Meeting report

American Society for Clinical Oncology 39th Annual Meeting, Chicago, Illinois, USA, 31 May to 3 June 2003: Breast cancer neoadjuvant and adjuvant chemotherapy – prognostic and predictive markers

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Abstract

The annual American Society of Clinical Oncology congress is the largest forum for cancer professionals in the world, promoting new developments in cancer medicine. A wide spectrum of subjects relevant to breast cancer research and treatment was covered in this year's meeting, including chemotherapy in the neoadjuvant and adjuvant settings, molecular and gene profiling studies, and use of more conventional prognostic and predictive markers of outcome. This report discusses some of the highlights in translational and clinical aspects of early breast cancer management presented at the meeting.

Keywords: adjuvant, chemotherapy, gene profile, marker, neoadjuvant, predictive, prognostic

Introduction

The American Society of Clinical Oncology (ASCO) Annual Meeting is a leading educational and scientific event for oncologists, clinical researchers, academics and other health care professionals involved in multidisciplinary cancer care. This year the congress was held in Chicago, Illinois, from May 31 to June 3. The theme for the 39th annual meeting was 'Commitment, care, compassion: honouring people with cancer'. The goal of the meeting was to promote communication among cancer related medical specialities and the exchange of ideas arising from ongoing advances in oncology. This encompassed the areas of pathophysiology, diagnosis and management, and included innovations in therapies. For the first time this year, an oral presentation session was devoted to pharmacogenomics. A wide range of translational scientific research relevant to breast cancer was covered as well as new clinical data pertinent to breast oncology management.

Gene profiling in translational breast cancer research

Worldwide, many research groups are concentrating on breast cancer gene expression and molecular profiling, and this area was given significant coverage at the ASCO meeting. The first presentation in the meeting's plenary session, given by Lajos Pusztai from the MD Anderson group, dealt with the predictive nature of profiling in terms of response to chemotherapy. Their group described the use of gene expression profiling in predicting complete pathological response (pCR) to neoadjuvant chemotherapy with a paclitaxel and anthracycline combination (abstract #1 [1]). In 21 patients the overall accuracy of response prediction based on a group of five genes (three oestrogen sulphotransferases, nuclear factor 1/A, and histone acetyltransferase) was 81% and the positive predictive value for pCR was 75%, with an overall specificity of 93%, although sensitivity fell to 50%.

ASCO = American Society of Clinical Oncology; CMF = cyclophosphamide, methotrexate and fluorouracil; COX = cyclo-oxygenase; ECMF = epirubicin, cyclophosphamide, methotrexate and fluorouracil; ER = oestrogen receptor; FEC = fluorouracil, epirubicin and cyclophosphamide; GCSF = granulocyte colony-stimulating factor; HR = hormone receptor; pCR = complete pathological response.

The group from Baylor College (abstract #32 [1]) presented their work on gene expression patterns for *de novo* and acquired resistance to docetaxel. Twenty-four patients had paired samples before and after four cycles of docetaxel 100 mg/m^2. Docetaxel resistance occurred in 54% of the tumours and 46% were sensitive. Resistant tumours showed elevated baseline expression of some transcriptional genes and genes involved in repair/synthesis. Docetaxel-sensitive tumours showed higher baseline expression of mitochondrial proteins related to apoptosis. After 3 months of docetaxel chemotherapy, both the resistant and the sensitive groups exhibited the 'resistant' profile, suggesting that *de novo* and acquired chemotherapy resistance have the same or similar genotype. This work has now been published in detail in the *Lancet* [2].

The group from Yamato, Japan (abstract #34 [1]), looked at oligonucleotide microarrays in 20 patients receiving neoadjuvant chemotherapy with doxyfluoridine 800 mg/m^2 days 1–14 and docetaxel 60 mg/ m^2 day 8 every 3 weeks for four cycles. Out of 76 genes, among the good responders 15 genes were upregulated, including diubiquitin, ICAM-3, N-myc, and RNA-helicase, whereas 13 genes were downregulated.

Clearly, the hope is that molecular profiling in breast cancer will provide both a prognostic tool, as described elegantly by van 't Veer and coworkers [3] in their seminal paper published in *Nature*, and also a tool for predicting response to different chemotherapeutic agents. Molecular profiling may also identify groups of genes, which may provide targets – at a single gene and a pathway level – for the development of more specific therapeutic molecules.

Neoadjuvant chemotherapy

The neoadjuvant setting in breast cancer provides excellent opportunities as a 'biomarker discovery laboratory' (abstract #33 [1]) and a test ground for newer treatment combinations. A number of abstracts focused on primary systemic chemotherapy, including the molecular translational research discussed above. Efforts to identify good predictive factors for response are well placed because the outcome measure occurs early and can inform research on larger trial samples in the adjuvant setting.

The important features of the neoadjuvant presentations are summarized in Table 1. pCR is highlighted as the most significant early outcome measure in these studies. We understand from the work of Chollet and coworkers [4] that, irrespective of initial prognostic factors in a tumour, when pCR is achieved this correlates with a disease-free survival of over 80% at 10 years. The highest pCR seen in this group of abstracts is that from Limentani (abstract #131 [1]), with a 36% pCR to docetaxel 60 mg/m^2 and vinorelbine 45 mg/m^2 given every 2 weeks with granulocyte colony-stimulating factor (GCSF) support, with the addition of herceptin in the HER2-positive population.

Perhaps the most noteworthy of the neoadjuvant abstracts is that from Ramirez-Ugalde and coworkers from Mexico City (abstract #160 [1]). Patients with stable or progressive disease following standard anthracycline-based neoadjuvant chemotherapy were treated with weekly 5-fluorouracil, gemcitabine and dexamethasone during radiotherapy to the breast (50 Gy with 10 Gy boost). A pCR rate of 28% was noted, with attainment of minimal residual disease in a further 23%, making surgery possible in 47 out of 49 patients. This is a truly remarkable achievement in this group of breast cancer patients selected for their refractoriness to anthracyclines. Further evaluation of the combination of chemotherapy and radiotherapy may be useful in this poor prognosis group.

Early breast cancer: adjuvant chemotherapy

Mamounas presented the updated results of the NSABP-B28 study, which examined the addition of four cycles of paclitaxel 225 mg/m^2 to the standard of four cycles of doxorubicin and cyclophosphamide (abstract #12 [1]). A total of 3060 patients were randomized, and the study now has a median follow up of 64 months. Disease-free survival shows a relative risk for relapse of 0.83 (P=0.008) in favour of the addition of paclitaxel, although overall survival did not show the same advantage (relative risk 0.94, P=0.46). There appeared to be no interaction of taxanes with oestrogen receptor (ER) positivity, although a confounding factor may be the concomitant treatment of ER-positive patients with tamoxifen. There are at present no significant differences in death rates between the standard and experimental arm. This is perhaps because the prognosis of patients in the study is very good and that at median follow up of 64 months it is too early to detect any differences. This study supports the earlier findings of CALGB 9344 [5], which indicated benefit from the addition of taxanes, although the CALGB 9344 study suggested a definite interaction between ER status and benefit from taxanes. In ER-negative disease there are now more studies showing lack of interaction than studies showing positive interaction [6].

This report reiterates the difference in biology between hormone receptor (HR) positive and negative disease. Analysis of relapse and survival in the first 5 years is more informative for the HR-negative group, in which the majority of events occur within this time frame, rather than for the HR-positive population, in which events occur more often after 5 years (abstract #55 [1]). Similarly, the interaction of chemotherapy treatments appears to produce more effect in the HR-negative population within the first 5 years, and in the HR-positive population after this time [7]. This must be remembered when analyzing adjuvant

Table 1

Summary and findings of neoadjuvant chemotherapy trials

Abstract no.	Treatment	*n*	pCR
1	Paclitaxel weekly and FAC	24	25% (breast and lymph nodes)
32	Docetaxel 100 mg/m^2 q 3 weeks × 4	24	0%
33	Doxorubicin 75 mg/m^2 × 3; then docetaxel 40 mg/m^2 q week × 6	70	12.5%
34	Doxyfluoridine 800 mg/m^2 D1–14; docetaxel 60 mg/m^2 D8 q 3 weeks	20	14%
35	Paclitaxel doxorubicin standard or DD × 6	460	ER$^-$ 26% ER$^+$ 8%
37	Paclitaxel + doxorubicin × 4 then CMF × 4	451	23%
80	Epirubicin 120 mg/m^2 q 3 weeks ± tamoxifen	211	ER$^-$ 23.4% ER$^+$ 4.6%
83	Vinorelbine 25mg/m^2 D1 + 8 and epirubicin 60 mg/m^2 D1 versus AC × 6	411	15% both arms
85	TAC × 2: then PR to TAC × 6 (107 patients) <PR to TAC × 4 (24 patients) or vinorelbine and xeloda × 4 (20 patients)	151	19% 26% for clinical responders to TAC
86	Vinorelbine/herceptin	28	29% cCR+PR 93%
107	Epirubicin 60mg/m^2 D1, CDDP 60 mg/m^2 D1, xeloda 1000 mg/m^2 BD D1–14	48	27%
131	Docetaxel 60 mg/m^2 + vinorelbine 45 mg/m^2 q 2 weeks + GCSF + herceptin in HER2$^+$	33	36%
140	Gemcitabine 1 g/m^2, epirubicin 90 mg/ m^2, paclitaxel 175 mg/m^2 q 3 weeks	22	22.7%
143	Docetaxel 100 mg/m^2 q 3 weeks × 4	42	10%
160	Anthracycline SD or PD; 5FU 500 mg/m^2/w + gemcitabine 100 mg/m^2/w + dexamethasone 16 mg throughout radiotherapy (50 Gy +10 Gy boost)	47	28% MRD (+pN0) 23%
163	Docetaxel 75 mg/m^2 + doxorubicin 50 mg/m^2 + cyclophosphamide 500 mg/m^2 × 4 q 3 weeks	37	8%
190	Docetaxel 100 mg/m^2 q 3 weeks × 6	88	19.8%

CMF, cyclophosphamide, methotrexate and fluorouracil; ER, oestrogen receptor; 5FU, 5-fluorouracil; FAC, 5-fluorouracil, doxorubicin and cyclophosphamide; GCSF, granulocyte colony-stimulating factor; pCR, complete pathological response; TAC, docetaxel, doxorubicin and cyclophosphamide; PR, partial response; <PR, less than a partial response; cCR, complete clinical response; CDDP, cisplatin; DD, dose dense; SD, stable disease; PD, progessive disease; MRD, minimal residual disease; +pNO, pathological node negative.

studies that include a high proportion of HR-positive women (66% in this study).

The National Epirubicin Adjuvant Trial (NEAT) trial (abstract #13 [1]) was presented by Dr Chris Poole from the Cancer Research UK Institute and Cancer Trials Unit in Birmingham. This is the first of the large adjuvant chemotherapy trials to come from the UK, and shows a very significant advantage for epirubicin, cyclophosphamide, methotrexate and fluorouracil (ECMF) chemotherapy in terms of both disease-free and overall survival when compared with standard classical cyclophosphamide, methotrexate and fluorouracil (CMF) for six cycles. The study is the most strongly positive of the very few individual trials that demonstrate an advantage for anthracycline-based chemotherapy. This advantage is demonstrated across all stratification groups. The study has been reported as a preplanned meta-analysis with a smaller trial run by the Scottish Cancer Therapy Network, which asked broadly similar questions. The event-driven analysis was carried out 18 months later than anticipated, suggesting that the results for patients treated on the standard CMF arm were considerably better than had been predicted before the trial started.

The trial has both proved an advantage for the Bonadonna block-scheduling anthracycline approach [8], and improved outcomes for breast cancer patients in the UK by insisting on adherence to the two classical CMF schedules (oral or intravenous cyclophosphamide). Direct comparisons in the metastatic setting had already shown three-weekly CMF to be inferior, and the analysis by Bonadonna and coworkers of their own original CMF study [9] showed that less than 85% dose delivery of the

classical CMF resulted in inferior outcomes. At ASCO 2002 the group reported that the ECMF regimen is tolerable [10]. This study provided further confirmation of the benefit from anthracycline-based treatment and shows that, unlike four cycles of doxorubicin and cyclophosphamide, which was shown to be equivalent to CMF, the ECMF block-scheduling is definitely superior. The emergence of acute myeloid leukaemia/myelodysplastic syndrome in the fluorouracil, epirubicin and cyclophosphamide (FEC) D1 and 8 studies (the only other studies to show in a 'stand alone way' the superiority of anthracyclines) raises concerns [11]. To date no cases of acute myeloid leukaemia have been reported in the NEAT and Scottish studies, although at present follow up is shorter.

Following the recently successful CALGB 9471 adjuvant study [12], which showed a strongly positive result for dose dense therapy, it is of considerable interest to see early reports of piloted adjuvant treatments from this group. Abstract 46 [1] described an adjuvant phase II study of dose dense FEC followed by weekly paclitaxel and docetaxel. This pilot study looked at both feasibility and efficacy. FEC (500/100/500 mg/m^2) was administered every 2 weeks for six cycles with GCSF support, followed by weekly paclitaxel (80 mg/m^2) and docetaxel (35 mg/m^2) for 18 weeks (a total of 30 weeks of treatment). This schedule produced significant toxicity with grade 3/4 pneumonitis in four out of 44 (9%), requiring prolonged hospitalization. This complication seemed wholly attributable to the dose dense FEC. Seventeen patients proceeded with the second phase of weekly taxanes for 18 weeks, and after completion of this two out of 17 patients (11%) developed severe pleural and pericardial effusions, again necessitating hospitalization. This protocol is not being further developed for high-risk patients, and may interestingly set a new limit to the amount of intensification achievable with GCSF support alone rather than stem cell haematological support.

Fumoleau (abstract #91 [1]) presented data for the French Adjuvant Study Group (FASG). This was a 7-year analysis of the benefit/risk ratio of epirubicin in adjuvant chemotherapy trials (3577 patients). When used at classical doses up to epirubicin 100 mg/m^2 per cycle, the benefit/risk ratio in operable breast cancer remains in favour of epirubicin-based adjuvant chemotherapy. A 10-year update of the FASG 05 trial (FEC50 versus FEC100) presented by Bonneterre (abstract #93 [1]), analyzing benefit/risk ratio after adjuvant chemotherapy in node-positive early breast cancer patients, confirmed the advantage at 10 years of FEC100 over FEC50.

Prognostic/predictive markers (conventional)

A number of abstracts were presented on more conventional tumour markers as both predictive and prognostic factors. The British Columbia Tissue Micro-Array Project (BCTMAP; abstract #9 [1]) examined the impact of cyclooxygenase (COX)-2, HER2 and aromatase expression in 930 patients with breast cancer enrolled in phase II/III clinical trials. Expression of HER2 and COX-2 but not aromatase was associated with poorer breast cancer specific survival; however, positivity for both COX-2 in addition to HER2 did not increase the relative risk for death related to breast cancer when compared with all other groups. The data were felt to support the likelihood of interactions between COX-2, HER2 and aromatase pathways.

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) reported on 512 patients in ABCSG Trial 5 (abstract #10 [1]). Premenopausal HR-positive patients were randomized between CMF chemotherapy and combined hormonal therapy with tamoxifen and goserelin. High p27Kip1 expression was observed in 413 patients. Combination endocrine therapy was superior to CMF in patients with high p27Kip1 expression but not in low expressing patients. Adjusted relative risks for relapse and death after combined endocrine therapy when compared with CMF were as follows: high p27Kip1 0.52 (95% confidence interval 0.32–0.83; $P=0.006$) and 0.51 (95% confidence interval 0.21–1.25; $P=0.14$) for relapse and death, respectively. In women with low p27Kip1 expression there was no difference in response for CMF or combined hormone therapy. These results suggest that p27Kip1 may be a useful marker for selection of patients for combined endocrine therapy in this premenopausal group. ER status was shown in neoadjuvant trials to predict response to neoadjuvant chemotherapy (abstracts #35 and #80 [1]). ER-negative patients had higher rates of pCR to chemotherapy. Increased responsiveness is also related to Ki67 positivity. This is confirmatory evidence to support the hypothesis of interaction between different tumour biology (ER-positive versus ER-negative disease) and response to chemotherapy. Recent clinical data from trials sequencing tamoxifen and chemotherapy support the use of sequential hormone therapy after completion of chemotherapy to produce better outcomes for patients.

Ravdin and coworkers (abstract #55 [1]) looked at the predictive factor of ER-negative tumours in the adjuvant setting. They concluded that ER-negative status should not be used as the sole criteria for deciding on adjuvant chemotherapy in node-negative patients. This poster presented some interesting survival curves from diagnosis comparing the ER-negative group with the ER-positive one. The prevalence of death from breast cancer rose quickly in the ER-negative group and peaked at 3 years with only a small dip at 4 years, before a 'twin peak' at 5 years. The ER-positive curve showed a slow increase in risk for recurrence through time with the two survival curves crossing at 8.5 years from diagnosis. These survival curves are of considerable interest and attest to the

different tumour biology of ER-positive and ER-negative disease, and to the way in which these two different types of breast cancer might interact with chemotherapy treatment.

The group from the MD Anderson Cancer Center (abstract #56 [1]) reported on the prognostic value of epidermal growth factor receptor expression, and its ability to add to the prognostic effect of HER2 over-expression. The Guy's Group (abstract #144 [1]) with the MRC Cancer Trials Unit presented their estimates for overall survival probabilities and probable benefit for adjuvant systemic therapy (both hormonal and chemotherapy). The predicted survival at 10 years from this model of a 55-year-old with a 30 mm grade 3 tumour with two positive nodes was as follows: no treatment 38%; chemotherapy alone 47%; hormonal therapy for ER-positive tumour 64%; and hormonal therapy plus chemotherapy 69%. This represents an improvement in absolute terms of 31% in 10-year survival, with substantial contributions from both chemotherapy and hormonal therapy.

Conclusion

The 39th ASCO Annual Meeting showcased many interesting developments in clinical and translational research that are relevant to breast cancer, allowing dissemination of useful information to people working in cancer related medical specialities. Improved understanding of the pathogenesis of breast cancer, emerging prognostic and predictive strategies, and developments in clinical data for therapeutic interventions will significantly influence our breast cancer practice in the future.

Competing interests

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