S35 CEF versus CMF in premenopausal women – Recent update

M. Levine, V. Bramwell, K. Pritchard, L. Shepherd. *National Cancer Institute of Canada Clinical Trials Group, Canada*

The results of clinical trials evaluating the efficacy of anthracycline chemotherapy in axillary node positive breast cancer have been inconclusive. Premenopausal women with node positive breast cancer were randomly allocated to receive either cyclophosphamide (100 mg/m^2 orally, Days 1–14), methotrexate (40 mg/m^2 IV, Days 1 & 8) and fluorouracil (600 mg/m^2 IV, Days 1 & 8) (CMF) or cyclophosphamide (75 mg/m^2 orally, Days 1–14), epirubicin (60 mg/m^2 IV, Days 1 & 8) and fluorouracil (500 mg/m^2 IV, Days 1 & 8) (CEF). Each cycle was administered monthly for six months. Patients on CEF received antibiotic prophylaxis with cotrimoxazole two tablets twice a day. The median follow-up is 59 months. 169 (47.1%) of the 359 CMF patients developed recurrence compared to 132 (37.6%) of the 351 CEF patients. The corresponding 5 year relapse-free survivals are 53% and 63% respectively, P = 0.009. 107 (29.8%) CMF patients have died compared to 85 (24.2%) CEF patients; 5 year survivals are 70% and 77% respectively, P = 0.03. There was one case of congestive heart failure in a patient who received CMF compared to none in the CEF group. Acute leukemia occurred in five patients in the CEF group. The results of this trial demonstrate the superiority of CEF over CMF in terms of both relapse-free survival and overall survival in premenopausal women with axillary node positive breast cancer.

S36 New developments in high-dose chemotherapy for breast cancer

Russel Basser. *Department of Clinical Haematology and Medical Oncology, Royal Melbourne Hospital and Western Hospital, Vic, Australia*

Breast cancer is now the most common indication for high-dose chemotherapy (HDC) with autologous stem cell support in the USA. This activity is based on promising results from numerous phase 2 studies, although there are now data from at least 3 small randomized trials. Most approaches employ standard-dose induction therapy followed by a single myeloablative dose. However, a number of investigators have reported results of high doses of single agents with cytokine and stem cell support (high-dose sequential therapy), or multiple cycles of non-ablative therapy with stem cell support. While the patients initially treated with HDC had metastatic breast cancer, a shift in focus has occurred so that many studies are now investigating the efficacy of HDC in patients with poor prognosis, early stage disease. We developed a regimen of 3 cycles of dose-intensive epirubicin 200 mg/m^2 and cyclophosphamide 4 mg/m^2 with stem cell given after each cycle in a pilot study of 100 patients with 10+ nodes. The median follow-up of surviving patients is now 40 months, and long-term morbidity is low. The efficacy of this treatment is now being tested in a randomized trial (IBCSG 15). Cautionary evidence of the selective nature of pilot studies of HDC in breast cancer has recently emerged that supports the need for completion of randomized studies prior to widespread adoption of this approach as a standard of care.

An important issue of uncertain significance is that of tumor cell contamination of blood products. A large number of studies have documented the presence of circulating breast cancer cells using sensitive immunohistochemical techniques or reverse transcriptase PCR. The presence of such cells is almost certainly predictive of early relapse of disease. While methods have been established to reduce the load of tumor cells infused into patients in stem cell collections after HDC without adversely affecting hematopoietic recovery, there is no proof that this improves patient outcome. Furthermore, assays for detection of circulating tumor cells have not been standardized, so that interpretation of the reported frequency of contamination of bone marrow and apheresis products (anywhere from 12% to 67%) is difficult.

Emerging technologies hold exciting prospects for further improving breast cancer treatment. Monoclonal antibodies to cellular oncogenes, such as her2/neu, have already been demonstrated to possess clinical activity, and are currently being evaluated in conjunction with standard-dose chemotherapy. Oncostatin M has recently been shown to inhibit hormone receptor-negative breast cancer cell growth *in vitro*, and is currently being assessed in preclinical *in vivo* models. Finally, agents that prevent the growth of cancer through inhibition of angiogenesis or tumor stroma raise the hope of treatments that circumvent the problems associated with chemotherapy resistance.

Friday, February 27, 1998 **17.00–18.00**

Session 10 Integrated Treatments: Quality of Life

S37 Quality of life assessment in the adjuvant setting: Is it relevant?

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In the adjuvant setting, the critical issue to consider in treatment decision-making is the trade-off between quality and quantity of life. The toxicities of adjuvant therapies must be balanced against the potential benefits of delayed recurrence and improved survival. In this presentation, we consider when quality-of-life assessment is relevant in this setting. Such assessments can inform patients about what to expect from their treatment, describe quality-of-life differences between treatments, provide an additional baseline measure with potential prognostic significance, inform clinicians about their patients' experiences with toxicities, indicate situations in which psychosocial interventions might be useful, and document patient adaptation to diagnosis and treatment. The relevance of quality-of-life assessment in the adjuvant setting will be illustrated by investigating one of the most controversial questions of today: when should chemotherapy be added to tamoxifen for postmenopausal patients? Data from the IBCSG Trial VII (J Clin Oncol 15:1385–1394, 1997) showed that adding three months of CMF (cyclophosphamide 100 mg/msq orally days 1–14; methotrexate 40 mg/msq i.v. days 1, 8; fluorouracil 600 mg/msq i.v. days 1, 8; repeated every 28 days) to Tamoxifen significantly improved disease-free survival compared with Tamoxifen alone. The Quality-adjusted Time Without Symptoms of disease or Toxicity of treatment (Q-TWiST) method was used to compare the adjuvant therapies with respect to quality-adjusted survival. The analysis indicated that the decision to use adjuvant chemotherapy in this setting should be based on patient preferences concerning the relative importance of treatment toxicity versus disease recurrence.

S38 Quality of life measurements in the IBCSG: Past, present and future

Ch. Hürny, J. Bernhard, A. Coates. *International Breast Cancer Study Group (IBCSG), Switzerland*

Past: Since 1986, the IBCSG is accruing a comprehensive longitudinal health-related Quality of Life (QL) data base in addition to biomedical data of patients with early breast cancer under and beyond adjuvant treatment with the aim to establish QL as a complementary outcome in randomized clinical trials and to get new insight in biopsychosocial interactions. Concerning methodology the IBCSG has made major contributions to the field in the development of global indicators, cross-cultural validation, impact of timing of assessments and working on practical and statistical issues of missing data.

Present: In two large-scale clinical trials (IBCSG VI and VII) adjuvant chemotherapy had a measurable adverse effect on health-related QL, but contrary to expectations this effect was transient and minor compared with patients adaptation/coping after diagnosis and surgery.

Future: In addition to the assessment of health-related QL the IBCSG is currently developing and applying a global indicator for a patient derived adapted utility concept in order to better assess the cost-benefit ratio of adjuvant treatment. However, the real challenge for the immediate future is the question how patients adaptation can be fostered within primary care.

S39 Impact of different adjuvant therapy strategies on quality of life (QOL) in breast cancer survivors (BCS)

P.A. Ganz[1], J. Rowland[2], B.E. Meyerowitz[3], K. Desmond[1]. [1]*UCLA, Los Angeles, CA, USA;* [2]*Georgetown University, Washington, DC, USA;* [3]*USC, Los Angeles, CA, USA*

Little is known about the long-term effects of adjuvant therapy on QOL and sexual functioning in BCS. Between January 1996 and June 1997, we surveyed 1,110 BCS who had been diagnosed with early stage breast cancer between 1 and 5 yrs earlier (average 2.8 yrs since diagnosis). The BCS were recruited in two large metropolitan cities in the U.S.A. BCS completed a survey battery that contained standardized measures of QOL (MOS-SF-36, Ladder of Life), mental health (MOS Mental Health Index, CES-D), symptoms, social support, body image, marital/partner functioning, and sexual functioning. In this sample,

N = 359 had received Tamoxifen (TAM) alone, N = 181 received chemotherapy (CHEM) alone, N = 300 received CHEM + TAM, and N = 270 received no adjuvant therapy (NO RX). There were significant differences in the mean age of each group, with the TAM group being the oldest (mean 62.5 yrs) and the CHEM group being the youngest (mean 46.7 yrs). Both age and time since diagnosis were controlled for in all statistical analyses. We found no significant differences in global QOL, mental health score, fatigue, or depression among the four BCS groups. The NO RX group had an MOS SF-36 Physical Functioning Composite Score that was at the median for a normal healthy population, while those in the adjuvant treatment groups scored slightly but significantly lower ($P = 0.02$). The MOS SF-36 Mental Health Composite Score was not significantly different among the groups and approximated the normal population. Current sexual functioning was significantly worse for patients who had received any CHEM ($P = 0.0001$) compared to NO RX. Hot flashes, night sweats, and vaginal discharge were reported more often in BCS on TAM ($P = 0.0001$). Vaginal dryness and pain with intercourse were reported significantly more often in BCS treated with CHEM. Overall, BCS function at a high level, similar to healthy women without cancer. However, compared to BCS with NO RX, those who received CHEM have significantly more sexual problems, and those treated with TAM experience more vasomotor symptoms.

Saturday, February 28, 1998 **8.15–10.00)**

Session 11 Clinical Research Around the World: Review of Trials of Cooperative Groups

S40 North American adjuvant breast cancer trials

J.S. Abrams. *National Cancer Institute, Bethesda, MD, USA*

The National Cancer Institutes in the U.S. and Canada sponsor Cooperative Groups to perform randomized trials in distinct subsets of early breast cancer. For women with ductal carcinoma in situ (DCIS), two trials (ECOG-5194 and RTOG-1026) are evaluating adjuvant breast irradiation (RT) in women with "good risk" lesions. NSABP trial (B-21) tests whether adjuvant breast RT, tamoxifen or both are needed for women undergoing lumpectomy for invasive tumors ≤ 1 cm. In node (−), receptor (+), invasive tumors, two trials are evaluating whether the somatostatin analog, octreotide, can add to tamoxifen (NSABP B-29 and MA-14). For women at higher risk of relapse, the focus has been on improving chemotherapy. The roles of dose intensity and dose density have been evaluated at dose levels requiring either G-CSF or stem cells. INT-0137 has tested concurrent doxorubicin/cyclophosphamide (AC) versus the same drugs administered sequentially at maximal doses with G-CSF. NSABP B-25 increased doses of C (up to 2400 mg/m^2) and INT-0148 escalated doses of A (up to 90 mg/m^2) compared to standard doses of the AC regimen. CALGB 9082 randomized patients with ≥ 10 (+) nodes to high dose chemotherapy with stem cell support vs. the same drugs at lower doses with G-CSF. The introduction of taxanes into adjuvant regimens has been a major area of investigation. Following AC, patients have been randomized to paclitaxel or no further therapy in INT-0148 and NSABP B-28 and to docetaxel in NSABP B-27. With the introduction of taxanes, dose density is being reevaluated in a trial (CALGB-9741) that compares AC followed by paclitaxel (T) to the three drugs given sequentially with both regimens given either every 2 or 3 weeks. For women with 4–9 nodes, sequential A-T-C with G-CSF is being compared to AC × 4 followed by high dose chemotherapy with stem cell support. Two studies are targeted to women <65–70 y.o. INT-0151 tests whether fenretinide can add to tamoxifen in women with node (+), receptor positive disease and CALGB-9343 studies whether breast RT can be safely omitted from conservative therapy in tumors <2 cm. when tamoxifen is given.

S41 Clinical research around the world: IBCSG trials

A. Coates. *IBCSG Scientific Advisory Committee, University of Sydney and Royal Prince Alfred Hospital, Sydney, Australia*

The International Breast Cancer Study Group (IBCSG) was established in 1977 as the Ludwig Breast Cancer Study Group. It involved member institutions from Switzerland, Australia, New Zealand, Sweden, Italy, Slovenia, South Africa, Spain, Canada, Hong Kong and at various times from other countries. It has completed seven trials in three generations, and has a further 8 trials currently open. Total accrual exceeds 11,000, and more than 8000 patients are in active follow up.

Early trials established the pattern of addressing important biological questions, and adapting the randomisation to the risk group of the patient. The first two generations of trials demonstrated that combined modality chemoendocrine therapy was superior to endocrine therapy alone or no therapy in node-positive postmenopausal patients; that a single peri-operative cycle improved disease-free survival in node negative patients, but was inferior to more prolonged therapy in node-positive patients, and that six conventionally-timed cycles of CMF were as effective as seven cycles commenced in the peri-operative period.

Recently reported trials in node-positive patients showed that three early cycles of CMF chemotherapy added to tamoxifen in postmenopausal patients, while late reintroduction of chemotherapy appeared detrimental, particularly in patients with ER-negative tumours. In premenopausal patients six initial cycles was superior to three, especially in younger patients.

Current studies in node-positive patients are addressing the role of a gap between courses of different chemotherapy, and the relative value of the antioestrogens tamoxifen and toremifene. In node-negative, premenopausal patients ovarian suppression with goserelin is being tested either instead of or added to CMF, while the value of initial CMF before tamoxifen is being tested in node-negative postmenopausal patients. For high risk patients a triple-transient regimen is being compared with conventional dose therapy.

Planning for future trials recognises the need for rapid accrual of large numbers of similar patients, and therefore the need for Inter-Group collaboration. The emergence of the Breast International Group as a consortium of European, Australasian and Canadian cooperative Groups is important to the rapid evaluation of new agents and strategies.

S42 Scandinavian/nordic adjuvant trials in breast cancer

H.T. Mouridsen. *Copenhagen University Hospital, Denmark*

The scandinavian breast group (SBG) was established 1989 with members from Denmark, Norway, Sweden, Finland and Iceland representing surgery, histopathology, oncology, statistics and basic research.

In 1993 SBG analysed all ongoing adjuvant studies in the nordic countries. It appeared that 20 protocols were ongoing, analysing 7 major questions. The individual trials only occasionally recruited sufficient number of patients to enable valid conclusions within a reasonable time.

As a result of this analysis a Clinical Trials Committee was established, the objective being to coordinate trials in primary and advanced disease.

Recently closed trials include:

(1) Post, node pos, rec pos/unknown. TAM 1 yr vs TAM 2 yr (DK, Iceland) (N = 1750)
(2) Post, node pos + neg. TAM 2 yrs vs TAM 5 yrs (Sweden) (N = 3545)
As a result standard adjuvant endocrine therapy is now TAM, 5 yrs.
So far standard adjuvant chemotherapy is CMF.

Trials ongoing for the moment include (N indicate number of patients randomized Oct. 1997).

(1) Pre, node pos, rec pos: castration vs CMF (N = 700)
(2) Pre and post, high risk, rec neg and pre node neg, grade II–III: CMF vs CEF ± pamidronate (N = 1150)
(3) High risk ≥ 8 pos nodes or ≥ 5 nodes, rec neg, and grade II–III or high s-phase. High dose chemotherapy + stemcell transplantation vs dose escalating therapy (N = 460)

According to present criteria of entry to adjuvant studies the theoretical annual numbers of patients in the nordic countries eligible for adjuvant studies with chemotherapy is 1000 and for endocrine therapy 1500. However, a substantial proportion of patients do not accept to be randomized and huge numbers are required in future adjuvant studies. Therefore SBG is keen to establish international collaboration.

S43 EORTC and big trials

M.J. Piccart, L. Biganzoli, A. Goldhirsch. *Breast International Group,*

The overview has been a remarkable undertaking in trying to shed some light in the darkness of our Breast Cancer (Br CA) adjuvant clinical trials: it has indeed provided us with a considerable enrichment in our understanding of the disease and of its interactions with current adjuvant treatment modalities. However, the overview probably represents a "treatment" for the "suboptimal health" of our current clinical research and this treatment has its own limits.

A European Intergroup called BIG has therefore been set up with the hope to give an exponential growth to European research in the adjuvant treatment of Br CA and to stimulate collaboration with the already existing American Intergroup.

Priorities for the coming years include a) support to: 1) a Scandinavian Trial looking at the issue of Hormonal Replacement Therapy 2) an EORTC trial looking at the potential anti-angiogenic and anti-invasion effects of a new anti-oestrogen given at the time of surgical biopsy 3) an IBCSG trial looking at biphosphonates given at the time of loco-regional relapse 4) an EORTC initiative to focus on the issue of fertility in very young Br CA patients as well