Breast Cancer Update

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Centre for Clinical Research in Cancer

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The Cancer Council Victoria

BREAST CANCER UPDATE

June 2004 Issue No. 52

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***** **Last Issue – No. 51 – December 2003** *****

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***** Last Issue – No. 51 – December 2003 *****

Editorial

Dr Jacquie Chirgwin
Medical Oncologist
Box Hill & Maroondah Hospitals

This edition is jam-packed with informative articles and is well worth spending half an hour to read cover to cover. I am very grateful to all the willing contributors.

I will keep my bit short this time because of this (and because my flight may leave without me!). I will tell you a brief story though that relates to Bob Brown's article on hormone receptor measurement. Recently, a patient of mine presented with PV bleeding and following further investigation was found to have a diffuse uterine infiltration with metastatic adenocarcinoma consistent with her primary breast cancer diagnosed three years earlier. The current disease, however, was ER positive, however the primary had been reported as ER negative. The testing was repeated on the original specimen, and this time was reported as ER ++ 50%. She rightly asks "would adjuvant Tamoxifen have made a difference to my prognosis?" What can be done about our difficulties with HR testing? Surely we should be setting up QI systems and guidelines (including minimum case loads for doing ER) nationally. Also, I have heard that some institutions are no longer performing PR status because of the low occurrence of PR positivity in ER negative patients. I must say I think this is unwise as it invites us to miss a few patients who will benefit from hormonal interventions and takes away the extra information that PR status provides: an increased chance of benefit from hormonal treatments when positive, and perhaps a discerning factor as to which patients benefit particularly from Aromatase inhibitors when negative.

And, lastly... Can anybody shake up Roche (and the makers of Navelbine) to get their act together and have the Navelbine – Herceptin combination funded?

Hormone Receptor Testing

Dr Robert W Brown
Pathologist
Melbourne Pathology

Introduction

Hormone receptor status, particularly oestrogen and progesterone receptor status has been used for decades as a predictive and prognostic marker for breast cancer (Table 1).

Table 1. Predictive power of combined ER/PR in patients with advanced/metastatic breast cancer receiving endocrine therapy.

Phenotype	Incidence (%)	Response rate (%)
ER+/PR+	58	77
ER+/PR-	23	27
ER-/PR+	4	46
ER-/PR-	15	11

Allred et al. Mod Pathol 1998;11(2):155-168[1].

Biochemical methods were used in these assays for many years but in the last decade these have been replaced by immunohistochemistry (IHC). The biochemical methods were expensive, difficult to perform and required fresh tissue, so were not amenable for use on archived tissue and there was uncertainty as to the composition of the sample tested. Occasionally false positive results could be obtained from normal tissue or from an in-situ component where the invasive component was negative. When specific antibodies to different locations on the oestrogen receptor became available, immunohistochemistry, which was readily available in most histopathology laboratories, rapidly became the method of choice. The ability to use paraffin blocks enabled repeat testing and access to archived material.

ER/PR Scoring Methods

Reporting of immunostaining for ER/PR varies considerably between laboratories as does the assessment of what constitutes a "positive" result.

Several attempts at a numerical scoring system have been attempted (i.e. H-score, QIC score, Quick score (various), IRS and Total score). All use a combination of intensity of staining and the percentage of cells that stain. The International Breast Cancer Study Group (IBCSG) has adopted the Total Score, which was developed and validated in San Antonio, USA[1,2].

This method provides three values based on assessment of all of the tumour population in the section (Table 2).

Validation of the method was carried out on 1,982 primary breast cancers and the results compared with the traditional biochemical assay on the same tumours and to clinical outcome. They used antibody 6F11, one of the two antibodies in common use in Victoria. Concordance with LBA was 86% and in multivariate analyses with patients receiving adjuvant endocrine therapy alone, ER status determined by IHC was better than that determined by LBA at predicting improved disease free survival. They determined that a TS of >2 was the optimum cut-off point for predicting improved outcome. In their study almost 10% of the patients had from 1 to 10% of cells staining. These would conventionally have been reported as negative. Occasional odd cases will show a rare cell (<<1%) staining strongly which gives a score of 1+3, Score 4/8. I am unaware as to how this small subset behaves.

Leake et al[3] estimate the likelihood of response to endocrine therapy for IHC scores as:

Zero - indicates that endocrine treatments will definitely not work

2 or 3- small (20%) chance of response

4 – 6 - even (50%) chance of response

7 or 8 - good (75%) chance of response

The majority of laboratories in Australia use 10% of cells showing any staining as the cut-off for positivity and this is likely to remain the case.

Table 2. Total Score Method for Hormone Receptor Scoring.

Proportion Score (PS)	Intensity Score (IS)	Total Score (TS)
0 = no staining	0 = no staining	TS = PS + IS
1 = <1% of tumour cells stain	1 = weak	(Range 0, 2-8)
2 = 2 – 10%	2 = intermediate	
3 = 11 – 33%	3 = strong	
4 = 34 – 66%		
5 = 67 – 100%		

Quality Assurance in ER/PR Testing

Immunohistochemical assays vary considerably between laboratories both in technical performance and evaluation of results. A UK quality assurance study[4] of 200 laboratories from 26 countries showed over 80% demonstrated ER positivity on the medium and high expressing tumours, but only 37% scored adequately on the low expressing tumour. A German study showed a correct score by 30% of laboratories and a false negative result in 11%[5].

In 2003, the Australian QAP undertook two exercises on hormone receptors. In the first, 26% of sections were considered satisfactory and in the second 41% were satisfactory and another 31% were borderline. The problems lie in the low expressing tumours rather than with moderate or high expressing ones. Progesterone receptor assay performed much better at 75% and 76%. The committee believes that optimisation of antigen retrieval is the key to improving performance of ER assays and plan further exercises to achieve that end. Other studies have shown that the use of surfactants to facilitate the spread of antibody on the slide severely reduces ER expression[3], and Clone ID5 immunoreactivity is significantly related to antibody incubation time and the detection system[6].

Conclusion

The importance of receptor status in the management of breast cancer is accepted. The difficulties with the ER assay is a concern and it would seem prudent that until better standardisation of this test is achieved, retesting of negative assays should be considered before denying patients the endocrine option.

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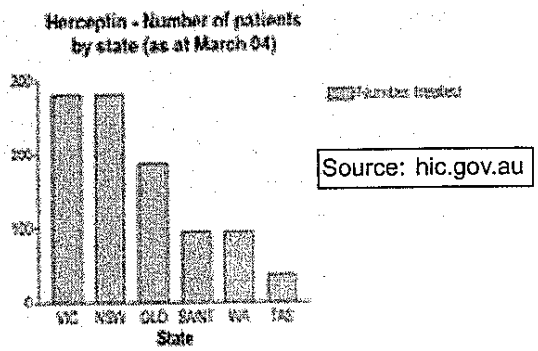
Trastuzumab (Herceptin) Usage in Australia

Dr Fran Boyle
Medical Oncologist
Royal North Shore Hospital, Sydney

Herceptin was first registered for use in Australia in 2000, for patients with metastatic breast cancer overexpressing Her2 receptors (either as monotherapy or in combination with taxane chemotherapy). Its high cost precluded all but sporadic usage until it was funded by the Health Insurance Commission in December 2001, following significant lobbying by both clinicians and consumer groups. The arrangements for approval for individual patients were, and remain, unusual, since it is outside the PBS process. After initial documentation of eligibility (with pathology reports and patient consent), monthly phone approvals must be sought by the oncologist.

There was, as expected, an initial rapid influx of patients who had been waiting for funded access, and within the first 6 months 332 patients had been registered. Since that time, as depicted in the graph below (figures from www.hic.gov.au), new registrations have been fairly steady (apart for June 03, a bumper month, giving the lie to the notion that no work gets done when ASCO is on). Over 2 and a half years, a total of 1000 patients have had funded access to the drug, approximately 50/50 spit between monotherapy and taxane combinations. It is difficult to discern from the HIC figures the average duration of usage. Women of all ages have been prescribed Herceptin (see figure below) – little is known of their tolerance. 133 patients are known to be deceased, and 311 have been withdrawn – it is not known the proportion withdrawn for reasons of toxicity vs progressive disease. Usage across states would appear to be appropriate (see figure below).



The programme has run smoothly for the most part, with dedicated staff handling the HIC lines. Weekly usage is the only approved mode of delivery at present, with the 3 weekly data emerging slowly from clinical trials, and not yet submitted to the TGA. Combinations with either paclitaxel or docetaxel are permitted, with the vinorelbine data not yet submitted for approval. These modifications remain in the hands of the sponsoring company, Roche, and the HIC has made it clear that unregistered combinations will not attract funding. Total expenditure was predicted at around 11 Million per year, and this has been exceeded, although the exact details are not in the public domain. Impact on survival in the population setting is not known, due to lack of appropriate data sets. Data from Canada presented at ASCO in 2003 (Chia et al) demonstrated improved survival in the population cohort of patients diagnosed with metastatic disease in the Herceptin /Capecitabine era, suggesting that observed survival benefits in clinical trials do translate into more general settings. The opportunity for a true cost-benefit analysis in the Australian context is not provided by the current programme.

If you have any questions that have not been adequately addressed by this summary, please contact Anne Ireland on (02) 6124 6885 at the HIC.

CNS Metastases in Patients on Herceptin

One clinical issue that has arisen with use of Herceptin in patients with metastatic breast cancer is the perception that brain metastases are more frequently observed. Analysis of the cohort of the first 40 patients treated in Northern Sydney indicates that 40% have developed CNS metastases (including a high proportion with posterior fossa disease). Only 2/3 were symptomatic at the time. In our series all patients received whole brain radiotherapy, and 5 had lesions resected. These lesions continued to overexpress Her2 when tested. Over 80% of

these patients had at least some response of their systemic disease (29% SD, 53% CR+PR). The median survival from the time of diagnosis of CNS metastases is 18 months, and patients with CNS metastases did not have a significantly worse prognosis overall (Wiseman et al, COSA 2003). We have considered several possible explanations for this phenomenon:

Hereptin does not penetrate the blood brain barrier, and so cannot reach the target which does not appear to be lost.

Taxanes also do not penetrate well, and neither do anthracyclines, which these patients had frequently received in the adjuvant setting. Our usage of chemotherapy in a different manner may therefore contribute to the problem. Carboplatin may be of assistance in this regard, and the recently completed BCIRG 007 study may shed light on this issue.

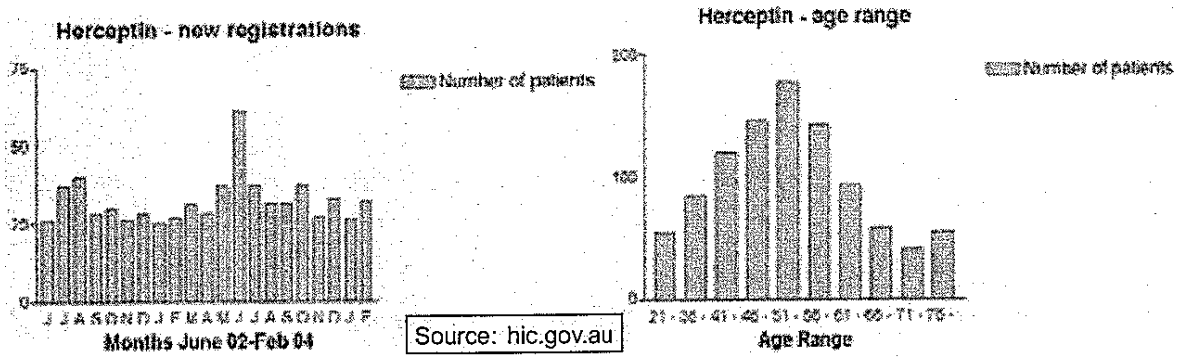
These patients may be living longer than previously, and are not dying of systemic disease, thus allowing CNS metastases to emerge.

Active treatment should therefore be considered if systemic disease is controlled, since survival may be relatively long. This may include surgery for lesions which are single, accessible, in the posterior fossa, and/or are causing hydrocephalus. Follow-up of whole brain radiotherapy will reduce the risk of relapse. Isolated CNS relapse should not be considered a failure of Herceptin therapy.

We might also consider screening for CNS metastases when scanning patients to assess their systemic disease. This may not alter survival, but may have other benefits:

- avoiding neurological damage, which repairs poorly,
- avoiding anticonvulsants, which impair the effectiveness of taxane chemotherapy, and
- minimising the period of time patients are barred from driving.

The challenges that this highly targeted therapy present in changing the natural history of the disease, and our approach to treatment, are just beginning to emerge.



My Journey Kit

Breast Cancer Network Australia has produced a comprehensive Kit for women diagnosed with breast cancer within the last 12 months. The My Journey Kit is a fabulous resource developed by women who have had breast cancer. It is available free of charge by calling 1300 785 562. Please pass this information on to women who have been newly diagnosed with breast cancer.

The My Journey Kit includes information about breast cancer and its treatment, useful contacts and resources and practical advice from other women who have had breast cancer. It includes the My Journey Personal Record, where women can record details of their appointments, treatments, costs and questions.

4th European Breast Cancer Conference

Hamburg, Germany, 16 - 20 March 2004

Dr Jacquie Chirgwin
Medical Oncologist
Box Hill & Maroondah Hospitals

One of Germany's most affluent cities welcomed around 4,000 registrants to rainy winter weather. Fortunately, we were a week late for subzero temperatures. It goes without saying that the EBCC meetings have their distinct European flavour, reflecting European conservatism in oncological management, as well as European style and taste in the mundane aspects of conference organisation; the mainly excellent food and beverages (avoid cholesterol measurement any time soon however), and classy hotels. It was also of note that this was not a conference to hear major new data presented for the first time – but perhaps the scheme of things is changing, with significant early results appearing first in journals, without prior presentation at major meetings (eg. Adjuvant Exemestane Study). Is this the way of the future? Is it good?

So, this was a meeting for debate and discussion of most clinical aspects of Breast Cancer, this time with a particular focus on adjuvant hormonal treatment. It provided an excellent forum in which to reflect and consider the implications of trial results for our day-to-day practice, for current trial participants and for the planning of future trials. An enjoyable and informative aspect of the EBCC's is the lunchtime Oxford Union style debates. There were three debates that I will summarise, together with related data that was presented, which in fact will cover much of the value of the meeting. There was also a "Late Breaking Session" on the Aromatase Inhibitors in adjuvant breast cancer management, as well as several other presentations of interesting and/or updated results that I will summarise.

The First Debate: 'This house believes that biological markers are measured well in clinical practice'

The motion was **Proposed** by F. Penault-Llorca (France); N. Brunner (Denmark) and **Refuted** by G. Viale (Italy); R. Holland (The Netherlands)

There appears to be plenty of data showing poor concordance of results of ER measurement, between different laboratories, but somewhat better results for PR. The poor agreement between labs appears to relate both to the actual preparation and staining of the slides and also to observer interpretation of results. For such an important predictive marker as ER, this is a significant problem that can seriously impact on the optimum management of patients.

The situation for HER2 is no better; agreement on IHC HER2 results, vary considerably. Although for "central reference" laboratories, about 96% of HER2 3+ are also FISH positive, this is not the case for local laboratories. For HER2 2+, about a third will be FISH positive; it is therefore important that these are also not misclassified locally.

It was argued that some countries have adopted quite intense quality assurance programs to minimise these problems, and that in particular, laboratories that do less than 150 breast cancer cases per year should send their tumour markers to a central laboratory for measurement.

There is no easy answer to these problems; the best that seems possible is careful quality assurance and audit; routine mechanisms for this are needed in all countries. Suffice to say, the "Nays" had this one in the bag.

The Second Debate: 'This house believes that early disclosure of positive results of randomised trials is of benefit to the patient and the scientific community'

The motion was **Proposed** by Don Berry (USA); Joyce O'Shaughnessy (USA) and **Refuted** by Rich Gelber (USA); Ian Tannock (Canada)

All four speakers are eloquent presenters and presented persuasive arguments supporting their side of the debate. Early benefits of new treatments rarely are lost with further time, surely

we should use these early results to guide treatment choices, as well as design of new trials. In the majority of instances, disease free survival benefits (at least in Breast Cancer) have later translated into overall survival benefits; perhaps it is not ethical to withhold these treatments.

However, disease free survival benefits are usually all that is available when these results are released. Such early release of results mean that the risk:benefit relationships (long term especially) are not known and it seems prudent not to change standard practice because of these results. In fact, all the early release of results seems good for, is stopping trials early, and often sabotaging the trials, with the end result that overall survival benefits can never be estimated.

This is an important contemporary issue which deserves debate and for which we need to carefully plan. The most obvious answer seems to be to design trials and "stopping rules" such that these are only triggered when OS benefit is demonstrated. Being a conservative European audience, again the "Nays" had it!

The Third Debate: 'This house believes that there is enough data to bury Tamoxifen'

The motion was **Proposed** by Walter Jonat (Germany); P. Lonning (Norway) and **Refuted** by: Kathy Pritchard (Canada) and Hazel Thornton (Consumer advocate, UK)

Much data was presented and noise generated regarding what appear to be superior results for adjuvant treatment with all aromatase inhibitors, when compared to old fashioned Tamoxifen. It is time to let go of Tamoxifen, they argued; what patient wants to take an inferior drug....

But, whose government can pay for everybody to have an aromatase inhibitor (AI)? It seems likely that not all patients benefit more from an AI, than Tamoxifen; and it is certainly likely that some have an increased incidence of side effects. We need more research on which patients benefit; and indeed, perhaps the best treatment of all is a sequence of Tamoxifen and AI. Countries with minimal resources cannot afford more than Tamoxifen. It is likely that there will always be a role for Tamoxifen in advanced disease. No, Tamoxifen is not yet dead and buried! Most of the audience agreed that Tamoxifen should be preserved, although there was some notable dissent from some consumers. So the "Nays" had this one too!

All three debates were delivered with considerable humour and were a great way of generating discussion of controversial issues. Their success, though, does depend on the talent of the presenters.

Late Breaking Session on Aromatase Inhibitors

The International Exemestane Study (IES) results had just appeared in the New England Journal of Medicine (11/3/04). These results were presented by Charles Coombes. Altogether, 4742 patients were enrolled from 367 centres, with around 1,000 patients on sub-protocols (bone density, endocrine side effects and QOL). 8.5% of patients remain on study treatment, 16.5% had unknown ER and 32% had prior chemo. Results show an absolute difference of 4.7% (86.8-91.5%) - in the 3 year DFS. OS hazard ratio is 0.88 (in favour of Exemestane), which is not statistically significant. Hypertension and IHD seem possibly to be increased, as well as osteoporosis. We need to wait patiently for more long-term results.

Tony Howell presented the current ATAC results showing an absolute disease free survival (DFS) difference at 48 months of 2.6% in favour of the Arimidex arm (HR positive only). An Italian Study (Boccardo, SABCS 2003) of 448 patients HR+ve, node+ve patients completing 2-3 years of adjuvant Tamoxifen, were randomised to continue or to swap to Arimidex. After a median follow up of 3 years, there was an approximate 10% improvement in event free survival for those swapping to the Aromatase Inhibitor (P=0.0002). It is of note that in the ATAC study, the relapse rate peeks before 2.5 years. In the UK, the cost of adjuvant Arimidex is estimated to be £11,000 per life year gained being an annual cost of £6.4million (<4% UK 2003 Breast Cancer Budget). This compares to £17 million spent on Herceptin.

Ian Smith presented the MA17, or late Letrozole study results. The median follow up is only 2.4 years, and the absolute DFS benefit was 6.3% (P=0.0008); the benefit was seen in both node negative and node positive populations. As has been widely discussed, this study has been stopped because this result crossed the

boundaries of the pre-defined stopping rules. It is likely therefore that we will never know OS results for this intervention.

What of the ATLAS study, where predominantly 5 vs 10 years of Tamoxifen is being tested? Martine Piccart told us over 13,000 patients have been randomised to date, together with another 5,500 in the similar British ATTOM study. 600 events have occurred to date and the IDMC has allowed the trial to continue. The stopping rules of this study, however, are only crossed when an OS benefit is demonstrated. One day, therefore, we will hear OS results from this study, without its conduct being compromised by early suggestions of benefit (or detriment). However, will we have to wait so long that the result will no longer be relevant?

This series of studies and results (or lack thereof) nicely demonstrate the dilemma of when results should be released, and how we should respond to them. There is a strong argument that OS data are the only ones that should precipitate early release of results and stopping of studies, both because major shifts in patterns of management are best guided by this, and in order to prevent loss of useful information that occurs when trials are closed early. However, there is value from making early DFS results available; this can impact on good patient care (eg. allowing an alternative to Tamoxifen for some patients) and can enhance trial design and speed up progress. It seems a compromise is needed, which can be best attended in the way our trials are set up in relation to how they are run and what the stopping rules are.

I will mention just one more interesting presentation, this one by Rob Coleman, on bisphosphonates and skeletal metastases. Breakdown products of type 1 collagen (as a result of bone destruction by metastases) can be measured in urine, eg. NTX. It appears the level of this is a very good marker of disease activity and reflects response to treatment/ disease progression well. A kit is being developed to measure NTX in the Clinic. Measurement of this may be a very useful way to monitor progress of patients with bone metastases - currently often quite a challenge with difficulties in bone scan interpretation. Zometa does appear to be 20% better than Pamidronate in multiple event analysis (P=0.025); it may be synergistic with chemotherapy (eg. Paclitaxel) and perhaps with Doxorubicin (if chemo administered before Zometa, there appears to be synergy in producing apoptosis in MCF7 cell line; in the reverse order there is no synergy). Conclusions regarding the value of adjuvant bisphosphonates are still awaited.

So, a meeting for reflection and discussion, to go away from with renewed enthusiasm, and new ideas for trials and patient management...

Ten Years of Women's Voices

Ms Sue Lockwood
Breast Cancer Action Group

Ten years ago in April 1994, Marcia O'Keefe wrote a letter to *The Age* about the need for an advocacy group for women with breast cancer in Victoria. Enough women replied to set up the Breast Cancer Action Group. It was the very first breast cancer advocacy group in Australia. And many of the other groups developed from our experiences, including advocacy groups in other states, and the Breast Cancer Network Australia. Marcia had previously had some unhappy experiences with IVF treatment. She transferred some of her concerns about the lack of information provided to women at diagnosis, informed consent, continuity of care to breast cancer and the Breast Cancer Action Group.

Like all good ideas, Marcia's identification of the need for action came at the right time. There were many different influences on the development of consumer groups, e.g. the development of the National Breast Cancer

Centre about this time, the extraordinary influence that the AIDS community had had on public policy and the fast tracking of new drugs, the investment in women's health more generally, the rise of evidence based medicine and its focus on the needs of patients. All these and other social attitudes combined to ensure that the Breast Cancer Action Group was in the right place at the right time.

Subsequently, the development of plans for the improvement in services to women with breast cancer, through the work of BreastCare Victoria has meant that the voices of women with breast cancer have been heard loudly and clearly in Victoria.

But the women have done their bit as well. They have been prepared to become representatives, they have been trained and supported, they have learnt heaps about their disease and the health system, they have been prepared to work long hours for no financial reward and they have been committed to ensuring that the voices of as many women as possible have been heard.

Some of the issues we have been involved with are

- performance indicators & standards for public hospital breast units
- waiting times for radiotherapy
- development of lymphoedema services
- reporting of breast cancer issues in the media
- access to breast care nurses across the state
- effective and efficient provision of external breast prostheses
- provision of Herceptin to women with advanced breast cancer in conjunction with Breast Cancer Action Group NSW and Breast Cancer Network Australia
- services for women with advanced disease
- a drop in center for women, their partners and children
- improved information resources designed especially for the needs of women
- clinical practice and consumer guidelines for women with early and advanced breast cancer and women with ductal carcinoma in situ, lobular carcinoma in situ and atypical hyperlasia
- services for women under 40.
- speaking to national and international conferences and clubs and societies
- messages on early detection of breast cancer
- direct involvement with the formulation of clinical trial protocols such as SNAC

There have been many achievements. But we are particularly proud of three. In July this year a new system for the provision of external breast prostheses was introduced. This is 7 years after women started pursuing the issue. This system will be a vast improvement on the current one. Another is the current emphasis on lymphoedema. No longer do we hear the statement that "none of my women get lymphoedema". It is acknowledged as a potential problem which causes great distress to women and as a result women are being offered information and support through lymphoedema clinics. Thirdly, breast care nurses are now widely available to women in Victoria. This is, in part, due to the support for this concept from women and the obvious improvements in service which have resulted from the skills of breast care nurses.

We have not done this alone; we have worked closely and productively with clinicians, breast care nurses, health officials, researchers, and others. We've worked in hospital, state, national and international arenas. We've tried and, I think, largely succeeded in working in partnership with these all different groups. These relationships have been one of the hallmarks of our success.

There will be more work to do over the next few years. But one of the major challenges for breast cancer consumer representatives is how to translate what we have learned into support for the development of consumer groups in other cancers.

2003 San Antonio Breast Cancer Symposium

Dr Geraldine Goss
Medical Oncologist
Box Hill and Maroondah Hospitals

San Antonio is a lovely place to visit in December; the weather was warm, the city very attractive and the meeting overall very interesting. Margaritas-sensational! Clearly the importance of this meeting is growing, and it is increasingly a respected forum for presentation of important new data. It is certainly less frantic than ASCO, and thus allows for sessions where cases can be presented by audience members to a panel of experts, and meet the professor sessions involve meeting and discussing data with leaders in the field. Some selected highlights included:

Extended Adjuvant Therapy with Letrozole

The study was a randomized, double-blind, placebo-controlled examining the use of 5 years of letrozole versus placebo for women with ER positive breast cancer following 5 years treatment with tamoxifen. The primary endpoint was disease-free survival (DFS), with secondary endpoints of overall survival (OS), quality of life and long-term safety. A total of 5187 women were followed-up for a median of 2.4 years. During this period, 207 breast cancer events were recorded, 75 in the letrozole group and 132 in the placebo group, an absolute difference of 2.2%. The projected differences for letrozole vs placebo groups at 4 years of follow-up: 4-year DFS of 93% vs 87% ($P \leq 0.001$); 4-year OS of 96% vs 94% (p=NS). An unplanned subgroup analysis showed at least as great benefit among women with node-negative disease than those with node-positive disease. Hot flashes, arthralgia, arthritis and myalgia were significantly more common in the letrozole group ($p<0.05$) and there was a trend towards a higher rate of newly diagnosed osteoporosis in the letrozole group. The strengths of the study were its design and large patient numbers, but the weaknesses included immaturity of the data in terms of overall survival and long term safety. No patient had actually completed 5 years of therapy, so optimal duration of letrozole is unknown. Overall survival figures will never be available since women on the placebo arm were offered active treatment. Perhaps subgroup analyses may reveal those more likely to benefit, however emerging data looking at sequences of tamoxifen and aromotase inhibitors as adjuvant therapy suggest that the sequencing rather than the duration may be important. Hopefully over the next few years the optimal use of adjuvant hormonal therapy will be elucidated.

The New Taxane

Abraxane is a nanoparticle bound paclitaxel which is cremaphor free. It has higher intratumor concentrations of paclitaxel and more antitumour activity than Taxol in animal models. In this study patients were randomly assigned to abraxane 260 mg/m^2 without routine premedication (n=229) or Taxol 175 mg/m^2 with premedications (n=225). The primary goal was to demonstrate non-inferiority/superiority of Abraxane to Taxol based on best confirmed response after 6 cycles of treatment. Abraxane therapy resulted in significantly higher response rates and longer time to tumor progression than Taxol in both an investigator-assessed dataset (31.4% vs 16.4%, $p<0.001$; 21.9 wks vs 16.1 wks, p=0.029), and an independently reviewed dataset (24.0% vs 11.1%, $p<0.001$; 21.0 wks vs 15.4 wks, p=0.014). Grade 3/4 hypersensitivity reactions were not observed among Abraxane treated patients, and Gr 4 neutropenia occurred less frequently for Abraxane (7% vs 19%, $p<0.001$). The incidence of Gr 3 sensory neuropathy was 10% for ABX vs 2% for TX, ($p<0.001$) with no episodes of Gr 4 neuropathy. Nail changes and severe fluid retention occurred infrequently, with no septic deaths. Thus ABX increased the therapeutic index of paclitaxel with less toxicity. This promising agent has clear activity among heavily pretreated patients with a very favourable toxicity profile and further studies in breast and other cancers are awaited with interest.

Adjuvant Therapy for Older Women

The risk of breast cancer increases with age and currently almost half of the new patients diagnosed with breast cancer in the U.S. are 65 years and older. These issues were discussed in a forum focussing on adjuvant therapy in the elderly. Although studies of adjuvant therapy have suffered from insufficient representation of the over 70 age group, extrapolating from patients 50 to 69 years old in trials analyzed by the EBCTCG suggests that patients above 70 are likely to derive the same benefits as other postmenopausal women in reducing the annual risk of relapse and death. Figures presented regarding life expectancy suggested that a 70 year old woman can expect an average of 16 further years of life, while an 80 year old can expect another 9 years. Despite this, older women with breast cancer are less likely to have mammographic screening, less likely to be offered breast conserving surgery, and breast radiation, and less likely to be offered adjuvant systemic therapy. Although breast cancer tends to have more favorable biologic characteristics in older patients, age and stage adjusted survival is similar for older and younger patients - the exception being the very young (<40 years) and the very old (85+ years). Clearly comorbidity is the critical factor in deciding on optimal treatment but age alone should not exclude women from optimal adjuvant therapy. Older patients should be considered for chemotherapy if they have reasonable life-expectancy (5-10 years) and large, ER and PR-negative, node negative (N-) lesions or if they are node-positive (N+). Additional data were presented regarding quality of life among older women suggested that body image disturbance following mastectomy is much greater than that following breast conservation, and that age again should not be the sole determining factor in choice of surgical approach.

TAC versus FAC: Update

Data from this study involving 1,491 women first presented at ASCO 2002 with a median follow-up of 33 months and 289 events showed significant improvement in disease free survival (DFS) in favor of TAC. At San Antonio the second interim analysis at a median follow-up of 55 months with 399 DFS events was reported. For DFS, there were 172 events on TAC and 227 on FAC: 80% and 75% of pts on TAC were alive and disease-free at 4 and 5 years respectively, vs.71% and 68% on FAC. For OS, there were 91 events on TAC and 130 on FAC: 89% and 87% of pts on TAC were alive at 4 and 5 years respectively, vs. 85% and 81% on FAC. There were no changes in the toxicity profile since the first interim analysis. TAC is clearly one of the most active adjuvant treatments in patients with node positive early breast cancer, although with much greater toxicity, especially of febrile neutropenia. It seems likely that optimal adjuvant therapy will include both anthracycline and taxane, however optimal dose interval and sequencing of these drugs is not yet known.

An enjoyable and informative meeting!

National Breast Cancer Centre Report

Clinical Guidelines for Young Women with Breast Cancer Released

The National Breast Cancer Centre (NBCC) has developed Clinical practice guidelines for the management and support of younger women with breast cancer to assist younger women with breast cancer and their doctors in making decisions about all aspects of their care.

The impact of a diagnosis of breast cancer and the treatment considerations for a woman aged 40 years or younger may be quite different from those of an older woman with this disease.

Although the incidence is lower in younger women, they are more likely to be diagnosed with larger, more aggressive tumours and have worse disease-free and overall survival outcomes compared with their older counterparts.

Younger women are also more likely to experience psychological distress. Issues of body image, sexuality and fertility are especially

significant for younger women. In addition, the decisions about treatment must be balanced against the survival benefits and impact on the quality of life.

The NHMRC approved Clinical practice guidelines for the management and support of younger women with breast cancer are available free to clinicians. Information for younger women with breast cancer, including questions to help women in their discussions with their treatment team has been developed and is available on the National Breast Cancer Centre website. This information is intended to complement NBCC publications: A guide for women with early breast cancer and A Guide for women with metastatic breast cancer.

Consumer Friendly Guide to DCIS

What's the difference between ductal carcinoma in situ (DCIS) and invasive breast cancer? Why does it need to be treated? And what are the treatment and support options? These are commonly asked questions by the 1200 Australian women diagnosed each year with DCIS. While most women's prognosis is excellent, many women may still feel confused because DCIS has a similar clinical diagnosis and treatment as invasive breast cancer. The NBCC's guide, Ductal carcinoma: Understanding your diagnosis and treatment, is written in a friendly, easy-to-read format with anecdotes from women who have been diagnosed and treated for this condition.

The publication of this consumer guide follows the NBCC's release in September of the clinical recommendations for the management of DCIS, LCIS, ADH and ALH (http://www.nbcc.org.au/bestpractice/dcis/). Consumer Information about other pre-invasive breast changes, lobular carcinoma in situ (LCIS) and atypical hyperplasia (AH) is also available. Copies of NBCC publications can be downloaded from www.breasthealth.com.au or can be ordered through; email directorate@nbcc.org.au or Freecall 1800 624 973. The National Breast Cancer Centre is funded by the Australian Department of Health & Ageing.

The Ovarian Cancer Program Report

First Clinical Practice Guidelines for the management of women with epithelial ovarian cancer. Australia's first guidelines for treating women with ovarian cancer, have been approved and are being printed by the NHMRC.

The guidelines have been developed by the Australian Cancer Network and the National Breast Cancer Centre's Ovarian Cancer Program. The Ovarian Cancer Program will undertake the dissemination of the guidelines using a number of strategies such as interactive seminars for clinicians and health professionals in metropolitan and regional areas across Australia. The guidelines will be available in June.

National Ovarian Cancer Forum Report Available

In February the Ovarian Cancer Program hosted a national forum – Ovarian cancer: health service delivery supporting best practice – in Sydney. The forum was co-sponsored by the Australian Government Department of Health and Ageing; OvCa Australia; The Australian Cancer Network; and the Gynaecological Research Fund (Westmead Hospital).

Included in the 80 people who attended the forum, were clinicians and allied health professionals involved in the care of women with ovarian cancer; senior representatives from federal and state health departments and relevant medical colleges, consumers and consumer organizations. The Ovarian Cancer Program will use the issues highlighted at the forum to guide its work in ovarian cancer.

A report about the forum, including copies of the presentations, is now available. Publications from the Ovarian Cancer Program can be downloaded from the Ovarian Cancer Program website www.ovariancancerprogram.org.au. Copies of the guidelines can also be ordered through the website or email: directorate @nbcc.org.au or Freecall 1800 624 973.

The Ovarian Cancer Program is managed by the National Breast Cancer Centre and is funded by the Australian Department of Health & Ageing.

For information about these and other projects from National Breast Cancer Centre, Freecall 1800 624 973, email: directorate@nbcc.org.au or visit www.breasthealth.com.au

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Key Published Articles Listing—Breast Cancer

Title	Author & Journal
Adjuvant chemotherapy followed by Goserelin versus either modality alone for premenopausal lymph node negative breast cancer: A randomised trial	IBCSG. J Natl Cancer Inst December 2003; 95(24): 1833–1846.
Ovarian ablation as adjuvant therapy for premenopausal women with breast cancer – Another step forward – Editorial	Pater JL and Paruleker WR. J Natl Cancer Inst December 2003; 95(24): 1811–1812.
Adjuvant endocrine therapy compared with no systematic therapy for elderly women with early breast cancer: 21-year results of International Breast Cancer Study Group Trial IV	Crivellari D, Price K, Gelber RD, et al. J Clin Oncol 2003; 21: 4517–4523.
A randomised trial of Exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer	Coombes RC, Hall E, Gibson LJ, et al. New England Journal of Medicine March 2004:350 (11): 1081–1092.
Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structural review	Peppercorn JM, Weeks JC, Cook EF & Joffe S. Lancet 24 January 2004; 363(9405): 263–270.
Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience	Berclaz G, Li S, Price KN et al Annals of Oncology 2004; 15: 875-884

Key Published Articles Listing—General

Title	Author & Journal
Potential health risks of complementary alternative medicines in cancer patients	Werneke U, Earl J, Seydel C, et al. British Journal of Cancer 26 January 2004; 90(2): 408–413.
What's the harm? Alternative medicine is not everything to gain and nothing to lose	Shermer H. 10 November 2003. www.sciam.com/
The current position of complementary / alternative medicine in cancer	Ernst E. European Journal of Cancer November 2003; 39(16): 2273–2277.

The regulation of complementary health: Sacrificing integrity?	Parker MH. Medical Journal of Australia 15 September 2003; 179(6): 316–318.
It's natural so it must be safe – Editorial	Smith A. Australian Prescriber 2002; 25(3): 50–51.
Interactions between complementary medicines and warfarin	Myers SP. Australian Prescriber 2002; 25(3): 54–56.
An analysis of newspaper reports of cancer breakthroughs: Hype or hope?	Ooi ES & Chapman S. Medical Journal of Australia 15 December 2003; 179(11/12): 639–643.
Public funding of large-scale clinical trials in Australia – Letter to Editor	A Rodger. Medical Journal of Australia 2004; 180(5): 255.
Making sense of trial results: Outcomes and estimation	O'Connell RL, Gebski VJ and Jeech AC. Medical Journal of Australia 2004; 180(3): 128–130.
Comparison of outcomes in cancer patients treated within and outside clinical trials: Conceptual framework and structured review	Peppercorn JM, Weeks JC, Cook EF & Joffe S. The Lancet 24 Jan 2004; 363(9405): 263–270.
The Clinical Support Systems Program	Leigh JA, Long PW, Phillips PA & Mortimer RH. Medical Journal of Australia 2004; 180 (10 Suppl):S74-S75
Turning an idea into reality to improve patient care: The development of the Clinical Support Systems Program	Sewell J, Leigh JA & Long PW. Medical Journal of Australia 2004; 180 (10 Suppl): S76–S78.
The Ethics of Early Stopping Rules: Who is Protecting Whom?	Cannistra SA JCO May 2004 22; (9): 1542-45