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SYMPOSIUM

Breast cancer – from bench to bedside

147 INVITED

Expression of the c-erbB-4/her-4 growth factor receptor in breast cancer

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In order to examine the expression of the c-erbB-4 growth factor receptor protein in normal tissues and in tumours we have made polyclonal and monoclonal antibodies which react in formalin-fixed paraffin-embedded tissues. Using these reagents to detect protein expression by immunohistochemical staining and antisense RNA probes in *in situ* hybridisation we have determined c-erbB-4 expression in a wide range of normal foetal and adult tissues. c-erbB-4 was expressed in the lining epithelia of the gastrointestinal, urinary, reproductive and respiratory tracts as well as the skin, skeletal muscle, circulatory, endocrine and nervous systems. The developing brain and heart notably express high levels of the receptor.

We have also examined the pattern of c-erbB-4 expression in a survey of common solid tumours. Loss of expression was noted in 40–80% of adenocarcinomas and up to 100% of squamous cell carcinomas whereas overexpression was observed in 10–20% of cases.

We are currently analysing a series of 180 breast cancers for expression of c-erbB-4 and whether this has any relationship to clinical or molecular variables.

148 INVITED

Tumour suppressor genes in breast cancer

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Tumour suppressor genes (TSG) codes for proteins normally involved in suppression of cell growth and cell proliferation. Loss of function of TSGs may lead to tumour formation. Both inherited and somatic inactivating mutations in TSGs have been identified in breast cancers. Only a handful of genes have been proved to be classical TSGs. Several genes showing Loss of Heterozygocity (LOH) in tumours as well as germline mutations in hereditary cancer syndromes have been identified. Germ line mutations in the *BRCA1, BRCA2,* and *TP53* genes predispose to breast cancer. Tumours from individuals with such germ line mutations have lost the other copy of the gene leading to total inactivation of the TSG in question. Somatic mutations and LOH leading to inactivation of the Rb, TSG101, p16 as well as the TP53 gene are found in breast carcinomas. So far the most frequently involved gene is the TP53 gene. Mutation in this gene has been shown to be both a prognostic and a predictive marker. Analyses of TP53 mutations in breast carcinomas may give valuable information of prognosis, choice of treatment, and for selection of patients for novel treatment strategies.

149 INVITED

The immune response to breast cancer

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Purpose: Cytokines are produced by breast tumour cells and elevated levels of IL6, VEGF and M-CSF have been associated with cancers of poor prognosis. The question we asked was how the production of large amounts of M-CSF is a macrophage differentiation and survival factor and its presence at high concentrations in the tumour might impair differentiation of dendritic cells and favor macrophage differentiation.

Methods and Results: In vitro studies have confirmed this hypothesis and our results clearly demonstrate that concentrations ranging from 1245–16,600 pg/ml (75–1000 U/ml) were able to dedifferentiate immature dendritic cells to macrophages by both phenotypic and functional analysis. Plasma levels in breast cancer patients showed median levels of 380 pg/ml (range 33 to 2564 pg/ml). In a clinical vaccination program, prevaccination M-CSF levels were highest in a patient who progressed early and lowest in patients who showed a response. In an independent study, a striking, though infrequent, feature was the marked infiltration of $CD1a^+$ monocyte derived cells in p53 overexpressing tumors, a phenotype which was most pronounced in both tumours with a mutation in codon $175^{ang\text{-}his}$. CD1a is an MHC class I-like protein, expressed mostly on immature or mature human dendritic cells (DC). These cells are derived from monocytes and thought to be involved in the presentation of lipids and peptides to T cells. The presence of $CD1a^+$ inflammatory cell infiltrates correlated significantly with p53 overexpression ($3–4^+$) ($p = 0.035$) and with the expression of HLA class II (DP, DQ, DR) by tumour cells ($p = 0.025$). Furthermore, these tumour cells had low immunsotaining for M-CSF ($p = 0.04$) and patients with p53 overexpressing tumours also had low circulating M-CSF plasma levels ($p = 0.05$).

Conclusions: M-CSF production by tumour cells impairs dendritic cell differentiation suggesting that cancer patients with high circulating levels are unlikely to respond to immune manipulations as a consequence of functional incapacity to produce effective antigen presentating cells. Patients with low levels may be able to develop a spontaneous cellular immune response.

150 INVITED

Inactivation of E-cadherin in breast cancer

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The E-cadherin protein is located in the cell membrane of many epithelial cells and is involved in cell-cell interactions and probably also in signal transduction.

The E-cadherin gene is located on chromosome 16q in a region exhibiting frequent loss of heterozygosity (LOH) in breast cancer. In recent years, it was shown that a subset of breast carcinomas containing LOH in this region contain inactivating E-cadherin gene mutations. A more detailed analysis of these tumors revealed that most invasive lobular carcinomas exhibit inactivation of the E-cadherin gene, whereas inactivation of E-cadherin is never found in invasive ductal carcinoma.

The E-cadherin protein is located in the cell membrane and its cytoplasmic tail interacts with alpha-, beta- and gamma catenin. In all tumors with loss of E-cadherin expression alpha- and beta-catenin expression is also lost and gamma-catenin expression is lost in 50% of these cases. Loss of expression of alpha-, beta- or gamma-catenin in the absence of E-cadherin inactivation is very rare.

In lobular carcinoma in situ (LCIS) of the breast, expression of E-cadherin is also absent and in a limited number of cases inactivating mutations in the E-cadherin gene have been identified in LCIS. This indicates that inactivation of E-cadherin takes place before the tumor cells become invasive and is an early step in breast cancer development.

It appears that there is a distinct genetic pathway leading to the development of invasive lobular carcinoma of the breast and that inactivation of E-cadherin is a crucial step in this pathway.

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The final answer? Breast conserving therapy versus radical mastectomy: long term follow up on randomized trials

151 INVITED

Long-term follow-up of the first breast conservation trial (Guy's Wide Excision Study)

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Breast conservation therapy is now accepted as a proven approach for selected patients with operable breast cancer. It important to appreciate

that the first randomised trials, which were carried out at Guy's Hospital, indicated the need for good local control and the increased mortality from breast cancer which occurred when treatment was sub-optimal. In the first trial (E Series) 374 women aged ≥50, with T1, T2, N0 and N1 tumours were randomised to either Halsted mastectomy and post-operative radiotherapy or wide excision and post-operative irradiation. Both groups were given 25–27 Gy to the gland fields and the wide excision group received additionally 35–38 Gy to the breast.

Hence the wide excision group had no axillary surgery and subsequent axillary irradiation using what is now regarded as a low dose of radiotherapy. The first analysis of this trial indicated that increased risk of axillary relapse was restricted to N1 cases and so a second trial was conducted with entry only for those with clinically negative axillae (N0 series). Of 255 cases entered, 133 were randomised to mastectomy and 122 to wide excision. The same radiotherapy schedule was used as in the E Series.

In the E Series, after 25 years follow-up, local relapse occurred in 26% of the mastectomy group and 50% of the wide excision group ($\chi^2 = 21.6$, $p < 0.001$). The breast cancer specific mortality rate at 25 years was 56% in the mastectomy group and 63% in those treated by wide excision ($\chi^2 = 5.33$, $p = 0.02$). For those in the second NO trial, after 25 years local relapse occurred in 18% of the mastectomy cases and 54% of the wide excision group ($\chi^2 = 30.6$, $p < 0.001$). There were significantly more distant relapses in the latter group ($\chi^2 = 6.32$, $p = 0.01$), and a significant increase in breast cancer deaths (57% versus 44%, $\chi^2 = 4.27$, $p = 0.04$).

These two trials, conducted before the widespread introduction of systemic adjuvant therapy, both indicate the long-term effects of inadequate primary treatment. Inadvertent failure to treat the axilla effectively led not only to significantly increased axillary relapse rates but also to more deaths from metastatic disease.

152 INVITED

NSABP Protocol B-06: A randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer – Results after 15 years of follow-up

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Background: Previous reports from Protocol B-06 conducted by the National Surgical Adjuvant Breast and Bowel Project demonstrated the worth of lumpectomy and breast irradiation in the treatment of invasive breast cancer. This report updates the findings through an average of 15 years of follow-up.

Methods: Patients with tumors 4 cm or less and either clinically negative or clinically positive axillary nodes were randomly assigned: 1) total mastectomy and axillary dissection, 2) lumpectomy and axillary dissection, or 3) lumpectomy and axillary dissection followed by breast irradiation. There are 1851 eligible patients with known axillary nodal status and follow-up data available.

Results: No significant differences were found in overall disease-free survival, distant disease-free survival, or survival between those patients who underwent total mastectomy and those treated by lumpectomy alone or lumpectomy followed by breast irradiation. After 15 years of follow-up, the cumulative incidence of ipsilateral breast tumor recurrence (IBTR) was 36% in the group treated with lumpectomy alone and 12% in the group treated by lumpectomy and breast irradiation.

Conclusions: The findings continue to demonstrate that lumpectomy followed by breast irradiation is an appropriate treatment for women with operable Stage I and Stage II invasive breast cancer.

153 INVITED

The Milan experience in surgical strategies for early breast cancer (overview on prospective trials with latest end-results)

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This is an up-date of distant results of conservative treatment for breast cancer of limited size (2–2.5 cm in major diameter). Results are dated March 1998, according to the last report of our study control office.

Three different patient series had been entered into controlled randomized studies (Milan I, II, III). The fourth series consists of women conservatively treated in the routine (out-trial patients).

Milan I – Halsted Mastectomy vs. QU.A.RT (Quadrantectomy, Axilliary complete dissection and Radiotherapy on the residual gland). Activated 1973. Accrual 1973–1980 – 701 cases (349 vs. 352). Median follow-up 240 months. Overall survival: Halsted 60.1% – QU.A.RT 59.6. Local Recurrences: Halsted 2.29% – QU.A.RT 8.2%.

Milan II – QU.A.RT vs. T.A.RT (T = tumorectomy). Activated 1985. Accrual 1985–1989 – 705 cases (360 vs 345). Median follow-up 126 months. Overall survival: QU.A.RT 79% – T.A.RT 77%. Local Recurrences: QU.A.RT 8.0% – T.A.RT 19%.

Milan III – QU.A.RT vs. QU.AD (no RT). Activated 1987. Accrual 1987–1989 – 567 cases (294 vs 273). Median follow-up 95 months. Overall survival: QU.A.RT 88.4% – QU.AD 88.3%. Local Recurrences: QU.A.RT 4.7% – QU.AD 17.6%.

Out Trial series – 1,526 cases treated by QU.A.RT (1970–1984). Median follow-up 171 months. Overall survival 69.5% Local Recurrences 9.5%.

154 INVITED

The impact of local control in early breast cancer. Update of the EORTC trials

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The EORTC trial 10801 randomized patients with stage I and II breast cancer between radical mastectomy (RM) and breast conserving therapy (BCT). The study included patients with tumors of up to 5 cm with a microscopically incomplete resection. The long term results (median follow-up 13 years) still show that the survival is similar in both treatment arms. In patients with a local recurrence treated with salvage therapy, disappointing local control and survival rates have been observed, both in those initially treated with mastectomy or breast conserving therapy. In order to investigate which patients would benefit from RM or BCT, a joint analysis was performed within the DBCCG, which carried out a similar study making it possible to analyse a total number of 1670 patients. These results showed that patients <35 yrs had a higher local recurrence rate with BCT compared with RM. The number of patients included <35 yrs, however, was very small. In all other patient categories similar local control and survival rates were observed. In the consecutive EORTC trial, investigating the value of a boost dose, which included 5569 patients, young age (<40 yrs) was again one of the major prognostic factors for local control. The major difference between the young age group and the older patient group was the higher number of patients with an initially incomplete excision and smaller volume of the resected breast tissue surrounding the tumor.

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Psychosocial issues in the management of breast cancer

155 INVITED

Why do cancer doctors burn out and can it be prevented?

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There is ongoing concern about the mental health of doctors generally. Combining the results of three recent large UK studies, the estimated prevalence of psychiatric morbidity among hospital consultants is 28%. This is similar to levels reported by junior doctors, but clearly in excess of the 18% reported among the employed general population. Cancer doctors appear to be at no greater risk of burnout and psychiatric morbidity than other consultants. This is despite the particular stresses inherent in cancer medicine arising from the frequent exposure to death and dying and the conflict between the curative goals, on which most training is based and the palliative goals of much cancer care.

Across all specialist groups, job satisfaction appears to protect significantly consultants' mental health against the adverse effects of job stress. The predominant source of job stress reported by consultants is overload and its effect on home life. Major sources of job satisfaction include dealing well with patients and relatives, having professional status and esteem, having a high level of autonomy and variety in the job. Feeling insuffi-