Genetic profiling in breast cancer

Of women with early breast cancer who receive chemotherapy 70 - 80% do not benefit from the treatment, but 1 - 5% with an 'excellent' prognosis experience recurrence and should have been given the benefit of the extra therapy. More accurate markers are needed to reflect the disease prognosis and predict response to treatment.

A prognostic marker is associated with clinical outcome irrespective of treatment given, e.g. tumour grade, size and lymph node involvement. A predictive marker, e.g expression of estrogen or progesterone receptors (ER or PR), predicts clinical benefit from a particular treatment. Online guidelines help refine the situation. The Adjuvant!online and St Gallen guidelines are commonly used. Despite the above, many women with early breast cancer will receive unnecessary adjuvant treatment.

An ideal marker gives information about prognosis and predicts response to treatment. Can gene profiling answer this need? Micro-array analysis is commonly used in genetics laboratories. The tumour is broken down and a DNA micro-array probe is programmed to extract complementary mRNA. Thousands of genes may be extracted at precise locations. Polymerase chain reaction (PCR) amplification then ensures that enough mRNA is available for analysis.

In 2000, Perou *et al.*[1] analysed 8 102 genes in 65 breast specimens. Some were pathological specimens (including carcinoma and fibro-adenoma) and some were normal breast tissue. Normal breast tissue and fibro-adnomas had a similar genetic pattern. Tissue from primary and metastatic lesions from the same individuals showed the same pattern of gene expression. The authors grouped breast cancers into four groups: ER+ve luminal A, ER+ve luminal B (poorer prognosis), basal-like (triple –ve), and Erb B2+.

Van't Veer *et al.*,[2] from the Netherlands, looked at the gene profile of 98 primary breast cancers: 34 had developed metastatic disease in less than 5 years, and 44 had no evidence of metastatic disease after 5 years. They tested 5 000 genes and identified 70 that were most consistently associated with tumour behaviour. They extended their research to look at a total of 295 patients.[3]

Paik *et al.*[4] tested genes they predicted would be the most important in determining carcinoma behaviour. A 21-gene probe was tested on 668 tumours from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Trial, which looked at ER+ve patients treated with tamoxifen. A recurrence score (RS) was generated and compared with the outcome of the patients. A reasonable correlation between RS and the development of metastases was noted.

Both groups have done further validation studies looking at patients with no adjuvant treatment (the numbers are limited), patients receiving aromatase inhibitors, and whether genetic profiling can be used to predict the response to chemotherapy.

At least 5 micro-array gene assays have been developed for commercial use; the 70-gene micro-array assay (Mammaprint) and the OncoDx are available in this country. The Mammaprint utilises fresh carcinoma tissue from a core taken at the time of primary surgery. It is a decisive assay: 97% of patients are stratified into high or low risk of experiencing recurrence. The OncoDx is only validated for ER+ve patients and divides patients into low risk, intermediate risk or high risk of recurrence. The assay can be done on preserved tissue so can be requested postoperatively.

When micro-array gene analysis has been used as a predictive tool, 30 - 45% of patients have had their treatment modified: the majority have been advised not to have chemotherapy.

Micro-array analyses are not routinely used in South Africa. Their cost (R20 000 - R30 000) is currently not covered by most medical aids. Adopting the technique as a routine predictive marker is controversial. The EGAPP working group (Evaluation of Genomic Applications in Practice and Prevention)[5] noted that independent tests of validity showed that 12 - 19% of samples failed owing to tissue sampling/processing, and that the initial validation studies were done on whole tumour specimens and not core biopsies. Of relevance to South Africa is that the study populations of the validation studies were patients of predominantly European descent. They noted the lack of long-term follow-up with the comment 'No studies determined whether use of assay in place of or in addition to current clinico-pathological markers … improves outcomes based on traditional management.'

Other groups have a guarded approach to the use of genetic profiling. The American Society of Clinical Oncology (ASCO) guidelines include '[In] Node–ve, ER+ve pts, Onco Dx may be used to predict risk of recurrence … and identify patients ... [who will get the] most therapeutic response to tamoxifen and may not [therefore] require chemo.' The 2009 St Gallen guidelines were vaguer: '[The] use of a validated multi-gene profiling assay warranted as adjunct … in cases where indication for chemotherapy remains uncertain.' The FDA have approved MammaPrint for use as a prognostic tool but not 'to predict or direct response to therapy or select optimal therapy'. The South Africa Oncology Consortium guidelines suggest that it should be considered for 'ER+ve, HER2-ve tumours 0.5 - 5 cm in size and node negative or a micrometastasis <2 mm'.

A randomised study to ascertain whether the use of genetic profiling improves patient outcome is needed. Two trials should provide us with the answers. The Trial Assigning IndividuaLized Options for Treatment (Rx) (TAILORx) will use OncoDx to assign patients into 3 groups. Patients with a low-risk score will be managed with hormonal therapy alone, the intermediate group will be randomised to chemo/no chemo, and those with a high RS hormone level will be treated with chemotherapy. The MINDACT trial (Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy) uses Adjuvant!Online and MammaPrint to classify patients as at high or low risk. Patients deemed at high risk will receive chemotherapy; those with a low risk of recurrence will have no chemotherapy. When the results are discordant they will be randomised to chemotherapy or no chemotherapy.

Genetic profiling will become a common tool when deciding whether or not patients should receive chemotherapy and may be extended into predicting response to surgery. Until we have clear evidence that it improves patient survival, its use should be limited.

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