THE AUSTRALIA NEW ZEALAND BREAST CANCER TRIALS GROUP: SOME CONTRIBUTIONS TO BREAST CANCER TRIALS

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Abstract

The Australian New Zealand Breast Cancer Trials Group was formed in 1978 after the first adjuvant therapy trials were published. This commenced a new era of clinical trials and the commencement of substantial global collaboration, particularly with the International Breast Cancer Study Group. The Australia New Zealand Group is currently conducting 46 trials encompassing prevention and early and advanced disease. In the Australia New Zealand Breast Cancer Trials Group model the elected Board of Directors is responsible for legal and financial affairs, the Scientific Advisory Committee sets the research agenda and the Operations Office is responsible for conduct of the research program. The Australia New Zealand Breast Cancer Trials Group Statistical Centre is contracted out to the National Health and Medical Research Centre Clinical Trials Centre. The Australia New Zealand Group has had peer reviewed research funding (National Health and Medical Research Council) since 1979 and has contributed to more than 400 peer reviewed publications. The research program has always been based on quality science and multidiscipline collaboration. The Breast Cancer Institute of Australia was established to foster education and involvement of consumers in research. Important contributions have already been made by Australia New Zealand Breast Cancer Trials Group researchers to the documented falls in breast cancer mortality and further improvements can be expected from new targeted therapy trials.

The Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) had its origin in 1975. At that time new advanced breast cancer trials in Cardiff were comparing first line treatment with tamoxifen or chemotherapy and initiating quality of life measurements in cancer patients. Results from the initial trials of adjuvant chemotherapy compared to no adjuvant chemotherapy were published, the L-PAM trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP) by Bernard Fisher and colleagues[1] and the CMF trial from the Istituto Nazionale Tumori, Milan, by Gianni Bonadonna and colleagues.[2] The CMF trial, investigating 12 months of adjuvant CMF versus no adjuvant chemotherapy for women with positive nodes, showed that after 27 months median follow-up, relapse rates were reduced by 78%, (control 24%, CMF 5.3%). Twenty-seven months was a very short follow-up time for analysis by today's standards, but the results from both adjuvant trials were sufficiently striking to change practice and launch a new era of randomised clinical trials (RCTs) evaluating various new adjuvant systemic therapy regimens. The recent early and strikingly positive results from the first trastuzumab adjuvant trials are likely to have a similar impact.[3,4]

In January 1977, Dr Jan Stjernsward from the Lausanne Branch of the Ludwig Institute of Cancer Research (LICR) invited a small group of researchers[i] to a meeting in Lausanne to discuss the implications of these results and the possible conduct of trials by a new international collaborative group. This in turn resulted in the formation of the Ludwig Breast Cancer Study Group (LBCSG), and LBCSG trials I-IV were planned (the final design being completed on a table napkin in a Lausanne Hotel) and commenced in 1978. These initial four adjuvant trials were a logical extension of the Milan CMF trial and emerging data suggesting that tamoxifen might be a valuable adjuvant therapy for postmenopausal women.

From the outset, the new LBCSG was substantially influenced by Australian and New Zealand researchers who actively pursued collaboration and rigorous science. Because the advantage for CMF in the Milan trial seemed less in postmenopausal women (and was not separately significant for this group), LBCSG trials III and IV retained a control arm – subsequently confirmed as a wise decision. The 20-year CMF results were published in 1995[5] and by this time it had become apparent that CMF had less effect in postmenopausal women. Overall, there was a 34% reduction in relative risk of relapse and a 26% reduction in the relative risk of death. In premenopausal women, DFS was 37% and 26% and OS 47% and 24% for the CMF and control groups respectively. In contrast, in postmenopausal women, DFS was 26% and 24% for CMF and control and OS was 22% in both groups. We have subsequently relied on the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Overviews for evidence that chemotherapy does indeed provide advantages for postmenopausal women.[6]

Concurrent with Jan Stjernsward's initiative, a group of oncologists at the Welsh National Medical School in Cardiff showed in randomised controlled trials (RCTs) that chemotherapy and endocrine therapy produced

i Those invited to the first "LBCSG" meeting included Kurt Brunner, John Forbes, Percy Helman, Ken Stanley, Carl-Magnus Rudenstam, John Simpson, Martin Tattersall, Marvin Zelan. They were soon joined by Alan Coates, John Collins, Ian Russell, Franco Cavali, Juri Lintner, and Hans-Jorg Senn. Aron Goldhirsch and Richard Gelber became very actively involved soon afterwards

similar outcomes for women with advanced breast cancer.[7] Pioneering studies of quality of life (QoL), using LASA (Linear Analogue Self Assessment) scales for the first time in oncology, established that endocrine therapy was associated with a better QoL despite a smaller response rate.[8]

Formation of the ANZ BCTG

The ANZ Group was initially established in the Department of Surgery, University of Melbourne at the Royal Melbourne Hospital in 1978 (with one data manager, one computer, one National Health and Medical Research Council grant and 14 collaborating institutions) and relocated to the Department of Surgical Oncology, University of Newcastle, at the Newcastle Mater Hospital in 1987.

In 1977 a young and enthusiastic group of oncologists[ii] returned to Australia and New Zealand from centres in North America and Europe and brought experience and ideas from Cardiff, the Eastern Co-operative Oncology Group and the MD Anderson Hospital in particular. A similar meeting to that held in Lausanne led to the establishment of the new ANZ Group. The first ANZ BCTG trial, ANZ 7801/2, commenced in 1978. It compared first line treatment of advanced breast cancer with cytotoxic therapy (AC), endocrine therapy (tamoxifen in postmenopausal women and oophorectomy in premenopausal women) and also combined therapy with both modalities.[11] These trials were the logical extension of the Cardiff trials and a small premenopausal trial from the Mayo Clinic and were successful.

From the outset it was recognised that sufficient accrual in Australia and New Zealand to complete adjuvant trials in a reasonable time was not plausible, so adjuvant trials were supported through collaboration with the new LBCSG. In 1975, there was no mammography screening and women with breast cancer presented because of clinical symptoms; patients were treated with a radical mastectomy (usually a Halsted mastectomy), lymph glands were not counted, steroid receptors were not measured, there was no adjuvant systemic therapy and breast cancer mortality had probably not changed for some 2000 years. The largest of the initial LBCSG adjuvant trials had just 491 patients. It soon became apparent that clinical trials introduced new standards of care – in LBCSG I-IV, lymph nodes had to be counted and examined, pathology protocols were standardised, follow-up was according to an agreed protocol and an international quality review facilitated reliable measurement of steroid receptors for the first time. This was the beginning of "evidence-based medicine" for management of breast cancer.

Lessons from the initial trials

After a median follow up of 20 years, women in LBCSG trial I (premenopausal with 1-3 positive nodes), had an OS of 54% and a DFS of 40%, clearly better than what might have been expected before adjuvant chemotherapy. LBCSG Trial II produced the first evidence that in premenopausal women with an endocrine sensitive tumour, the combination of endocrine therapy (oophorectomy) and chemotherapy might be superior to chemotherapy alone. This was the forerunner of current trials for premenopausal women investigating combinations of chemotherapy and endocrine therapy. In LBCSG III, the first evidence was obtained that, in postmenopausal women with endocrine sensitive tumours, there may be no difference in efficacy between chemotherapy and additional tamoxifen (even with just 12 months therapy - current tamoxifen therapy is five years), but in women with endocrine insensitive tumours, tamoxifen is no better than control and chemotherapy is indeed superior to both tamoxifen and control. These analyses by steroid receptors status were retrospective. They identified new questions and hypotheses which led to International Breast Cancer Study Group (ISBCSG) trials 8 and 9, with prospective stratification by steroid receptor categories, and now in 2006, to new trials for chemotherapy and endocrine therapy for young premenopausal women with endocrine sensitive tumours. Progress may seem slow, however the importance of quality data, sufficient accrual, prospective stratification, prospectively planned sub-studies and broad collaboration were important in the beginning and remain so today. And new hypotheses based on Trials I-IV have been largely proven. Today endocrine therapy is confined to endocrine sensitive tumours.

After LBCSG trial V accrual was completed in 1985 the LICR decided to focus on laboratory research and confined its LBCSG trials support to follow-up of trial V. The LBCSG continued with a new name and structure, the IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG trials, contributing 20% of total international accruals and many of the scientific ideas.

In 1978 advanced breast cancer was increasingly being treated with cytotoxic chemotherapy, particularly in the US. ANZ BCTG 7801/7802 was the largest advanced trial done at that time with accrual of 408 patients. First line treatment with chemotherapy or combined modality therapy produced no apparent advantage in terms of survival and QoL was compromised. There was almost no receptor data, as tissue biopsies were not often done for the relapsed patient and very few women had receptors measured at the time of their primary treatment. Despite this it was clear that patients treated with initial endocrine therapy had a similar survival and a superior initial QoL.[9] Today the availability of tissue from women with advanced breast cancer is becoming very important to reliably selecting optimal treatments based on biological assays; increasingly we are able to identify the many patients who do benefit from chemotherapy and targeted therapies. In 2006 we now have active targeted therapies to treat advanced breast cancer and can approach it as a potentially curable disease.

ii The first "ANZ BCTG Group" included Michael Byrne, Alan Coates (first appointed SAC Chair), John Collins, John Forbes (first Group Coordinator), Grantley Gill, Ron Kay, John Levi, Ray Lowenthal, Don McNeil (first Statistician), Stuart Renwick, Ian Russell, John Simpson, Ray Snyder, Eric Stevens, Martin Tattersall and Robert Woods

Wider international collaboration

The EBCTCG Overviews[6] have been vitally important in answering major questions and consolidating evidence-based treatments. They have been strongly supported by the ANZ BCTG and the IBCSG. The overviews have added a new dimension to RCTs and have provided the most reliable evidence to support the use of many current treatment strategies, including ovarian ablation, tamoxifen in premenopausal women and for longer durations (for hormone sensitive tumours), combination rather than single agent chemotherapy and anthracycline containing chemotherapy regimens. The demonstration in the overviews of reduced rates of contralateral breast cancer for women taking adjuvant tamoxifen, was a sound basis for IBIS I and other tamoxifen prevention trials.[10,11]

However some adjuvant trials today test a specific treatment modality and involve defined patient subsets for "targeted" therapy evaluation. These trials are very large and future overviews may be simpler and more rapid than the five-yearly EBCTCG overviews involving much broader patient groups. The first CMF trial involved 386 pre and post-menopausal women. The initial adjuvant aromatase inhibitor trials, evaluating anastrozole, exemestane and letrozole, collectively involved more than 22,000 patients;[12-14] the tamoxifen duration trials and tamoxifen prevention trials both involved more than 20,000 women. The importance of collaboration has never been more apparent.

The Breast International Group (BIG) was established to increase accrual for the large trials needed to address important questions in patient subgroups - including use of taxotere, trastuzumab (Herceptin), aromatase inhibitors and new targeted therapies directed against cellular molecular targets. The ANZ BCTG is a founding member of BIG and has also collaborated with other groups to contribute to other trials. This collaboration has involved trials for ductal carcinoma in situ, as well as prevention with Cancer Research UK and the International Breast Cancer Intervention Group (IBIS), the Clinical Trials Service Unit at Oxford (ATLAS), the North American Intergroup (menstrual cycle and surgery timing trial and the new endocrine trials in younger women), trials of the Breast Cancer International Research Group (BCIRG, now CIRG) and groups established to conduct the ATAC (Arimidex Tamoxifen Alone or Combined)[14] and IES (International Exemestane Study).[13] This collaboration has been valuable and has provided early access to new agents and quality research for researchers and patients.

Growth of the ANZ BCTG

The ANZ Group has continued to conduct its own advanced breast cancer trials. Accrual has generally been adequate for this however wider collaboration is required for trials where treatments are targeted to smaller patient subgroups. The ANZ Group has built an international reputation for its work with advanced breast cancer, from ANZ 7801/02 through trials of intermittent versus continuous therapy, endocrine modalities, high dose CT and new agents. From the beginning, the ANZ Group has explored QoL studies and helped establish QoL measurements as the norm rather than an add on for many trials – led globally by Alan Coates.[15]

The ANZ BCTG is a breast cancer clinical trials research group which uniquely encompasses trials for prevention and both early and advanced breast cancer. The ANZ BCTG model includes an elected Board of Directors, responsible for legal and financial affairs; the Scientific Advisory Committee (SAC) responsible for setting the scientific agenda; the Operations Office which is responsible for all aspects of conduct of the research program; and the ANZ BCTG Statistical Centre currently contracted to the National Health and Medical Research Council (NHMRC) Clinical Trials Centre. The Group Coordinator and SAC Chair are appointed by the Board. The SAC is not representative – it simply requires individuals with the knowledge and ability to contribute to the scientific agenda of the group.

The ANZ BCTG established the Breast Cancer Institute of Australia (BCIA) as an operating division for education, consumer involvement and fundraising. Australia does not have a 'National Cancer Institute' to provide infrastructure and operational funding for collaborative groups; hence, the BCIA is vitally important to help the ANZ BCTG to conduct its clinical trials research program in accord with scientific priorities. The establishment of the ANZ Consumer Advisory Panel (CAP) and the IMPACT program (Improved Participation and Advocacy for Clinical Trials) have enhanced our research programs substantially by involving consumers in the research agenda. CAP members comment on all ANZ BCTG protocols, particularly on patient materials and issues that will affect accrual to the trial. The IMPACT program now includes mentoring of individual consumers at the group's Annual Scientific Meeting and provides information about trial results for women who have been on ANZ BCTG trials.

Current research program

The ANZ Group has grown substantially since 1997 and now collaborates with more than 80 institutions, more than 300 researchers in Australia and New Zealand and many more globally. It has had continuous NHMRC support since 1979 and has had more than 400 publications in peer-reviewed journals – many resulting from international collaboration. Currently 46 trials are being conducted, including: (i) follow-up of trials completed and published; (ii) trials with accrual completed and follow-up continuing whilst awaiting analyses, including the definitive taxane based adjuvant chemotherapy trial (BIG 2-98/IBCSG 20-98) and the only trial of continuous versus sequential aromatase inhibitor adjuvant therapy (BIG 1-98/IBCSG 18-98); (iii) trials open to accrual and; (iv) trials with endorsement from the SAC to be commenced.[17] Since 1978 more than 10,600 women have been entered on breast cancer trials through the ANZ BCTG with total trials accrual of more than 70,000 women. The group continues to evolve and meet new research challenges and is well placed to translate future research discoveries into better outcomes for patients.

Conclusion

Through its commitment to clinical trials the ANZ BCTG has made important contributions to the falling mortality of breast cancer in developed countries. It has done this simply by focusing on the quality of the science and pursuing collaboration with good researchers. The Group has pioneered involvement of consumers in breast cancer research through its CAP and IMPACT Program. It has also helped establish QoL measurement as a key part of breast cancer trials.

We will see further improved outcomes for women and improved understanding of the biology of breast cancer. Improved use of existing treatments, new biological targeted agents, gene expression based targeted therapies, unravelling the biology of stem cells and the metastatic process and new prevention strategies can all produce better outcomes for patients with or at risk of early or advanced breast cancer. Each of these requires collaborative research and documented controlled outcome data. Our clinical trials agenda is even more important today than it was in 1978 and will remain so for some time.

A tribute

The standing and achievements of the ANZ BCTG and the IBCSG are a tribute to the contributions of my friend and colleague Alan Coates. His rigorous and robust scientific leadership of the SAC, his remarkable breadth of scientific knowledge, his humanity and his wise counsel have been of great benefit to his colleagues and many patients worldwide. □

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