

## Breast Cancer and Novel Therapeutic Treatments

a report by

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Breast cancer remains the most common malignancy among women, with an average lifetime risk of approximately 10%. Despite the continued rise in incidence of the disease, with almost half a million deaths annually worldwide, mortality rates have fallen over the past two decades. This is testimony to the success of interventional strategies such as screening and adjuvant systemic therapies that permit diagnosis of breast cancer prior to *de novo* formation of micrometastases or the obliteration of established foci of disease at distant sites. It is this burden of micrometastatic disease outside the breast and regional tissues that represents the most fundamental and challenging aspect of breast cancer treatment.

### Biological Models

In accordance with Fisher's hypothesis of biological pre-determinism, these micrometastatic foci can remain dormant and be activated many years after initial diagnosis.<sup>1</sup> It is now acknowledged that not all cases of early breast cancer are systemic at the outset with distant micrometastases pre-existent at presentation. Breast cancer is a heterogeneous disease with a variable and unpredictable natural history. We have entered a new era in breast cancer management where disease is 'small' and more likely to be confined to the breast and regional nodes.<sup>2</sup> This 'stage migration' is attributable to heightened public awareness coupled with screening programmes and has led to an increased proportion of smaller-sized (<2cm) node-negative tumours. Some of these tumours will behave in a Halstedian manner with minimal proclivity for haematogenous dissemination and the formation of micrometastases at an early stage in the neoplastic continuum. A spectrum, or intermediate paradigm, is emerging that encompasses elements of Fisher and Halsted but is less restrictive than either hypothesis in pure form.<sup>3</sup> Modern methods of molecular profiling may permit tumours to be assigned to one group or another based on biological behaviour with appropriate intensities of loco-regional and systemic treatments. Those patients without micrometastatic disease at presentation do not require adjuvant systemic therapy and fewer than 10% of those receiving chemotherapy for node-negative disease derive any benefit. It may be surmised that, as tumour size has fallen progressively in recent years, a lower proportion of patients will have micrometastases at the time of diagnosis and a correspondingly greater

proportion will have disease limited to the loco-regional tissues. For these patients, inadequate primary loco-regional treatment will lead to higher rates of local recurrence, which, under these circumstances represents a determinant of distant disease and can directly affect survival by acting as a source for micrometastases.<sup>4</sup> The biphasic pattern of recurrence with peaks at 1–2 and 4–5 years suggests that dormant micrometastases may be stimulated by the act of primary surgery, which can remove sources of angiostatin with initiation of microangiogenesis and the dissemination of tumour cells. Administration of antiangiogenic agents in a pre-surgical schedule may suppress this angiogenic kick-start and interrupt the 'conversation' between breast cancer and endothelial cells.<sup>5</sup>

### Loco-regional Treatment

The latest overview by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has confirmed an overall survival benefit at 15 years from local radiation treatment to either the breast, following breast conservation therapy, or the chest wall after mastectomy. The absolute reductions in local recurrence at five years and mortality at 15 years are 19 and 5%, respectively.<sup>6</sup> This represents one life saved for every four local recurrences prevented by radiotherapy at five years. Though these survival benefits are relatively modest, they emphasise the importance of surgery and radiotherapy in avoidance of persistent disease and relapse in loco-regional tissues that can act as a source for micrometastases and directly impair long-term survival. There is a risk that minimal effective treatments may compromise loco-regional control in some patients. It is essential that all forms of breast conservation surgery achieve histologically negative margins and that radio-biological equivalence to conventional external beam therapy is demonstrable for newer techniques of breast irradiation such as intra-operative, partial-breast and intensity-modulated radiotherapy. Skin-sparing mastectomy (SSM) represents the latest phase in the development of progressively less mutilating forms of mastectomy for breast cancer treatment.<sup>7</sup> The oncological equivalence of SSM to standard forms of modified radical mastectomy has never been validated in prospective controlled trials. There is a potential risk of increased local recurrence when periareolar incisions are adopted in a blanket manner or when general (breast) surgeons are coerced into performing 'pure' skin-sparing resections when these are inappropriate.<sup>8</sup> Long-term data on rates of loco-regional and distant recurrence will clarify relative indications for SSM, but, in the interim, selection criteria and quality control issues must be monitored and subjected to ongoing audit and evaluation.<sup>9</sup> A small group of patients may be suited to an oncoplastic technique in which a relatively large resection of breast tissue is performed with subsequent transposition of remaining breast parenchyma to reshape the breast. In the event of margin positivity, further re-excision can be difficult and a complete



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mastectomy may be necessary. The majority of patients are best managed with either standard breast conservation (wide local excision) or SSM with immediate breast reconstruction.

### Sentinel Node Biopsy

The technique of sentinel node biopsy is now widely practised in many centres around the world and has become a standard of care. This minimalist approach to axillary management has relevance to earlier stage disease, where node negativity is more common. A review by the American Society of Clinical Oncology Technology Assessment panel reaffirmed that dual localisation techniques with a combination of blue dye and isotope maximises identification rates (>90%) and are associated with high negative predictive values (>95%) with a short learning curve.<sup>10</sup> Overall false-negative rates are between 5 and 10% (mean 8.4%) and are minimised by intra-operative digital examination and the removal of nodes that are suspicious but neither hot or blue. This 'sentinel plus' technique has merged with blue-dye-assisted node sampling, which is popular in the UK and may be the most pragmatic approach when nuclear-medicine facilities are limited.<sup>11</sup> Removal of three to four nodes accords with anatomical patterns of lymphatic drainage to the axillary basin.<sup>12</sup> There is a lack of consensus on whether some patients with smaller invasive tumours can avoid sentinel node biopsy and, conversely, whether this technique is less accurate for tumours exceeding 3cm. Pre-operative axillary ultrasound and core biopsy are likely to select out a high proportion of node-positive patients, and intra-operative node examination may reduce numbers of patients requiring a delayed axillary procedure.<sup>13</sup> There are persistent uncertainties about the significance of micrometastatic deposits within the sentinel node(s), especially when only a single node is involved. More intense scrutiny of nodal tissue with immunohistochemistry/polymerase chain reaction (PCR) potentially upstages 20–30% of patients with risk of overtreatment. Consequences of the failure to remove non-sentinel nodes remain unknown, although rates of axillary relapse following sentinel node biopsy are very low (2% at three years) and these are unlikely to translate into any meaningful reduction in long-term survival.<sup>14</sup> Ongoing trials will determine whether complete axillary dissection is mandatory in all sentinel node-positive patients, or whether it could be omitted in some cases without detriment to loco-regional control or overall survival.<sup>15,16</sup> A range of options for axillary management based on risk/cost–benefit analyses, together with patient choice, will probably prove to be the ideal practice.<sup>17</sup>

### Systemic Treatments

It is the presence of distant micrometastases at presentation that ultimately determines a patient's clinical fate. Systemic therapies target these microscopic foci of tumour and their modes of action are increasingly based upon an understanding of the biological events underlying disordered growth patterns. The microenvironment of a tumour contains a pool of growth factors, which may be stimulatory or inhibitory to cell growth. These form a component of the complex language of intercellular communication that is often disrupted in the malignant state, leading to the autonomous growth of cells. Some channels of communication persist and cancer cells can be tamed or re-regulated. This concept of 'cell control' rather than 'cell kill' exploits the similarities between cancer and normal cells.<sup>18</sup> Chemotherapy schedules based on cytotoxicity are unlikely to modulate levels of growth factors in any consistent and meaningful manner. Rather than selectively enhancing or suppressing cellular functions, the primary action of chemotherapeutic agents is to

indiscriminately kill cancer cells by dislocating biochemical pathways, interfering with DNA repair processes and inducing 'cell suicide' (apoptosis). The newer biological response modifiers exploit these natural growth regulatory mechanisms and target mitogenic pathways at various levels: ligand, growth factor receptor or post-receptor signal transduction.

### Biological Response Modifiers

These translational approaches are exemplified by trastuzumab or Herceptin, which is a humanised recombinant monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER-2). This is expressed in normal and malignant breast epithelial cells, but overexpressed in 20–30% of all breast cancers. In pre-clinical studies, overexpression of the HER-2/neu oncogene results in increased rates of proliferation, loss of contact inhibition, enhanced growth in soft agar and a more tumorigenic phenotype *in vivo* with greater metastatic potential. Recent trials have shown that the use of Herceptin for 1–2 years following standard chemotherapy regimens in HER-2-positive patients prolongs disease-free survival and reduces rates of relapse by up to 50%.<sup>19</sup> Inhibition of HER-2 overexpression can restore or increase oestrogen receptor (OR) expression, thus overcoming endocrine resistance and allowing further hormonal manipulation.<sup>20</sup> A potential novel target related to HER-2 is the protein GP88, which is expressed in invasive ductal carcinoma but not in benign tissue. Laboratory models suggest that this can constitutively activate HER-2 by phosphorylation and prevent subsequent inhibition by Herceptin.<sup>21</sup> Dual targeting of HER-2 and GP88 may prove to be more clinically effective than the use of Herceptin as a single agent. The relative magnitude of gains from Herceptin is similar across all subgroups and there is less than a 20% chance that benefit will be lost with more prolonged follow-up. There is compound cardiotoxicity from combined therapy with Herceptin and taxanes that should be sequenced when baseline left ventricular ejection factor (LVEF) is suboptimal. The enzyme topoisomerase 2 is amplified in 35% of HER-2-positive patients and a fluorescence *in situ* hybridisation (FISH) assay for this enzyme may help identify those patients most likely to respond to taxanes and Herceptin.

Tumour growth is dependent upon new blood vessel formation and inhibitors of angiogenesis are entering clinical trials as a combined adjuvant. Xenograft tumour models have shown marked reductions in tumour growth when trastuzumab is administered concomitantly with anti-vascular endothelial growth factor (anti-VEGF) antibodies. A phase I trial of trastuzumab and the anti-angiogenic agent Avastin (bevacizumab) has confirmed this combination to be clinically safe and effective. A phase II study is currently underway to further evaluate this combination. Avastin is also being incorporated into standard regimens of anthracyclines/taxanes for locally recurrent and metastatic breast cancer.<sup>22</sup> A regimen of repetitive, low-dose chemotherapy and bevacizumab is effective against metastatic breast cancer, but metronomic chemotherapy alone is not (for example, low-dose oral cyclophosphamide).

There are potential problems with targeting downstream post-receptor signal transduction pathways. Complex interactions and 'cross-talk' exist, permitting compensation by adjacent pathways (functional redundancy) and disturbance of normal regulatory loops by therapeutic intervention. Inhibition of more distal steps, for example by mammalian target of rapamycin (mTOR) inhibitors, can result in reflexive activation of more proximal steps (e.g. Akt. tyrosine kinase). Activity may be

abrogated only by use of multiple inhibitors, and central signalling 'nodes' such as cyclin B1 are important and perhaps obligatory targets for sustained growth inhibitory effects. Animal models have shown promising responses from a combination of an aromatase inhibitor and the tyrosine kinase inhibitor gefitinib. This combination has not shown enhanced response rates compared with gefitinib alone in a pre-surgical schedule, though a greater reduction in rates of cell proliferation was evident for dual therapy.<sup>23</sup> A phase III study of letrozole and lapatinib in metastatic breast cancer has shown a 30% improvement in time to progression (10 months versus 13 months; hazard ratio (HR) 0.769). Lapatinib inhibits all possible hetero-/homodimers of HER-2/3 and should have superior efficacy to gefitinib. Trials are ongoing investigating this agent in combination with trastuzumab or letrozole as neo-adjuvant treatment.<sup>24</sup>

Farnesyl transferase inhibitors (FTIs) and mTOR inhibitors may be too far down the signal transduction pathway and do not possess a specific target. Some phase III studies have shown mTOR inhibitors to improve the efficacy of neo-adjuvant letrozole (CC1779) and possibly reverse resistance to this agent (RAD001).<sup>25</sup> Other trials have been terminated early due to apparent increased cell survival and proliferation. Studies with FTIs and letrozole have shown negative results to date.

Both antihormonal therapies acting via the OR and biological response modifiers targeting specific growth factor receptor pathways are capable of inducing mitogenic signals that allow breast cancer cells to survive initial systemic treatments and promote the emergence of a cohort of cells from which resistance develops. A cell's response to particular therapies must be anticipated and 'escape' mechanisms co-targeted. Short-term pre-surgical studies in the neo-adjuvant setting provide the opportunity to study proliferation indices before and after surgery, and changes in gene expression patterns may be predictive of response to novel agents and possibly of longer-term outcomes.

## Aromatase Inhibitors

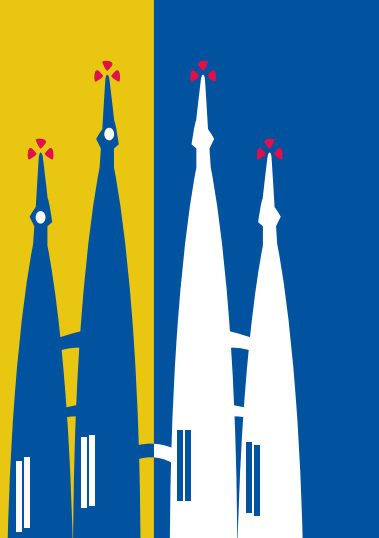
Aromatase inhibitors represent the most significant advance in the endocrine management of breast cancer since the introduction of tamoxifen more than 30 years ago. Despite an established role as first- and second-line treatment for metastatic breast cancer, the optimal strategy for the incorporation of aromatase inhibitors into standard adjuvant endocrine schedules remains unclear (see *Figure 1*). An upfront

aromatase inhibitor might be indicated in those patients at higher risk of relapse (node-positive, OR positive/progesterone receptor (PgR)-negative, HER-2-positive) for whom the amplitude of the hazard peak for recurrence is proportionately greater and could be suppressed or 'smoothed out' by an aromatase inhibitor more effectively than tamoxifen.<sup>26,27</sup> For those patients with lower hazards for relapse within the first 2–3 years, sequential therapy with tamoxifen followed by an aromatase inhibitor may be more appropriate and cheaper.<sup>28</sup> The absolute benefits of an aromatase inhibitor are very small in the first 36 months, during which period only 3.7% of patients relapse overall. Punglia and colleagues used a Markov analysis to develop models that simulated a 10-year, disease-free survival among OR-positive women with early breast cancer.<sup>29</sup> According to this analysis, switching from tamoxifen to an aromatase inhibitor after 2–5 years leads to a modest gain in disease-free survival compared with monotherapy with an upfront aromatase inhibitor for five years. This analysis has been criticised on the basis of heterogeneity of end-points with a 'dilutionary effect' of deaths without recurrence when disease-free survival is used that augments the relative benefits of switching.<sup>30</sup> A variation of the Markov model based on biological mechanisms was used to demonstrate that when time to recurrence was taken as the primary end-point, upfront aromatase inhibitors were the favoured option. Outcome benefits must be balanced against longer term risks in terms of bone health and cognitive function. Any cost analysis must take account of the subsequent adverse events prevented (thromboembolism, gynaecological conditions). There are concerns about the impact of severe oestrogen deprivation in women receiving aromatase inhibitors for chemoprevention. The use of 'add-on' agents to minimise the complications of aromatase inhibitors (e.g. bisphosphonates) detracts from a preventative strategy in the context of healthy women.

## Extended Adjuvant Endocrine Treatment

Though more than three-quarters of recurrences occur within the first five years, late events do occur and patients remain at chronic risk of relapse. Dormant cancer stem cells can be 'kick-started' many years after the primary treatment of breast cancer. Examination of hazard rates for recurrence within the extended adjuvant endocrine setting of the MA-17 trial implies there is a residual risk of recurrence in patients completing five years of tamoxifen. The HR for recurrence (letrozole: placebo) shows a trend to decrease over time and there is greater benefit from letrozole with more prolonged therapy.<sup>31</sup> ■

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