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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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

cytochrome P450 2D6, an enzyme known for 30 years to be genetically polymorphic. Endoxifen concentrations associate with CYP2D6 genotype and studies conducted in the prevention, adjuvant and metastatic settings suggest that patients with the CYP2D6 poor metabolizer genotype respond less well to tamoxifen treatment. There is a clear alternative to tamoxifen for these patients: the aromatase inhibitor class of drugs.

Despite the fact that aromatase inhibitors (AIs) appear slightly but definitively superior to tamoxifen as adjuvant therapy in postmenopausal women, the relatively low cost of tamoxifen makes it the only viable oral therapy in many countries, and the AIs are ineffective, monotherapy in premenopausal women. It is possible that the relative benefit of tamoxifen in extensive metabolizers of CYP2D6 may render the drug more effective than AIs in this group of patients. Recent data indicate that patients who are poor metabolizers of tamoxifen drop out of trials and from therapy at a notably lower rate.

A key recent trial (E-2100) demonstrated that the anti-VEGF antibody bevacizumab combined with paclitaxel showed greater reductions in DFS survival than paclitaxel alone, but the combination did not alter overall mortality. We have recently demonstrated that germline genetic variability in the VEGF receptor associated with outcomes in this trial which hada group that experienced overall survival benefits not different from placebo, and a group that survived on average a year longer. It is of note that variants in the same gene are also associated with risk for toxicity from bevacizumab therapy: hypertension.

Conclusions: These data suggest that germline genomic variability in candidate genes, but also in pharmacologic and physiologic pathways may be valuable approaches to further refining the targeting of patients with breast cancer to maximize efficacy, but also to reduce toxicity and thus to optimize the overall risk:benefit ratio of therapy for breast cancer.

21 Proffered Paper Oral

Genetic polymorphism of CYP2D6: a critical factor for early metastatic relapse in patients treated with adjuvant tamoxifen

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Current adjuvant hormonal therapy in postmenopausal women with breast cancer is debatable between upfront aromatase inhibitors and sequential treatment initiated with tamoxifen. We previously reported a retrospective analysis in order to identify risk factors of early systemic relapse among postmenopausal women treated with tamoxifen for an hormone-positive carcinoma in adjuvant setting (Debled, Cancer 2007). A distant recurrence occurred in 5.3% within the first 3 years of tamoxifen. Lymph node involvement and modified SBR grade were identified as independent predictive factors of early recurrence. Exploratory immunohistochemical analyses performed on tumors that subsequently recurred did not reveal any unusual expression of EGFR, HER2, or VEGF-R2 that could have suggested a role in tamoxifen resistance.

As genetic variation in tamoxifen-metabolizing enzymes may be another factor to consider, we examined the frequency of germline cytochrome P450 (CYP)2D6*4 variant genotype from normal tissue of early relapse patients. Results were compared to frequency of this variant in South-west French healthy people.

Materials and Methods: DNA was isolated from paraffin-embedded normal tissue from 22 patients having subsequently relapsed within 3-years adjuvant tamoxifen. After PCR amplification of CYP2D6 gene, the CYP 2D6*4 polymorphism was detected using restriction enzymes as previously described (Jin, JNCI 2005). Frequency of CYP2D6*4 variant was simultaneously determined by analysis of DNA from 100 local healthy blood donors.

Results: CYP 2D6*4 heterozygotes were in 14 among 22 relapsed patients (64%) compared to 40 among 100 healthy people. Difference is statistically significant (Chi-2 test, $p = 0.04$). No CYP 2D6*4 homozygote variant was observed.

Conclusion: As CYP 2D6 polymorphism does not appear to increase breast cancer risk, these results confirm a clinical relevant association between genetic variation in tamoxifen-metabolizing enzyme CYP2D6 and early relapse. Analyses of a larger number of relapsed patients are in progress. Results of a cohort of patients treated with adjuvant tamoxifen who did not relapse despite adverse prognostic factors (grade III and N+ >1) will also be available. Individual analysis of CYP2D6 genetic variant may be in the future an important factor to be considered for selection of patients who should receive upfront aromatase inhibitor treatment.

22 Proffered Paper Oral

Clinical implications of CYP2D6 genotyping on tamoxifen treatment in breast cancer

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Background: In October 2006 the FDA recommended an update in the tamoxifen label to reflect the increased risk for breast cancer recurrence in postmenopausal ER-positive patients who are CYP2D6 poor metabolizers. This recommendation however was based on only few studies at that time. More clinical studies addressing the relation between CYP2D6 genotype and tamoxifen efficacy have been performed and published since. An updated analysis of the literature is presented.

Methods: Searches were conducted of Medline, Embase, Web of Science, scientific meeting proceedings and manual review of references from eligible publications.

Results: 8 eligible studies were evaluated, 7 of which were retrospective analyses and one was published as abstract. One study investigated the effect in metastatic breast cancer in a small partially prospective cohort. Another study investigated the effect on prophylactic tamoxifen use. Five studies were in line with the FDA advice, however 3 studies (including the largest study) showed contradictory results. Possible explanations for the conflicting results are the inability to adjust for possible confounders – especially CYP2D6 inhibitor use – and the comparison of different groups of combined genotypes (*4/*4 + *1/*4 vs *1/*1 or *4/*4 vs *1/*1 + *1/*4). The 3 studies showing no or even an opposite effect were unable to account for some important confounders. Still, confounding bias is expected to be limited because of the influence of Mendelian randomization. Furthermore, mostly only the *4 allele has been investigated whereas other CYP2D6 variant alleles (e.g. *5, *9 and *41) may also modify the effect.

Conclusions: The clinical relevance of CYP2D6 genotyping to tailor tamoxifen therapy has not been fully clarified as present study results are inconsistent. In a small majority of studies an increased risk in poor and intermediate metabolizers is reported. The biological activity of tamoxifen is possibly modified by other factors, some influencing the major metabolite endoxifen (e.g. CYP2D6 inhibitor use). Therefore, at the Leiden University Medical Center, the Netherlands, a prospective study is started to associate complete CYP2D6 genotype by SNP array and endoxifen plasma concentration with breast cancer recurrence and survival, powered to detect a doubled risk of recurrence in poor CYP2D6 metabolizers ($n = 650$).

Wednesday, 16 April 2008 12:30–14:30

POSTER SESSION

Advocacy and education

23 Poster

Informational and supportive needs of women considering extended hormonal adjuvant treatment (ExHAT) – a Canadian survey conducted by SOLARIS (Summit of Opinion Leaders – Advocacy, Research, Information and Support)

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Background: The results of NCIC MA-17 led to the need to inform women of the potential benefits of ExHAT with Letrozole (L) following 5 years of adjuvant (adj) tamoxifen (T).

Method: In 02/2007, we convened a meeting of 30 key advocates/survivors in Canada (SOLARIS) to discuss this issue. Under the auspices of the Canadian Breast Cancer Network (CBCN), we conducted a 43 question National Survey addressing the informational and supportive needs of women who had completed at least 4 years of adjT. The survey was completed online or by mail through CBCN and Ipsos Reid between 12/04−28/05, 2007.

Results: There were 230 respondents (CI:+/-6.5%)-the vast majority responded through mail/website. Median age was 61.5 years (range