LVEF <50% (or below the facility's lower limit of normal) should not be treated with trastuzumab. The LVEF threshold may be relaxed only if their risk of disease recurrence is very high.
- Special consideration should be given before using trastuzumab in patients with ischaemic heart disease or significant valvulopathy, a baseline LVEF of 50%–55% before trastuzumab therapy, or a decrease in LVEF of more than 15% while on trastuzumab therapy.

Effects of various regimens on cardiotoxicity

- Sequential anthracycline–taxane–trastuzumab regimens may *possibly* be less cardiotoxic than concurrent regimens that include anthracyclines – i.e., anthracycline–taxane+trastuzumab.
- The anthracycline-free TCbH regimen (docetaxel, carboplatin, and trastuzumab) has a rate of severe cardiotoxicity that is one fifth that of the anthracycline-containing AC→TH regimen (doxorubicin and cyclophosphamide followed by docetaxel and concurrent trastuzumab).
- Until such time as optimal duration of trastuzumab therapy has been established, adjuvant treatment with trastuzumab should be maintained for 1 year (less only if disease recurs).

Monitoring

Given the relatively short follow-up times of the adjuvant trastuzumab trials and the incomplete recovery of cardiac function seen in those trials, even when heart failure medications are used, the panel emphasized the need for careful selection of patients, and consistent cardiac monitoring at 3-month intervals during the 1-year period of trastuzumab therapy.

- Assessment of cardiac function per established protocols is critical and must be endorsed for all patients.
- Either echocardiography or multiple gated acquisition scan should be used to establish baseline LVEF. The same imaging modality should be used at follow-up.
- Patients who experience cardiac symptoms or a greater than 10% absolute asymptomatic decline in LVEF while receiving trastuzumab may continue to undergo annual cardiac assessments following completion of trastuzumab treatment.
- There is no evidence at this time to support furter cardiac monitoring of patients who have completed chemotherapy and trastuzumab treatment with no cardiac symptoms and no signs of asymptomatic LVEF decline of greater than 10%.

These represent the minimum monitoring requirements. Patients with cardiotoxicity or other risk factors may require more frequent and more stringent monitoring.

Management of cardiotoxicity

- The 'stopping/restarting' rules used in the adjuvant trials were effective and are recommended with some modifications regarding recommendations for a cardiology consult or treatment of cardiac dysfunction (or both) when appropriate.
- All patients with heart failure and a LVEF <40% should be treated with an ACE inhibitor in combination with a beta-blocker unless a specific contraindication exists.
- ACE inhibitors should be used in all asymptomatic patients with LV dysfunction and a LVEF <40%.
- Beta-blockers should be considered in all patients with asymptomatic LV dysfunction and a LVEF <40%.
- Initiation of pharmacotherapy for trastuzumab-related cardiotoxicity must be carried out on an accelerated schedule, because the normal titration schedules can take several months to reach the optimal therapeutic dosage.
- The duration of treatment with cardiac medication must be individualized.
- Following withdrawal of trastuzumab therapy because of cardiac dysfunction, trastuzumab may be re-initiated on the basis of the same LVEF guidelines as the original initiation of therapy.

"What we would be really interested in is what happens to these patients five to 10 years down the road"