Conclusion: We have used embedded tumor cells (ETC) as internal calibrators for accurate process control and normalization of the immunobead quantitative RT-PCR technique. The specificity and detection rate of tumor cells in blood and bone marrow was significantly increased by molecular analysis of a multi-marker gene panel. The newly introduced surrogate markers from the networks of apoptosis, invasion, angiogenesis and stem cell phenotype should improve early detection of metastasis, monitoring of therapy response and efficacy and selection of tailored therapy regimes.

5091 POSTER

Predictive role of Her-2 receptors on primary tumour in patients with liver metastases from breast cancer treated by surgery

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Introduction: Hepatic resection is a well-established therapy for patients with liver metastases (LM) from colorectal or neuroendocrine carcinoma. However, for patients with LM from breast cancer, the role of surgery in management of metastases from breast cancer is not well-defined and still controversial.
The objective of this retrospective study is to evaluate outcomes after surgical treatment of breast LM and to identify factors associated with longterm survival.
Material and Methods: Tumour characteristics, treatments, and outcomes of patients undergoing resection for hepatic metastases from breast cancer from June 1995 to Augustus 2005 were analyzed. Patient demographics, tumor characteristics, treatment, and postoperative outcome were analyzed. The start date for follow-up and survival analyses was the date of surgery for LM.
Results: After median follow-up of 25.5 months (range: 5−80) from hepatic surgery, the median cancer specific survival and median disease-free survival (DFS) was 50 months and 16.6 months respectively. There was no postoperative mortality. Univariate analysis suggests that prechemotherapeutic number of HM (single vs multiple) was associated with CSS; estrogen and progesterone receptors on primary tumour were associated with improved DFS. Furthermore, positive Herceptine receptor (HerR) on primary tumour was associated with worse CSS ($p < 0.0102$).
Conclusions: In selected patients, resection of breast LM can be done safely. HerR on primary tumour could be representing an unfavourable predictive factor for CSS.

5092 POSTER

Molecular predictive factors of response to taxanes and anthracyclines in breast cancer: toward a targeted perspective for cytotoxic therapy

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Background: Anthracyclines and Taxanes are among the most active drugs in the treatment of breast cancer. Acute and long-term side effects are mainly cardiotoxicity for anthracyclines and neuropathy for taxanes. The objective of the study is to identify markers of response to anthracyclines and to taxanes in the aim of tailoring a treatment plan. Topoisomerase IIa (TopoIIa) is the anthracyclines target and MAPtau regulates the microtubules dynamic instability, target of taxanes. Some studies have shown a positive correlation between TopoIIa overexpression and MAPtau underexpression and responsiveness to Anthracyclines or Taxanes.
Material and Methods: TopoIIa and MAPtau protein expression were evaluated by IHC using monoclonal antibodies (Ki-S1 and A0024) in 36 breast tissues from women with advanced breast cancer, treated with anthracyclines and taxanes. The protein expression was related to response, as well as to other prognostic fatcors such as age, hormone receptors (HRs), c-erb, p53, ki67 and bcl-2. Response was assessed using RECIST criteria.
Results: Our early data suggest that TopoIIa overexpression (cut-off$\geqslant$12%) and MAPtau underexpression (cut-off <30%) correlate with objective response to anthracyclines (p 0.004) and to taxanes (p 0.007). HRs is related to probability of response to both drugs ($p < 0.005$), even in the subgroups TopoIIa negative and MAPtau positive. Bcl-2 overexpression seems to be related to response in the subgroup MAPtau positive (p 0.006). Other prognostic factors (age, c-erbB2, p53 and Ki67) are not related with response either to anthracyclines and taxanes ($p > 0.01$), in particular HER-2 gene amplification did not alter neither the response to anthracyclines (p 0.86) nor TopoIIa expression (p 0.4).
Conclusion: These preliminary data suggest that TopoIIa overexpression and MAPtau underexpression are related to response to anthacyclines and taxanes, respectively. The presence of HRs favourably affects response to treatment with both drugs; Bcl-2 overexpression is related to response only in the subgroup MAPtau positive, while HER-2 gene amplification is not related to response to anthracyclines or to TopoIIa expression. These results should be considered in a larger cohort of patients, also to identify the role of other factors in the subgroup of responders which are TopoIIa negative and MAPtau positive and the mechanism of resistance in non-responders which are TopoIIa positive and MAPtau negative.

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Beta-catenin stability, frizzled and cyclin D1 proteins expression in human breast cancer and its relation with their prognosis

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Background: Development and progression of breast cancer is associated with a number of genetic events, including changes in proto-oncogene and tumor suppressor gene expressions. Defects in components of Wnt signaling pathway including Adenomatosis Poliposis Coli (APC) tumor suppressor protein and β-catenin are known to cause colon and melanoma tumors. Beta-catenin is a central element in Wnt signaling pathway. Post-transcriptional accumulation of β-catenin in cytoplasm and subsequent translocation into the nucleus is thought to be the cause of its tumorigenic potential. Genes which have a definitive role on cell cycle control such as MYC and Cyclin D1 have important roles in development of tumors. Accordingly we have examined β-catenin stability, which is known to have the transcriptional activation affect on such genes mentioned above, in tissues from 118 primary breast cancer patients. Since there is no data on the inactivation of APC in breast cancers, we decided to focus on two other factors which could be the cause of β-catenin stability; 1) β-catenin mutations and 2) Wnt pathway.
Materials and Methods: We used immunocytochemical staining to investigate the stability and location of β-catenin, expression of FRP-1 and FRP-2 proteins as Wnt signaling inhibitors and the expression of Cyclin D1 as one of the genes controlled by β-catenin.
Results: β-catenin, Cyclin D1, FRP1 and FRP2 expression percentages were 53.5±32, 41.8±33, 25.0±26.9 and 31.6±28.3 respectively. When these results were correlated with factors including menopausal status, progesterone receptor positivity, Cerb2 positivity, lymph node involvement and staging no statistical significance was found. On the other hand in patients with Estrogen receptor positivity ($p = 0.0005$) and Ki67 positivity ($p = 0.037$) Cyclin D1 and in Ki67 positive patients FRP1 ($p = 0.024$) expression percentages were significantly high. β-catenin expression was increased only in p53 posivite patients ($p = 0.039$). Disease free and overall survival rates were not found to be correlated with β-eta catenin, Cycln D1, FRP1 ve FRP2 expression percentages. β-catenin localization and disease free and overall survival relation was also assessed 64 patients and existence of cytoplasmic localization of β-catenin was not found to affect survival rates.
Conclusion: β-catenin, Cyclin D1, FRP1 ve FRP2 expressions were not found to influence disease free and overall survivals.

5094 POSTER

Clinical and biological metastatic breast cancer (MBC) outcomes after discontinuation of treatment with bevacizumab plus metronomic capecitabine and cyclophosphamide: a retrospective analysis

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Background: Angiogenesis plays an important role in breast cancer development and progression. Bevacizumab is a humanized monoclonal antibody against VEGF, which showed activity in monotherapy or in combination with chemotherapy in MBC. We recently reported results of a phase II trial evaluating the association of bevacizumab plus oral metronomic capecitabine and cyclophosphamide in MBC, showing efficacy

and good tolerability. Preclinical and clinical data show that withdrawal of VEGFR inhibitors may be associated with a rapid tumor growth. We therefore conducted a retrospective analysis in patients who had discontinued trial treatment for progression of disease (PD) and who received a new treatment, in order to evaluate time to progression (TTP), progression free survival (PFS) and overall survival (OS) to the subsequent therapy.
Patients and Methods: Of the 46 patients enrolled in the phase II trial, 44 discontinued trial treatment: 41 for PD, 1 for an adverse event and 2 for personal decision. Two patients are still receiving trial treatment. Thirty-nine patients received a new therapy after progression: chemotherapy and hormonotherapy in 23 (59%) and 9 (23%) respectively, 3 (8%) received both and 4 (10%) were not evaluable. One patient had a rapid progression of disease and died and one was lost to follow up.
Results: Thirty of the 35 (85.7%) evaluable patients had a PD. Median TTP was 106 days, as compared to 229 days after treatment with bevacizumab. PFS at 6 months was 31% (95% CI: 16−46). Sixteen patients died with a median survival of 323 days, and a 6 months OS of 85% (95% CI: 67−93). We evaluated the correlation between serum PDGF-RB, Ve-CAD and circulating endothelial cells, measured at PD after bevacizumab, with TTP and OS: patients with levels of these markers lower than the median value achieved a significantly better TTP and OS with the subsequent treatment.
Conclusions: Though the mechanisms of resistance to bevacizumab are not well defined it is possible that resistance to bevacizumab results in relative resistance to subsequent therapies. Alternatively, rebound increases in VEGF on discontinuation of bevacizumab could result in a more aggressive disease. Much remains to be learned about biologic agents, in particular new trials need to establish whether these therapies should be continued at PD.

5095 POSTER

Elevated circulating estradiol levels are associated with a less aggressive tumour phenotype in postmenopausal breast cancer patients

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Background: It is difficult to correlate circulating hormone levels in premenopausal breast cancer patients with the biology of the tumors, due to physiological fluctuations in menstruating women. This difficulty is overcome in postmenopausal patients, since in them sex hormone levels tend to be constant over time.
Materials and Methods: Circulating hormone levels were measured in 161 previously untreated postmenopausal breast cancer patients within 72 hours of their planned surgery. The obtained hormone levels were correlated with tumor size, histological and nuclear grade, axillary nodal status, DNA-ploidy and Ki67-, c-erb-B2-, p53, Bax-, VEGF- and Nup88-expression.
Results: The only statistically significant correlations found between circulating hormone levels and all tested variables were an inverse one between estradiol and the expression of the apoptosis-associated *Bax* gene ($p = 0.009$), and again an inverse correlation between estradiol and the expression of c-erb-B2 ($p = 0.04$). When comparing hormone levels with each other, a significant correlation between estradiol and progesterone ($p < 0.0001$), an inverse one between estradiol and FSH ($p = 0.04$) and a direct one between LH and prolactin ($p = 0.001$) were found.
Conclusion: Although higher circulating estradiol levels have been repeatedly correlated with an elevated incidence of breast cancer, it appears that in postmenopausal breast cancer patients the tumors thus induced show a biologically less aggressive phenotype.

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The discordance between hormonal receptor status and c-erb b2 in primary and metastatic breast cancer

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Background: Metastatic breast cancer is one of the most common cause of death from cancer in women. the choice of the best treatment for breast cancer depends on several factors including the patient's age, performance status, menopausal status, as well as tumor size, tumor grade, lymph node involvement, hormonal receptor status, and c-erb b2 status.
The aim of this study was to determine the discordance between hormonal receptor status and c-erbb2 status in primary and metastatic breast cancer.
Materials and Methods: 38 patients with primary breast cancer who developed metastases on follow-up were enrolled into the study. the estrogen receptor (er), progesterone receptor (pr) and c-erb b2 status of the metastases were determined immunohistochemically and compared with the primary breast cancer. Positive hormone receptor status was defined as >5% immunohistochemical staining of tumor cells. c-erbb2 positivity was defined by cytoplasmic membrane staining of 2+ or 3+ intensity. 2+ intensity was assessed by fish or sish techniques.
Results: Variation of er status between primary and metastatic breast cancer was determined in 12 of the 38 (31%) patients and, variation of pr status was shown in 18 of the 38 (47%) patients. 6 cerb b2 negative primary breast cancer became immunohistochemical 3+ in metastatic cancer during follow up.
Conclusions: c erb b2 status is important in the management of metastatic breast cancer. the biological behaviour of primary breast cancer can vary in its metastases. in these metastases, a repeat biopsy may show the new features of the tumor. c erb b2-positive patients should be treated with trastuzumab-based therapy if no contraindications.

5097 POSTER

Poor response to systemic chemotherapy in metaplastic carcinoma of breast

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Background: Metaplastic carcinoma of the breast cancer (MCB) is a rare subtype of breast cancer, for which only anecdotal reports are available regarding its response to systemic chemotherapy.
Aim: To characterize chemotherapy response of MCB patients in a retrospective single-institute study.
Method: We retrospectively reviewed the records of the MCB patients diagnosed at National Taiwan University Hospital (NTUH) between Jan. 1988 and Aug. 2008. The patient-tumor characteristics, treatment modalities, treatment effect, and survival were studied.
Results: 39 MCB patients were identified from 7352 breast tumor patients undergoing biopsy or operation at NTUH. Initial bulky disease (T3−4) was found in 23 patients (56.4%). Expression of estrogen receptor and progesterone receptor were 10.2% and 20.5%, respectively. Nine patients (23.1%) underwent neoadjuvant chemotherapybefore surgery. The regimens included cyclophosphamide/epirubicin/fluorouracil, paclitaxel/cisplatin, vinorelbine/fluorouracil/leucovorin, capecitabine, docetaxel/capecitabine/cisplatin, and docetaxel/epirubicin/cyclophosphamide. Eight of them (89%) experienced disease progression. The response in one patient was not evaluable. Twelve MCB patients (30.8%) developed metastatic disease as initial presentation or during follow-up after primary treatment. Among them, 10 patients received chemotherapy. Only 2 patients (20%) had partial response, all the other 8 patients (80%) had progressive disease. All of the patients with metastatic diseases died of their diseases (3 year survival = 0%). The median survival after metastasis was only 11.3 months (range: 2.73−34.9 months).
Conclusion: MCB had poor response to systemic chemotherapy, either in neoadjuvant setting for locally advanced disease or in salvage setting for metastatic disease.
Key words: Metaplastic carcinoma, neoadjuvant chemotherapy, salvage chemotherapy

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Clinical outcomes and breast cancer subtypes in patients with brain metastases

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Background: Breast cancer is the second most common cause of brain metastasis. The aim of this study was to investigate clinical outcome by breast cancer subtypes in patients with brain metastases.
Materials and Methods: The authors retrospectively evaluated clinical data from 66 patients who had been diagnosed with breast cancer and brain metastasis between 2000 and 2009. Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth receptor-2 (HER2) statuses were tested by immunohistochemical staining. Four survival time intervals were compared according to the subtype (luminal, HER2+, triple negative (TN)): initial diagnosis to distant metastases, distant metastasis to brain metastasis, brain metastasis to death, and overall diagnosis to death.