BREAST CANCER BREAKTHROUGH IN GENE PROFILINGS?

Tygerberg Hospital's Breast Clinic chief, Professor Justus Apffelstaedt.

One in three breast cancer patients can be spared debilitating chemotherapy by a prognostic molecular test that identifies groups of genes governing metastatic dissemination, a group of Cape Town oncologists using the method claim.

So far 40 of the 50 samples they have sent off to the Netherlands Cancer Institute for the test (10 were spoilt due to 'technical issues') have given them dramatically improved treatment options because of the much improved prognostic accuracy.

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Where half of these patients would have received chemotherapy under traditional prognostication, only 16 actually received it, with the survival gain jumping from 8.9% to 18%.

Not only does the test (known as the MammaPrint diagnostic test) improve the prognosis and quality of life for patients but physicians are spared the grinding worry that they may be under-treating or over-treating patients.

Dr Rika Pienaar, a partner in the Panorama oncology practice that works in partnership with Tygerberg Hospital's Breast Clinic, said that initially the test was 'the most challenging thing to try'. 'It can give you a completely different answer to what you expected. I actually over-rode the first few tests but with time I think we're now selecting patients for the test better and we trust it. It certainly increases your confidence levels – you know, having to deal with that fear that you're under-treating or over-treating the patient and sparing toxicities to patients who are unlikely to benefit from chemo' she said.

Pienaar said multigene expression analysis approaches provided deeper insights into the biological heterogeneity of breast cancer, making for a more accurate tool to tailor treatments on single patients. The approach was 'profoundly different' from the current one which consisted of assigning treatments on the basis of average expected effects in broad categories of patients. This resulted in a tendency to treat many patients for the benefit of the few. An approach based on average estimates of the effect of chemotherapy lead 'inevitably to over-treatment and consequently, to an increase in the toxic burden of adjuvant therapy'.

Tygerberg Hospital's Breast Clinic chief, Professor Justus Apffelstaedt, said that low-risk genetic profile patients were now being saved from dreaded chemotherapy. Conversely, about one in three patients traditionally believed to be low risk (i.e. small tumours with no lymph nodes involved) were shown to have a high risk of developing metastases and could now be given chemotherapy.

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Apffelstaedt explained that the 'MammaPrint' test, cleared by the FDA in America and recently included in the St Gallen criteria for clinical decision-making in breast cancer treatment, uses advanced molecular technology to predict whether a patient's breast cancer will metastasise. It does this by assessing the activity of 70 genes in the tumour, establishing either a 'low-risk' or 'high-risk' profile. He says experienced doctors had observed that some patients with very early

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cancers, against all expectations, rapidly developed metastases and died. This led to several research groups towards the end of the 1990s embarking on projects to understand why.

In many cases, although the primary tumour was radically excised and tests conducted to ascertain whether metastases were present had proved negative, the patient later still presented with metastases to organs separate from the primary excision site.

This indicated that these metastases were present but undetectable by current diagnostic methods at the time of treatment.

How to 'red-card' non-lymph node metastases

As early as the 1950s breast cancer researchers first noted that about one in three patients whose lymph nodes were not infiltrated by cancer still went on to develop metastases and die, indicating that breast cancer can spread via the bloodstream without initially infiltrating the lymph nodes.

Assessment of the risk of metastases based on the size of the tumour, the presence of lymph node infiltration and the grade of the tumour is currently still widely used but reflects the biological basis of metastases only very loosely. This led to the vast majority of patients with breast cancer being put on chemotherapy, even though just 10 - 20% of people benefitted. This led to asking what other characteristics (besides tumour size and lymph node presentation) could 'red-card' aggressive tumours.

Apffelstaedt, a South African representative on the Breast Health Global Initiative, said that in the 1990s molecular genetic technologies became available to examine the mechanisms underlying the process of metastasis of tumours (transcriptional profiling). The activity of groups of genes governing the process of metastasis was distilled into 'transcriptional profiles'. Examples of these were MammaPrint test of the Netherlands Cancer Institute and the Oncotype Dx test (USA) and the Rotterdam Profile (University of Rotterdam). 'On average around 60% of patients have a poor and 40% a good prognosis profile. Those with a poor prognosis profile have a one in two chance of developing metastases and dying within 10 years. They therefore need aggressive chemotherapy to improve their survival, even in the case of small tumours and no lymph node infiltration,' he says.

In contrast, those who have a good prognosis profile have a 4-in-100 chance of developing metastases and dying within 10 years and therefore do not require aggressive therapy. This all added up to one in three patients saved from chemotherapy through the genomic transcriptional profiling.

Citing a paper published in *Breast Cancer Research and Treatment*[1] Apffelstaedt said tumours with a poor prognosis signature were more sensitive to chemotherapy. A meta-analysis of 1 627 patients confirmed that patients with a good prognosis profile derived very little benefit from chemotherapy, whereas those with a poor prognosis profile benefitted significantly.

Tissue samples are taken from a fresh tumour within 30 minutes of resection, put in a special medium and air-freighted to the Netherlands Cancer Institute for analysis in terms of an expert permit obtained from the South African Department of Health. This analysis takes about 10 days.

Substantial health economics implications

Apffelstaedt compares the R22 000 price tag for the MammaPrint test with the average R110 000 spent on chemotherapy and says efforts are afoot to provide the test in the state sector. These significant savings raise the ugly spectre of a revenue turf war between medical oncologists and laboratories.

Professor Manie de Klerk, head of Clinical Best Practice in the Metropolitan Health Group and Qualsa stable, said an evaluation of the cost-benefit impact of the test, if used stringently against an agreed management algorithm, produced a 'break-even point' for cost-effectiveness of the test (at R22 000 per test) at a chemotherapy cost of between R77 000 and R107 000 per patient, with the most likely break-even level being at about R88 000 for the cost of chemotherapy.

He said this was relevant only after patients, who in all cases would receive chemotherapy, had been excluded from multi-array genetic testing for breast cancer.

This included HER2/Neu-positive patients, triple negative (to oestrogen receptors and progesterone receptors and HER2/Neu2) patients and those elected for neo-adjuvant chemotherapy. Other guideline parameters, such as the specific histological type of cancer, tumour size and proper registers and review processes, needed to be firmly in place for the test to be proposed for funding, he added.

Apffelstaedt is confident that, properly used, transcriptional profiling will result in far fewer people presenting with metastatic disease. The technology allowed for the testing of individual genes, enabling far better treatment selection, often using less toxic chemotherapy.

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Pienaar said the test 'improves our ability to more precisely predict recurrence and allow us to forego unnecessary treatment in a large number of patients – without denying treatment to those who can most benefit from it'. She described transcriptional profiling as 'a major step in the right direction'.

Very few medical aids pay for the test (those that do require pre-authorisation). She described a paper, published in the *European Journal of Cancer* in 2004,[2] and uncovered by *Izindaba* background research, in which their claims for transcriptional profiling were challenged as 'pretty dated in terms of research progress.' The paper said that while the transcriptional profiling was 'of utmost importance from a clinical perspective', with potential economic impact on the health care system, classifications based on gene expression and on more conventional markers performed 'in parity'. Its authors concluded that 'the conventional markers are by no means outperformed as prognostic factors in breast cancer'. They said that the real value of the new transcriptional profiling data lay in the insights they gave into the important genes and pathways that underlie the disease outcome.

Pienaar emphasised that the latest test was 'not for every patient', with about 60% of breast cancers appropriate for the predictive protocol. 'We're waiting for the confirmatory European trial where they randomised cohorts according to the old and new diagnostic protocols, but some of the work is now coming through and is being accepted against international guidelines.'

Her and Apffelstaedts' group are the only ones doing the work in South Africa. 'These kind of (genomic) tests are very well accepted in the USA and Europe. They will change how we think about cancer and how we treat it. We look at whether the genes are switched on and discrete. It's about (the tumour's) behaviour and biological aggressiveness, the character and the personality of the cancer, not the size as in the old-fashioned way. Breast cancer is one of the best studied tumours in the world. The principle must just be applied correctly,' she said.

Chris Bateman

1. Straver ME, *et al. Breast Cancer Res Treat* 2009; 116: 359-369.
2. *European Journal of Cancer* 2004; 40: 1837-1841.