17 Proffered Paper Oral

Radiotherapy and/or Tamoxifen after conserving surgery for breast cancers of excellent prognosis: BASO II trial

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The BASO II trial was of intact breast irradiation (RT) versus No RT and/or Tamoxifen versus No Tamoxifen following breast conserving surgery, in patients with primary invasive breast cancers of excellent prognosis.

Primary objective: To determine the rates of local recurrence (LR) for the various regimes, defined as further cancer in the tissue or skin of the treated breast.

Secondary objectives: breast cancer specific survival rates; contralateral breast cancer rates.

Method: 2×2 design with entry allowed to one or other comparison as well as to both. Life table analysis (Log Rank) according to randomisation and to treatment received.

Results: Median FU 122 months. 10 year breast cancer specific survival (Life table) 98.5%.

The results of the randomisation (intention to treat) show that operative surgery without an additional treatment is significantly worse in terms of LR than treatment with either therapy and particularly so when treatment excluded both therapies. There was no significant difference in LR between the addition of RT alone and the use of Tamoxifen alone.

Analysis by treatment received

Treatment received	No LR n	LR n	LR%	LR rate p.a (%)
No RT no TAM	172	29	16.6	1.7
RT no TAM	172	10	5.5	0.5
TAM no RT	401	20	4.8	0.5
RT + TAM	376	4	1.1	0.1

Conclusions: Even in this group of early tumours of least aggression, wide local excision alone has a rate of LR over 1.5% PA. This rate is significantly reduced by receipt of either RT or Tamoxifen. Recurrence rate is very low at around 0.1% PA following receipt of both adjuvant therapies.

Wednesday, 16 April 2008 16:00–17:30

CLINICAL SCIENCE SYMPOSIUM

Pharmacogenetics – the host matters

18 Invited

Germline SNP analysis as a biomarker for the prediction response to therapy in breast cancer

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Background: Genetic factors are thought to play a role in resistance towards chemotherapeutic agents such as 5-FU. Approximately 30 genes are directly or indirectly involved in 5-FU metabolism, and genetic variation in any of these may contribute to anti-tumor response. Polymorphisms in these genes were analyzed in relation to tumoral mRNA levels of 5-FU metabolizing genes, response to chemotherapy and survival.

Materials: A total of 21 genetic variants were studied in 35 breast cancer patients treated with FUMI (5-FluoroUracil, mitomycin) and in a similar cohort of 90 doxorubicin treated breast cancer patients. Genotype distributions were compared using 109 healthy controls.

Results: No significant association was found between any polymorphisms and response to chemotherapy as measured by shrinkage of tumor. However, carriers of three copies of the TYMS 5′UTR repeat had shorter survival than non-carriers (P = 0.048) in the FUMI treatment group, but not in the doxorubicin treated group. Carriers of three copies of the repeat were also more frequently observed in both patients groups than in healthy controls (P = 0.034). Several highly significant associations were observed between genotypes and expression levels of 5-FU metabolizing genes. A SNP in codon 72 of TP53 was revealed to be a key regulator of 5-FU metabolizing genes such as DHFR and MTHFR, constituting 50% of all significant associations observed after FUMI therapy.

Conclusions: These data suggest that 3 copies of the TYMS 5′UTR repeat may give a treatment specific reduced survival in breast cancer patients, and that TP53 may have a direct, allele specific, role in 5-FU mediated response.

Future studies: Using the 109K array from Illumina we have further applied the whole genome analysis (WGA) approach to investigate the genetic background underlying different molecular subtypes of breast cancer, TP53 mutation status, hormonal receptor status and other clinical parameters such as presence of circulating disseminated tumour cells (DTC). Current data will be discussed.

19 Invited

Epigenetics and breast cancer – prediction of drug activity

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The recent application of genomic technology to the molecular profiling of breast cancers has unveiled their heterogeneous nature. It has been shown that accumulated mutations, genomic instability, epigenetic modification of the genome, genetic variability and environmental factors are involved in the development and uniqueness of a patient's disease. Novel genomic and epigenetic-based technologies have been developed to enhance the analysis of tumor samples including archival formalin-fixed paraffin-embedded samples. Breast tumors can now be studied with regard to genetic variation, genomic instability, gene expression, gene mutations, and methylation patterns. These areas of research are being made accessible through genome-wide screening technologies and will rapidly expand our knowledge of the biological determinants that contribute to the unique properties of each tumor and lead to the identification of genes that could be potential therapeutic targets for specific tumor subtypes (Abramovitz and Leyland-Jones, 2007; Brennan et al., 2007). The tumor expression of estrogen receptors (ERs) is a very important biomarker for prognosis and a marker that is predictive of response to endocrine therapy (Reid et al., 2005; Giacinti et al., 2006). The loss of ER expression is associated to a poor prognosis and, in a significant fraction of breast cancers, this repression is a result of the hypermethylation of CpG islands within the ER-alpha promoter. Hypermethylation is one of the best known epigenetic events in mammalian cells and specific inhibitors are currently being studied as new drugs able to restore ER-alpha expression in ER-alpha-negative breast cancer cells and to promote apoptosis and differentiation. Demethylating agents and histone deacetylase inhibitors are candidates to become new drugs in endocrine cancer therapy (Giacinti et al., 2006).

In conclusion, epigenetic modification of breast cancer genome may influence treatment response to a significant extent and modification of this process is an important new target for rational intervention.

References

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Giacinti L, et al. Oncologist 2006;11(1):1−8.
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20 Invited

Germline pharmacogenomics in the treatment of breast cancer

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Background: The treatment of breast cancer has improved markedly with the advent of increasingly individualized approaches. These include the targeting of endocrine therapy towards tumours that have ER or PR receptors, of the ant-HER2 antibody trastuzamab (Herceptin™) to tumours that overexpress the HER2 receptor, and the targeting of chemotherapy to patients with specific multigene RNA expression profiles such as the Oncotype Dx™ and Mammaprint™ tests. Despite this progress, tests that predict toxicity are needed as multiple chemotherapeutic and endocrine therapies become available. Germline genetic variability in the host may predict such toxicity and may also be a useful predictor of therapeutic efficacy but no germline tests have been developed or validated to date.

Results: We shown that active metabolites of the most widely used endocrine therapy, tamoxifen are generated through the action of