One major challenge is to understand the biologic basis for the relationship between lifestyle and BC outcomes. Circulating estrogens, insulin and other members of the IGF family of growth factors may play important roles.

Future research should examine prognostic effects of lifestyle interventions using randomized designs. Optimal approaches to weight loss, and types of physical activity most strongly associated with BC outcomes, should also be delineated.

213 Proffered Paper Oral

Factors affecting occupational returning in breast cancer survivors in working age: preliminary analysis from a 131-patient sample

M. Strada[1], M. Frascaroli[1], I. Jedrychowska[1], C. Innaurato[1], A. Bernardo[2], R. Palumbo[2], G. Poggi[2], C. Teragni[2], A. Amatu[2], G. Bernardo[2]. *[1]Fondazione Maugeri, Rehabilitative Oncology, Pavia, Italy; [2]Fondazione Maugeri, Medical Oncology II, Pavia, Italy*

Background: The correlations between survival and returning to work in cancer survivors is an issue of increasing interest, given the actual improvement in treatment strategies, and only a few data are available in the literature. Here we report the preliminary data from an analysis of a sample of 131 patients affected with breast cancer in working age.

Methods: One hundred thirty-one patients with surgically treated breast cancer, all in working age at the time of disease occurrence, were interviewed by a questionnaire including personal data (age at cancer diagnosis, familiarity for cancer, education degree, children, etc.), disease (co-morbidity, sequelae, treatment-related side effects, disease duration, rehabilitative treatment), the type of work (dependent, independent, physical, intellectual, full- or part time, flexibility). Statistical analysis was performed by using ?2 test and univariate/multivariate logistic regression model.

Results: Median age was 45 years (68 patients >45, 63 <45), 9 patients had elementary education, 66 secondary, 24 degree; 26 patients with co-morbidity and 63 with surgical sequelae, 50 referred treatment-related toxicities, 73 had received post-surgical rehabilitation. Working-related factors: independent in 33 patients, public dependent in 50, enterprise dependent in 48; physical work in 54 patients, intellectual in 77; 102 worked full-time and 26 part-time. Overall, 97/131 patients (74%) returned to work (77% dependent, 65% intellectual, 41% reduced duties; 54% flexible hours versus 44% at diagnosis). Thirty-four patients did not go back to work, because of disease/treatment-related sequelae (53%), changed working bent (41%), company policy (6%); 30% of them obtained civil invalidity, 23% old-age pension, 30% disease protraction, 17% remained out of work. The type of work and disease duration (< or >60 days) resulted the only two statistically significant factors; specifically, negative factors for physical work were the loss of technical knowledge and update and the psychological impact, while the flexible hours resulted a stimulating positive factor; no significant effect was found for socio-demographic characteristics, as well as for dependent/independent, full/part time work.

Conclusions: Our preliminary analysis showed a statistically significant impact of both work type and disease duration on working returning in breast cancer patients, but additional aspects of great importance on patient qualify of life are emerging (elaboration of EORTC and FACT-An questionnaires is ongoing).

214 Proffered Paper Oral

Age, clinical and psychological associations with fatigue following radiotherapy for early breast cancer – Results from 2208 women in the UK Standardisation of Breast Radiotherapy Trials (START) on behalf of the START Trial Management Group

J. Mills[1], G. Sumo[1], J. Haviland[1], J.M. Bliss[1], P. Hopwood[2]. *[1]The Institute of Cancer Research, Clinical Trials & Statistics Unit, Sutton, United Kingdom; [2]Christie Hospital NHS Foundation Trust, Psycho-oncology Service, Manchester, United Kingdom*

Background: Fatigue is a frequently reported symptom in women following early breast cancer treatment and may be increased with adjuvant breast radiotherapy. There are conflicting reports on contributing factors and whether fatigue persists in the longer term. The aim of this Quality of Life (QL) sub study is to investigate the effect of a range of other clinical and psychological factors and symptoms on fatigue in women following radiotherapy for early stage breast cancer in the START Trials.

Methods: In the START Trials a subgroup of women were recruited to a QL study and completed standardised questionnaires including the EORTC QLQ C-30, the BR23 and HADS at baseline (after surgery +/−adjuvant systemic therapy but before radiotherapy) and 6, 12, 24 and 60 months. Fatigue was measured as a symptom subscale comprised of 3 individual items. The effect of age, time from surgery, type of surgery, chemotherapy (CT), endocrine therapy and change over time were tested using a GEE model. Associations of fatigue with anxiety, depression, insomnia and physical functioning were estimated using Spearman's rank correlation.

Results: 2208 women consented to the QL study; mean age 56.9 years; 82.9% underwent conservative surgery; 33% had received CT. 2180 (99%) women completed baseline QL. Fatigue levels were highest at baseline (median 33.33) and decreased during follow-up (median 22.2). Feeling tired was the most highly scored individual item with 29% women reporting 'quite a bit'/'very much' at baseline, decreasing to 22% by 1 year and remaining stable to 5 years. The other 2 items showed a similar trend. An early effect of CT on fatigue was seen ($p < 0.001$) but decreased over time. Worse fatigue during follow-up was associated with worse fatigue at baseline ($p < 0.001$), earlier follow-up time ($p < 0.001$) and older age ($p = 0.007$). Worse fatigue scores were moderately to strongly associated with worse depression, anxiety, physical functioning levels and insomnia ($p < 0.001$).

Conclusions: There was no evidence of persistent fatigue after RT although a transient effect due to earlier CT was found. Fatigue improved over time for the majority of women. However, significant associations with older age, mood and physical functioning highlight a subset of patients most at risk of poorer QL that warrant a holistic assessment.

Thursday, 17 April 2008 12:30–14:30

POSTER SESSION

Adjuvant and neo-adjuvant therapy

215 Poster Discussion

The effects of concurrent or sequential administration of trastuzumab on radiation-induced pulmonary fibrosis in rats

C. Umay[1], N.S. Bese[1], S. Serdengecti[2], N. Kepil[3], C. Karaca[4], N. Sut[5], T. Altug[6], A. Ober[1]. *[1]Istanbul University Cerrahpasa Medical School, Department of Radiation Oncology, Istanbul, Turkey; [2]Istanbul University Cerrahpasa Medical School, Department of Medical Oncology, Istanbul, Turkey; [3]Istanbul University Cerrahpasa Medical School, Department of Pathology, Istanbul, Turkey; [4]Istanbul University, Department Experimental Animal Breeding and Research Laboratory, Istanbul, Turkey; [5]Trakya University, Department Biostatistics, Edirne, Turkey; [6]Istanbul University, Department Experimental Animal Breeding and Research Laboratory, Istanbul, Turkey*

Background: There is not enough data regarding the late effects of combination of T with RT. Lung is the most sensitive tissue to observe the late effects of irradiation. In this study we evaluated if concurrent or sequential administration of T has any impact for the development of radiation induced pulmonary fibrosis (RIPF)in rats.

Materials and Methods: 54 female wistar-albino rats were divided into 6 groups (G). The animals in G 1 (concurrent T) had irradiation in two hours of following T administration. G 2 (sequential T-RT) received irradiation, one week after T. G 3 (sequential RT-T) had irradiation first and received T one week after RT. G 4 (T only) had only T. G 5 (RT only) had only irradiation. The rats in G 6 (sham) were only observed. A single dose of 12 Gy was given to both lungs with an anterior field at 2 cm depth after simulation. T dose which was equivalent to 6 mg/kg adult dose was calculated for each rat, and injected by the tail vein. For sequential administration one week interval was given between T and RT which was shown to be the half life of T in rats. Animals were sacrificed 16 weeks after RT which was shown to be a sufficient period for the development of RIPF in rats. Both lungs were fixed by formalin and embedded in paraffin. Five-micrometer thick sections were stained with Masson's trichrome to visualize fibrosis and collagen. As quantative end point the extent of fibrosis for each field was graded on a scale from 0 (normal lung or minimal fibrous thickening of alveolar or bronchial walls) to 4 (total fibrous obliteration of the field). The mean score values were calculated for each group. Normality distribution and linearity were tested, then the One way ANOVA test and Tukey HSD post-hoc test were used to calculate the significance of the differences among groups.

Results: The mean value of fibrosis were 1.44, 1.77, 1.75 and 1.62 for G 1, G 2, G 3 and G 5 respectively, and there were no significant differences among the comparison of these 4 groups ($p > 0.05$). The mean value of fibrosis score was 0.25 for G 4 and 0.33 for G 6. The difference was not significant between these two groups ($p > 0.05$), When the mean value of fibrosis scores of the groups which had thoracic irradiation with or without T, compared with observation arm and the animals which received T only, the differences were statistically significant ($p < 0.05$).

Conclusion: This study shows that addition of T to thoracic irradiation either sequentially or concomitantly does not increase the RIPF in rats.

216 Poster Discussion

Interpretation of contrast enhanced MRI for early prediction of breast-cancer response to neoadjuvant chemotherapy: Initial results

C.E. Loo[1], H.J. Teertstra[1], S. Rodenhuis[2], M.J. Van de Vijver[3], J. Hannemann[3], S.H. Muller[1], M.J. Vrancken Peeters[4], K.G.A. Gilhuijs[1]. *[1]Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Radiology, Amsterdam, The Netherlands; [2]Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Medical oncology, Amsterdam, The Netherlands; [3]Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Pathology, Amsterdam, The Netherlands; [4]Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Surgery, Amsterdam, The Netherlands*

Background: The aim of this study was to establish changes in contrast-enhanced MRI of breast cancer during neoadjuvant chemotherapy that are indicative of pathology outcome. Additionally to establish a practical test to identify which tumors will not achieve a complete remission with the given chemotherapy and may benefit from a switch to an alternative regimen.

Material and Methods: Ninety-nine patients with invasive breast cancer >3 cm and/or at least one tumor positive lymph node scheduled to receive neoadjuvant chemotherapy were included. MR imaging was performed prior and during chemotherapy. All selected patients underwent surgery. In case residual vital tumor in the surgical specimen was found at pathology it was defined as non-complete remission. In the first 54 patients (training set), multivariate analysis with cross validation was performed on MRI features describing kinetics and morphology of contrast uptake. ROC analysis was employed to guide switching to a different chemotherapy regimen in patients at risk for non-complete remission, while maintaining first-line therapy in 95% of patients who will achieve complete remission. The practical test was evaluated prospectively on subsequent patients (validation set).

Results: Reduction of <25% in largest diameter of late enhancement in the tumor during chemotherapy was most predictive of non-complete pathological remission ($Az = 0.73$, $p < 0.00001$). The fraction of anticipated non-responders was 41% (22/54) in the training set and 40% (14/35) in the validation set. The fraction of complete remissions in the group of predicted responders was 44% (14/32) in the training set and 43% (9/21) in the validation set. The fraction of non-complete remissions in the group of predicted non-responders was 95% (21/22) in the training set and 79% (11/14) in the validation set after switching therapy.

Conclusion: Reduction of <25% in largest diameter of late enhancement during neoadjuvant chemotherapy shows potential to predict non-complete remission after therapy.

217 Poster Discussion

Impact of early adoption of systemic treatment modalities on mortality trends of breast cancer in Canada – implications for cancer organization processes

J. Ragaz[1], J.J. Spinelli[2], R. Semeniciw[3], W. Hryniuk[4], E. Franco[5]. *[1]McGill University, Medicine & Oncology, Montréal PQ, Canada; [2]British Columbia Cancer Agency, Biostatistics & Epidemiology, Vancouver BC, Canada; [3]Statistics Canada, Biostatistics & Epidemiology, Ottawa Ontario, Canada; [4]Cancer Advocacy of Cancer Canada, Medical Oncology, Toronto Ontario, Canada; [5]McGill University, Epidemiology, Montreal PQ, Canada*

Introduction: Mortality trends require correlation with therapies & interventions delivered.

Methodology: We compared Breast Cancer (BrCa) mortality trends, years 1950–2000, in Canada with data obtained by Statistics Canada. The trends were correlated with therapeutic and screening interventions, comparing data for the entire country (Canada) versus Provinces with different degrees of implementation of Provincial Community Oncology (PCOP) Programs for years 1975–1995, and funding provided.

Implementation was classified as LEVEL I: PCOP most uniform, with most funding (British Columbia); LEVEL II: PCOP medium (Ontario); LEVEL III: least uniform (Maritime Provinces* of New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland).

Results: Mortality was adjusted for each decade between 1950–2000, relative to 1950 (age-standardized BrCa death rate per 100,000 population): 30.1 for Canada, 31.4 for BC; 30.7 Ontario; 26.1 for Maritime Provinces.

We observed an earlier and more substantial BrCa mortality reduction in BC than in the rest of Canada, in parallel with wider and more uniform use of systemic therapies, before the advent of screening mammography.

Table. BrCa mortality trends relative to year 1950, by decade, between years 1950–2000

Years	1950	1960	1970	1980	1990	2000
Canada:	100%	102.6%	102.7%	99.8%	100.2%	81.7%
BC	100%	98.7%	96.5%	92.2%	85.2%	69.1%
Ontario	100%	103.4%	103.2%	101.4%	100.3%	81.7%
Maritime Provinces*	100%	105.2%	108.2%	114.4%	114.8%	104.1%

Conclusions: These data suggest that timely and widespread adoption of state-of-the art systemic therapies may have a strong impact on the extent of mortality reduction. Delaying the introduction of curative systemic therapies may have prevented early survival gains in some regions.

The emergence of multiple candidate agents with curative potential may overwhelm the clinical development pipeline with consequent delays in their introduction in oncological care. We propose an accelerated clinical development strategy that circumvents issues related to delayed implementation of novel interventions.

The five-point strategy includes: 1. the application of stage IV results into adjuvant trials; 2. fast-tracking novel agents into simultaneously-organized randomized stage IV trials; 3. wider use of neoadjuvant trials; 4. trials with concomitant guideline-treated controls; and 5. international coordination. Significance of these finding and proposals, with impact on broad societal implications, will be discussed in more detail.

218 Poster Discussion

Farnesoid X receptor (FXR) status complements the evaluation of estrogen receptor alpha (ER) in breast cancer (BC) patients and predicts benefit from tamoxifen

F. Journe[1], V. Durbecq[1], B. Haibe-Kains[1], C. Chaboteaux[1], G. Rouas[1], G. Laurent[2], D. Larsimont[1], M. Piccart[1], J.J. Body[3], C. Sotiriou[1]. *[1]University of Brussels (ULB), Institut Bordet Translational Research Unit, Brussels, Belgium; [2]University of Mons-Hainaut (UMH), Laboratory of Histology, Mons, Belgium; [3]University of Brussels (ULB), CHU Brugmann, Brussels, Belgium*

Background: FXR is a nuclear receptor for bile acids. It is normally expressed in liver tissue and the GI tract. We recently detected FXR in BC and reported a significant correlation between FXR and ER expressions. Moreover, we observed that FXR is associated with proliferation markers in ER+ BC. We also showed that chenodeoxycholic acid (CDCA) stimulates the proliferation of MCF-7 (ER+) cells through a physical interaction between FXR and ER, the latter resulting in ER activation. Finally, we demonstrated that CDCA increases the expressions of MMP-2/-9 in BC cells, indicating that bile acids/FXR might be involved in the invasiveness of tumor cells.

Material and Methods: We assessed the prognostic value of FXR expression in BC by retrospectively analyzing microarray data in a population of 2473 patients. We evaluated patient overall survival (OS) and distant metastasis-free survival (DMFS) in the total population and in subgroups characterized by ER, node and menopausal (age >50) status. We compared the prognostic value of FXR status with that of the proliferation marker Ki-67. In addition, we examined the predictive value of FXR with regard to response to tamoxifen.

Results: In the total population, a higher FXR expression was significantly associated with a shorter OS ($p = 0.003$; HR = 1.48; 95% CI [1.14−1.91]). The prognostic value of FXR was particularly good the in ER+/node+ subgroup ($p = 0.02$; HR = 2.16; 95% CI [1.32−3.54]), discriminating high versus low proliferative tumors as efficiently as Ki-67 level ($p = 0.008$; HR = 2.33; 95% CI [1.25−4.33]). In this subgroup of patients treated with tamoxifen, high FXR expression was significantly associated with a shorter DMFS ($p = 0.039$; HR = 2.20; 95% CI [1.04−4.64]). Additionally, the FXR prognostic value, with respect to OS evaluation, was also significant in the ER−/age $\leqslant$50 subpopulation ($p = 0.038$; HR = 1.75; 95% CI [1.03−2.97]), where Ki-67 determination is uninformative. In this subgroup, FXR tended to correlate with occurrence of distant relapses, but was significantly associated with late metastatic relapses (>1000 days) ($p = 0.002$; HR = 3.21; 95% CI [1.55−6.65]), which generally developed in skeleton.

Conclusions: FXR evaluation brings additional prognostic/predictive information mainly in ER− BC. In this subpopulation, FXR seems related to the occurrence of distant relapses, especially in young patients.