

A Brief History of Breast Cancer

Part III - Tumour biology lays the foundation for medical oncology

*Ritu Lakhtakia¹ and Ikram Burney²

تاريخ موجز لسرطان الثدي
بيولوجيا الأورام يضع الأساس لعلم الأورام الطبية

ريتو لكتاكيا وإكرام بيرني

To a tissue that's trying to grow

We hope these experiments show

With steroids phenolic

Don't get metabolic:

Just grab on, and never let go!

Limerick on the action of oestrogen on the oestrogen receptor.¹

THIS ARTICLE IS THE LAST OF A THREE-part series narrating a brief history of breast cancer that has traced the attempts by physicians to understand and conquer this disease since antiquity.^{2,3} The series chronicles the millennia during which crude and desperate surgery-only measures gave way to an understanding of the pathobiology of this hormone-responsive cancer. Tolling the knell on Halstedian heroic extirpations (1894) was the advent of chemotherapy and radiotherapy.^{4,5} On a historical timescale, the arrival of these new therapeutic modalities would be recorded as part of modern history. Remarkable insights into tumour biology in the last century have been the catalyst to the meteoric rise of medical oncology.

The Dividing Cell can be Killed

It is ironic that the birth of cancer chemotherapy occurred in the lap of chemical war weaponry; the fact that nitrogen mustard gas caused profound bone marrow depression was instrumental in the subsequent notion that it could also annihilate cancer cells. Following clinical trials, it received approval from the USA Food and Drug Administration for the treatment of patients with Hodgkin lymphoma. Sidney Farber's first pioneering triumph in achieving partial remission in a case of paediatric leukaemia in 1947 by administering aminopterin,⁶ as well as

the establishment of the National Cancer Institute Clinical Trials Cooperative Group Program in 1955,⁷ set in motion a wave of research that would strengthen as it gave rise to a new specialty. The principles of oncological management changed forever and resignation to certain impending death was no longer the fate of a patient diagnosed with cancer.⁶ Nascent medical oncologists would face struggles with incredulity and disbelief before the field would establish itself through clinical trials and scientific merit.

The term 'chemotherapy' acquired an entirely new connotation in the pharmacological lexicon as a generic synonym for anti-neoplastic drugs, far removed from its 19th century Ehrlichian usage for "chemicals against infections". It was subsequently prefixed by the adjective 'adjuvant' that promised greater success at inducing remission after the tumour burden had been reduced by surgical extirpation. The first beneficiaries were patients with osteosarcomas (treated with methotrexate)⁸ and colon cancer (treated with 5-fluorouracil).⁹ The landmark trials of Bernard Fisher, Chair of the National Surgical Adjuvant Breast and Bowel Project (NSABP) in the USA, and of Gianni Bonadonna, working in the Istituto Nazionale dei Tumori in Milan, Italy, proved that a combination of drugs with different mechanisms of action (commonly cyclophosphamide, methotrexate and 5-fluorouracil) significantly extended survival after the complete

¹Department of Pathology, College of Medicine & Health Sciences, Sultan Qaboos University; ²Department of Medicine, Sultan Qaboos University Hospital, Muscat, Oman

*Corresponding Author e-mail: ritu@squ.edu.om

surgical resection of breast tumours—particularly in more advanced cancers.^{5,10,11}

Women presenting with locally advanced breast cancer inspired a re-evaluation in the ways chemotherapy could be utilised. Could chemotherapy shrink an otherwise inoperable tumour, rendering it amenable to the knife with clear post-surgical margins? This assumption initiated the advent of neoadjuvant chemotherapy—another unique first for oncology—and breast cancer spearheaded its later application to other cancers. The ‘downsizing’ of a tumour had therefore moved from concept to standard practice.

Today, a wide choice of refined options exist for medical oncologists who are now long past the days of nitrogen mustard gas, notorious for its toxicity. Among the seminal drugs whose place in the anti-breast cancer armamentarium is secure, a few deserve mention. In the early 1970s, doxorubicin derived from a strain of *Streptomyces* formed the corner-stone of chemotherapy, acting by the intercalation of DNA and interruption of replication.¹² Paclitaxel, originally sourced from the bark of the Pacific yew tree in 1962, was found to disrupt microtubule assembly.¹³ Thirty years after its discovery, it generated excitement as a success story in treating ovarian cancer. However, it was soon tapped in 1994 for its effectiveness in treating the most common cancer in females—that of the breast.¹³ Capecitabine, introduced in 1998, acted by blocking DNA synthesis and transcription. It became one of the options for advanced or metastatic cancer after anthracycline and taxanes and had the added benefit of oral administration.⁶ These are just a few of the drugs which are now used to treat breast cancer and the list continues to grow!

Cell Signalling: *Enabling a multipronged attack*

The hormone responsiveness of breast cancer was a concept proposed long before Elwood Jensen’s discovery of hormone receptors on breast cancer cells in 1967.^{1,14} Circumstantial evidence existed as indicators of this, for instance in the fact that young women generally had a more aggressive form of the disease and because the removal of sources of oestrogen (e.g. via an oophorectomy or adrenalectomy) increased survival. Hormone receptor-positive tumours, either oestrogen receptors (ER) or progesterone receptors (PR), were found to be predictive of recurrence in several publications in 1977.¹⁵ This triggered the invention of receptor assays and, later on, direct demonstration of the receptors on the tumour cells. An arena was opened for targeted therapy, which was itself a new pharmacological

approach that would be emulated in the subsequent treatment of other cancers. Tamoxifen, a selective ER modifier (SERM), held promise for increased survival in receptor-positive tumours and was approved as an adjuvant therapy for post-menopausal women in 1986.^{16,17} The resultant dramatic changes in cancer recurrence and survival established its place in breast cancer therapy. Subsequently, a gonadotropin-releasing hormone analogue (goserelin) and aromatase inhibitors (anastrozole, letrozole and exemestane) have been shown to improve progression-free survival in an adjuvant setting.¹⁸

The saga of the *Her2* gene (now known as *Her2/neu*)—identified between 1982 and 1984 by the collaborative effort of a group of American scientists from the Robert A. Weinberg Group at the Massachusetts Institute of Technology, Rockefeller University and Harvard University—categorised breast cancers as Her2-positive or -negative.¹⁹ Multiple copies of the gene transcribe excess Her2 receptor proteins which causes tumour cells to be more responsive to growth signals, thus making the tumour more aggressive. The trajectory of medical oncology was to see the marriage of four disciplines—genetics, immunology, pathology and pharmacology—a success story of modern day interdisciplinary integration. A therapeutic monoclonal antibody became a viable option when research in the 1990s culminated in the emergence of targeted therapy in 1998 with the production of trastuzumab (an anti-Her2 molecule) by Genentech Inc. (Roche Group, San Francisco, California, USA).²⁰ Tumour biology had provided yet another impetus to cancer therapy. A subset of breast cancers which are particularly difficult to treat are triple-negative tumours (i.e. expressing neither ER, PR or Her2). These are effectively tumours without a target! However, a silver lining was found in the application of poly-adenosine diphosphate-ribose polymerase (PARP)-inhibitors that prevent cancer cells from repairing defective DNA and thus makes them chemo-sensitive. The last few years have witnessed the emergence of newer drugs with diverse claims: these may find their place in future historical reviews!

The Genie of Hereditary Breast Cancer Genes

Identified in 1994–1995, the tumour suppressor genes *BRCA1* and *BRCA2* provided scientific support for the notion of hereditary breast cancer.^{21,22} Their significance lay in the possibility that identification could result in closer surveillance for high-risk family members and give them the option of a bilateral salpingo-oophorectomy or prophylactic bilateral

mastectomy and the possibility of chemoprevention. In 1998, more than a decade after its approval to treat hormone receptor-positive cancers, tamoxifen provided another opportunity for use—this time in a risk-reduction role for such individuals.⁶

Personalised Medicine in the Century of Genetics

The first year of the 21st century opened with a 'tumour-on-a-chip' mood among breast oncologists and geneticists. Multigene arrays have raised the possibility of basing tumour prognostication and treatment on the genomic fingerprints of breast cancer.²³ Furthermore, breast cancer classifications based on molecular subtypes hold promise for personalising medicine.²⁴ Breast cancer is no longer considered one disease, but rather a mixture of at least four diseases: hormone receptor-positive and Her2-negative cancer; hormone receptor-positive and Her2-positive cancer; hormone receptor-negative and Her2-positive cancer, and triple-negative cancer. The targets are based on the response of the tumour and therapeutic decisions are made accordingly. The Oncotype DX[®] test (Genomic Health Inc., Redwood City, California, USA) and other similar commercial kits based on multigene assays have since opened a market for the new predictive and personalised practice of oncology. These tests allow for risk-stratification which obviates the need for cytotoxic chemotherapy among a low-risk subset of women with breast cancer.

Clinical Trials and Evidence-based Medicine: *The backbone of oncology*

With the dubious distinction of being the globally leading cancer in women, breast cancer has had a unique primacy in the 20th century in terms of clinical trials in oncology. Efforts to improve breast cancer outcomes launched the process by which large cooperative groups used evidence-based medicine to establish new standards of care, refining treatments in the adjuvant, neoadjuvant and metastatic settings. A series of large-scale phase III trials by the NSABP and meta-analyses published by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) are only two examples of how breast cancer physicians, surgeons, radiotherapists and statisticians have come together and paved the way for healthcare professionals dealing with other cancers.^{25,26}

A meta-analysis consisting of 133 studies and a total cohort of 75,000 women was one of the

earlier examples of evidence-based medicine in this context.²⁷ The concepts which Vincent T. DeVita and Bonadonna had postulated in the 1970s were verified by the highest levels of evidence in 1992. The role of adjuvant chemotherapy and hormone therapy was now established beyond a doubt; outcomes would improve for women with early and locally advanced breast cancer and their outlook would change forever. Further refinements by these and other groups, including the Breast Cancer International Research Group (BCIRG), established the role of anthracyclines as obligatory in all groups of patients as well as that of taxanes in high-risk groups.²⁸ Today, the concurrent or sequential use of anthracyclines and taxanes forms the backbone of adjuvant and neoadjuvant treatment in breast cancer.

Similarly, following the seminal meta-analysis by the EBCTCG in 1992, adjuvant hormone therapy became the standard of care for all women with hormone receptor-positive disease, which affects approximately 50% of pre-menopausal and 70% of post-menopausal women.²⁷ Additional progress by the NSABP, EBCTCG and other groups, such as the Breast International Group, includes the use of aromatase inhibitors in post-menopausal women, either as switch therapy or for extended use beyond tamoxifen.²⁹ Both strategies have led to an improvement in progression-free survival compared to tamoxifen, with different but acceptable side-effects. The use of the monoclonal antibody trastuzumab, which targets *Her2/neu* oncogene amplification in a metastatic setting, became the standard of care in the late 1990s. In 2005, four groups working independently (including the NSABP, BCIRG and Herceptin Adjuvant group) showed an unprecedented improvement in survival in the adjuvant setting with the addition of trastuzumab as the backbone of combination chemotherapy.^{30,31} The challenge had been transformed into an opportunity. Expression of *Her2/neu* protein on cancer cells was no longer fraught with apprehension, but rather with determination to improve survival with the use of targeted therapy. History had been made and the last decade has seen efforts to further improve outcomes by optimising the duration of trastuzumab treatment, adding another monoclonal antibody or receptor tyrosine kinase inhibitor and using antibody-drug conjugates.

The role of radiotherapy after mastectomy and breast-conserving surgery has also been indisputably established as a result of large cooperative group trials and meta-analyses. Postoperative radiotherapy after mastectomy has been shown to reduce local recurrence and improve overall survival even when systemic treatment is administered.³² After breast-

conserving surgery, treatment with radiotherapy reduces disease recurrence by half and breast cancer-related mortality by a sixth.³³

Renaissance in the Battle against Breast Cancer: *Surgical mutilation tempered*

At the beginning of the 20th century, attempts were already underway to reduce disfigurement and morbidity at the hands of the school of surgery promoting bold radical mastectomies. A notable first step was the move from radical to total mastectomies in 1971.⁶ In 1975–1976, the use of adjuvant chemotherapy provided the adjunct that would drive survival rates to heights that surgery alone could never achieve. Only six years later, a push to breast conservation created a movement for lumpectomies, with the added choice of ‘mopping up’ any residual tumor cells with radiotherapy. In Italy, Veronesi *et al.* were one of several groups around the world espousing the use of limited surgery in combination with radiotherapy.³⁴ The change from axillary dissection, with its attendant morbidity caused by lymphoedema of the ipsilateral arm, to sentinel node biopsy in selected groups has been referred to previously.²

BETTER TOGETHER

Multidisciplinary efforts in the management of breast cancer became the norm through insights into the growth kinetics and biomodulation of tumours. Pathological predictive and prognostic factors, especially ER, PR and Her2 expression, became invaluable in determining therapeutic options.³ Despite its relatively short lifetime, medical oncology has achieved its rightful place at the heart of multidisciplinary breast cancer treatment, dispelling dogma and enabling collaboration. It has demonstrated the range of its applications to patient care, from prevention to rehabilitation, by remaining grounded in evidence, accepting and discarding therapies through global trials and combining its own tools with the best of those from the disciplines of surgery and radiotherapy.

EARLY DETECTION AND PREVENTION GALVANISE THE ‘CURE’ MOVEMENT

In the last decades of the 20th century, the advent of mammographies ran parallel with attempts to catch the disease early and ensure a cure. This involved monitoring a subsection of women whose strong family history demanded surveillance. The adage that ‘prevention is better than cure’ was adopted

in both letter and spirit by breast physicians and surgeons. Preventative strategic options include chemoprophylaxis, bilateral salpingo-oophorectomies and prophylactic mastectomies in *BRCA*-positive women, making headlines when espoused by iconic celebrities.³⁵ In addition, the decreasing use of hormone replacement therapy has had a role in the overall decline of breast cancer. A host of chemoprevention options utilising SERMs also exist.³⁶

Lessons from the Foundation of Tumour Biology for Medical Oncology in Breast Cancer

From the mere decimation of tumour cells using single agent or combination chemotherapy to endocrine manipulation and targeted therapies, advances in breast cancer therapy have successfully anchored medical oncology in the *terra firma* of cancer therapy. The rise of this new discipline has been anchored by parallel, rapid and translational research in tumour biology. This has allowed the emergence of generations of drugs, either targeting the global cell cycle or specific receptors. As critical information regarding breast cancer genes and their interplay emerge, we bear witness today to the history of personalised medicine in the making.

Life comes with many challenges. The ones that should not scare us are the ones we can take on and take control of. Angelina Jolie.³⁵

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