

Abstract Code: 24

CLINICAL AND PATHOLOGICAL FEATURES OF BREAST CANCER IN ARAB COMPARED TO JEWISH WOMEN AT THE GALILEE AREA

(1) * PROF. ZIDAN JAMAL (1) DR. GESLIKOV MRAT (1) DR. BASHIR WALID
(1) ONCOLOGY INSTITUTE, ZIV MEDICAL CENTER, SAFED AND FACULTY OF MEDICINE, TECHNION, HAIFA

Introduction: Breast cancer (BC) is the most common malignancy in both Jewish and Arab women in Israel. Although the incidence of BC is lower in Arab women it is diagnosed in younger age and seems to have worse prognosis. Recent data have suggested considerable molecular differences in BC from various ethnical groups. Molecular features are increasingly used for predicting cancer prognosis and response to treatment. The purpose of this study to compare clinical, pathological and molecular characteristics of BC in Arab and Jewish women in the Upper Galilee

Patients / Methods: The files of 481 patients (pts) with breast cancer (BC) treated at the Oncology Institute, Ziv Medical Center between 2001 and 2007 were reviewed retrospectively. Type of breast operation and both clinical and all pathological findings of patients were summarized and correlated to the ethnicity of women.

Results: Of the total 481 pts 380 were Jewish and 100 were Arab women. The main age at diagnosis was 49,4 years for Arabs and 59,5 years for Jews ($p<0,01$). At diagnosis 3% of Arab pts had DCIS compared to 7,4% in Jewish pts, stage I in 19% and 49,9%, stage II in 36% and 31,7%, stage III in 33,3% and 7,6%, stage IV in 9% and 3,7% of Arab and Jewish pts respectively ($p<0,05$). Well differentiated, moderately and poorly differentiated in 12%, 59% and 29% compared with 43,9%, 41,4% and 12,5% in Arabs versus Jews. Estrogen receptor was 69% in Arabs and 79% in Jews. HER-2 overexpression evaluated by IHC and CISH was diagnosed in 39% of Arab pts and in 24% Jewish pts ($p<0,05$). Lumpectomy was done in 36% in Arabs versus 64% in Jews ($p<0,05$).

Conclusions: Our data demonstrate younger age and more advanced tumor at diagnosis in Arab compared to Jewish women. All pathological and molecular figures were more aggressive in Arab compared to Jewish women in Israel. Mammography for screening may be started at age 40 years in Arab women and treatment could be more aggressive.

Abstract Code: 25

CHROMOGENIC IN SITU HYBRIDIZATION (CISH) IS AS ACCURATE AND MORE PRACTICAL THAN FLUORECENT IN SITU HYBRIDIZATION (FISH) TO EVALUATE HER2 IN BREAST CANCER

(1) * PROF. ZIDAN JAMAL (2) DR. SZVALB SERGIO

(1) ONCOLOGY INSTITUTE, ZIV MEDICAL CENTER, SAFED AND THE FACULTY OF MEDICINE, TECHNION, HAIFA (2) PATHOLOGY DEPARTMENT, ZIV MEDICAL CENTER, SAFED

Introduction: Molecular genetic analysis is changing our perception of breast cancer (BC). The most promising biological marker in terms of predictive value for breast cancer (BC) treatment is HER-2. The two major methods for evaluation of HER-2 expression in BC are immunohistochemistry (IHC), which determines the expression of HER-2 protein and (FISH), which analyzes the HER-2 gene amplification. CISH is a relatively newly used method which enables detection of HER-2 gene copies through an immunoperoxidase reaction. CISH is based on bright field microscopy and does not require a dedicated fluorescence microscope and/or digital imaging software and allows a concurrent analysis of morphological features of the tumor cells and gene copy numbers. The aim of this prospective study is to compare the concordance of HER2 by IHC, FISH and CISH in BC.

Patients / Methods: Specimens of 100 women operated at our center for invasive BC were examined prospectively for HER-2 using both IHC and CISH test. All tissues were fixed in 10% buffered formalin and embedded in paraffin. 0.4 cm thickness tissues were obtained from tissue blocks and processed for IHC and CISH. IHC was carried out with Hercept test. Hybridization signals were detected using a CISH detection kit (Zymed), while gene copy signals were recognized as intranuclear brown dots in both neoplastic and non-neoplastic cells.

Results: HER2 tested by IHC was scored 0 in 53 cases, 1+ in 14 cases, 2+ in 9 cases and 3+ in 24 cases. CISH test for HER2 was determined as positive (high level amplification) in 26 cases and as negative (no amplification) in 74 cases. All tissues with HER2 0 and +1 (67%) by IHC were also negative by CISH ($p:0.001$). Two of the tissues determined +2 by IHC were positive by CISH and 7 were negative. All cases with +3 were positive by CISH. All tissues positive for CISH were found to be positive by FISH. CISH test costs 500 NIS compared to 3000 NIS for FISH.

Conclusions: There is a high concordance rate between IHC, CISH and FISH testing for HER2 in breast cancer. CISH is as accurate, more practical and less expensive than FISH. CISH may exchange FISH test molecular genetic analysis.

Abstract Code: 236

DUCTAL CARCINOMA IN SITU (DCIS) OF THE BREAST IN ISRAELI WOMEN TREATED BY BREAST-CONSERVING SURGERY FOLLOWED BY RADIATION THERAPY

(1) * DR. JIVELIOUK IRINA (1) PROF. CORN BENJAMIN (1) PROF. INBAR MOSHE (1) PROF. MERIMSKY OFER
(1) ONCOLOGY, TEL-AVIV MEDICAL CENTER AFFILIATED WITH SACKLER SCHOOL OF MEDICINE

Introduction: Lumpectomy followed by radiation therapy (RT) has become an accepted local management strategy for patients with small, mammographically detected ductal carcinoma in situ (DCIS) of the breast. The aim of this analysis is to describe control rates and patterns of relapse in a cohort of Israeli women with mammographically detected DCIS treated at a single medical center.

Patients / Methods: The files of 107 consecutive patients with DCIS were retrieved from the cancer registry of the unit of radiation therapy. All women underwent lumpectomy followed by definitive RT, administered in conventional dose-fractionation regimens). Oral tamoxifen, 20 mg per day, was prescribed to all but 2 patients with positive receptors..

Results: Within a median follow-up time of 52 months no local recurrence of any breast tumor was found. There was no correlation between event free survival and tumor size, focality, grading, hormone receptor status, administration of adjuvant hormonal therapy, timing of RT, and RT boost delivery. The 8-year overall survival, disease-free-survival, and event-free-survival were 100%, 92.100%, and 87%, respectively.

Conclusions: The results reported herein are consistent with short-term and intermediate-term outcomes that are better than the reported benchmarks from prospective randomized trials. Although this could reflect selection factors at a single institution it is also plausible that a genetically distinct disease is present in this local population. The results of prospective clinical trials of lumpectomy followed by RT in DCIS suggested relatively higher rates of early relapses than observed in the current report, even for the same periods of median follow-up. This observation remained unclear. A plausible, but unproven, explanation, is a genetically different disease in the local population, of which most of the women are Jewish.

Abstract Code: 238

DISCORDANCE BETWEEN HORMONE RECEPTOR PROFILE OF PRIMARY BREAST CANCER AND METASTATIC BONE DISEASE: SHOULD BONE MARROW BIOPSY BE CONSIDERED A STANDARD OF CARE?

(1) * DR. AMIR EITAN (1) DR. BROOM REUBEN (1) DR. FREEDMAN ORIT (1) DR. OOI WEI (2) DR. DONE SUSAN (3) DR. GIANFELICE DAVID (4) DR. BARTH DAVID (5) DR. KAHN HARRIETTE (1) DR. CLEMONS MARK (1) MEDICAL ONCOLOGY, PRINCESS MARGARET HOSPITAL, TORONTO, CANADA (2) PATHOLOGY, PRINCESS MARGARET HOSPITAL, TORONTO, CANADA (3) RADIOLOGY, TORONTO GENERAL HOSPITAL, TORONTO, CANADA (4) HEMATOLOGY, PRINCESS MARGARET HOSPITAL, TORONTO, CANADA (5) PATHOLOGY, SUNNYBROOK ODETTE CANCER CENTRE, TORONTO, CANADA

Introduction: The treatment of bone metastases in breast cancer patients is traditionally based on the hormone receptor status of the primary tumor. However, discordant receptor expression between primary and metastatic tumours has been reported in around 20-60% of cases. This study, therefore, aimed to prospectively explore the incidence of discordant receptor status in primary and metastatic bone disease, and to evaluate the role of bone marrow biopsies for the reassessment of receptor status.

Patients / Methods: 19 patients with known bone metastases underwent both a CT-guided bone metastasis biopsy, as well as bone marrow aspirate and trephine. The estrogen receptor (ER) and progesterone receptor (PR) of these samples was assessed and compared to those of primary breast cancer.

Results: Tumor cells were found in 13 (68.4%) of bone metastasis samples and in 9 (47.4%) of bone marrow biopsies. Discordance between the primary and metastatic samples was seen in 10 patients (52.6%). Among these, ER and PR changed from positive to negative in 7 cases and from negative to positive in 1 case. In 6 cases (31.6%), malignant cells were identified in both bone metastasis and bone marrow samples from the same patient. Among these, ER and PR were concordant in 100% and 83% of cases.

Conclusions: Given that it is commonly assumed that the receptor profile of metastatic disease is the same as the primary tumor, any discordance between primary and metastatic cancer can have a significant impact on the outcome of treatment choices. The receptor discordance rate in this analysis was similar that which has been reported in previous studies. Of interest, there appeared to be good concordance between bone metastasis and bone marrow biopsies. Therefore, bone marrow biopsy may be a simple, safe and well-tolerated way to obtain tissue to reassess receptor status of metastatic breast cancer, and should be considered before the more invasive bone metastasis biopsy.

Abstract Code: 239

RADIOLOGICAL CHANGES FOLLOWING SECOND-LINE ZOLEDRONIC ACID TREATMENT IN BREAST CANCER PATIENTS WITH BONE METASTASES

(1) * DR. AMIR EITAN (2) DR. WHYNE CARI (1) DR. FREEDMAN ORIT (1) MR. FRALICK MICHAEL (1) MRS. KUMAR RITU (2) DR. HARDISTY MICHAEL (1) DR. CLEMONS MARK
(1) MEDICAL ONCOLOGY, PRINCESS MARGARET HOSPITAL, TORONTO, CANADA (2) ORTHOPEDIC BIOMECHANICS, SUNNYBROOK HEALTH SCIENCES CENTRE, TORONTO, CANADA

Introduction: Initiation of bisphosphonate therapy in bisphosphonate-naïve patients is known to be associated with radiological changes such as increased bone density in both osteolytic and osteoblastic metastases. It is not known, however, whether switching from a second-generation bisphosphonate to a more potent agent is associated with similar changes. The aim of the study was therefore to prospectively explore radiological changes, as assessed by thoracolumbar CT scanning, in patients switching from an early generation bisphosphonate (i.e. oral clodronate or intravenous pamidronate) to intravenous zoledronic acid.

Patients / Methods: Breast cancer patients with progressive bone metastases despite use of an earlier generation bisphosphonate were switched to zoledronic acid as part of a study to evaluate the palliative benefit of this intervention. Quantitative computed tomography scanning of the thoracolumbar spine was carried out at baseline, and repeated 4 months after commencing zoledronic acid. The effect of this change of therapy was explored in terms of bone density, as well as volume of osteolytic and osteoblastic disease. Results: Fifteen patients were assessed. Switching of bisphosphonate therapy was associated with a significant increase in bone density, and an increase in osteoblastic volume. There was an insignificant trend towards reduced osteolytic volume. Similar findings were seen in a subgroup that did not receive prior radiation therapy to vertebral spine.

Conclusions: Switching from early generation bisphosphonates to a more potent agent is associated with radiological changes similar to those seen when commencing a bisphosphonate in treatment-naïve patients. This is consistent with the observed palliative benefit.

Abstract Code: 240

A PROSPECTIVE, RANDOMIZED, CONTROLLED, MULTI-CENTER STUDY OF A REAL-TIME, INTRA-OPERATIVE PROBE FOR POSITIVE MARGIN DETECTION IN BREAST CONSERVING SURGERY FOR BREAST CANCER

(1) * DR. ALLWEIS TANIR (2) DR. KAUFMAN ZVI (3) DR. LELCUK SHLOMO (4) DR. PAPPO ITZHAK (4) DR. KARNI TAMI (5) DR. SCHNEEBAUM SHLOMO (3) DR. SPECTOR RONA (3) DR. SCHINDEL ASHER (6) DR. HERSHKO DAN (7) DR. ZILBERMAN MOSHE (8) DR. SAYFAN JOEL (8) DR. BERLIN YURI (9) DR. HADARY AMRAM (2) DR. GUTMAN MORDECHAI (10) DR. CARMON MOSHE (1) HADASSAH HEBREW UNIVERSITY MEDICAL CENTER, JERUSALEM, ISRAEL (2) MEIR GENERAL HOSPITAL, KFAR SABA, ISRAEL (3) RABIN MEDICAL CENTER, BELINSON CAMPUS, PETAH-TIKVA, ISRAEL (4) ASSAF-HAROFEH MEDICAL CENTER, ZRIFIN BEER-YAAKOV, ISRAEL (5) TEL AVIV SOURASKY MEDICAL CENTER, TEL-AVIV, ISRAEL (6) RAMBAM MEDICAL CENTER, HAIFA, ISRAEL (7) THE BARUCH PADEH MEDICAL CENTER, PORIYA, ISRAEL (8) HAEMEK MEDICAL CENTER, AFULA, ISRAEL (9) SIEFF GOVERNMENT HOSPITAL, SAFED, ISRAEL (10) SHAARE ZEDEK MEDICAL CENTER, JERUSALEM, ISRAEL

Introduction: Re-operation after breast conserving surgery (BCS) is required to achieve negative margins in over 20% of patients. This randomized, controlled study was designed to examine the clinical utility of a real time device for margin assessment during BCS. Intra-operative positive margin detection and repeat surgery rates were compared in patients undergoing lumpectomy with or without the device.

Patients / Methods: The MarginProbe (Dune Medical Devices) is a surgical system for real-time breast specimen margin assessment used by the surgeon. It provides binary output per specimen margin. Breast cancer patients undergoing BCS were enrolled in a randomized, double arm, study incorporating 11 sites and 35 surgeons. In the device group, the surgeon applied the probe to the excised lumpectomy specimen, sampling 5-12 points per margin, and shaving additional tissue according to device readings. Margins suspected as positive by clinical, radiological, or frozen section were also re-shaved. Microscopic margins ≥ 1 mm were defined as requiring removal of additional tissue. Data were analyzed for the entire patient cohort and for a subset of patients with non-palpable lesions (N \geq NPL). Patients were followed for cosmetic outcome for 6 months.

Results: Three hundred breast cancer patients were enrolled and randomized in the study, including 173 (58%) with NPL. Re-lumpectomy rate was lower in the device arm, 5.6%, vs. 12.7% ($P=0.0027$). In the NPL sub-set repeat surgery (including mastectomy) rates were 9.8% vs. 20.9% ($P=0.02$) for device and control arms respectively, a 53% reduction in re-operations. In this sub-set repeat lumpectomy rates (excluding mastectomy) were 6.1% vs. 12.8% ($P=0.039$). Intra-operative identification of all positive margins was superior in the device arm, both in the entire patient cohort (59% vs. 40%, $P=0.054$) and in the NPL subset (76% vs. 39%, $P=0.039$). The superior margin identification in the device arm was associated with improved correct surgical reaction, defined as additional shaving of all histologically positive margins. There were no differences in excised tissue volume or cosmetic outcome between the two arms.

Conclusions: Intra-operative use of the MarginProbe for positive margin detection is safe and effective in BCS. The device contributes to guided intra-operative shaving of additional tissue and to a decreased rate of re-operations.

Abstract Code: 242

ZOLEDRONIC ACID PROTECTIVE EFFECT ON BONE LOSS IN POSTMENOPAUSAL WOMEN SWITCHED FROM TAMOXIFEN TO LETROZOLE IN THE TREATMENT OF EARLY BREAST CANCER

(1) * DR. SAFRA TAMAR (1) DR. BERNSTEIN MOLHO RINAT (1) DR. STEPHANSKY IRENA (1) DR. YAAL-HAHOSHEN NEORA (1) PROF. INBAR MOSHE (1) DR. GREENBERG JULIA (2) DR. GEFFEN DAVID
(1) DEPARTMENT OF ONCOLOGY, TEL AVIV SOURASKY MEDICAL CENTER, TEL AVIV (2) DEPARTMENT OF ONCOLOGY, SOROKA MEDICAL CENTER, BEER SHEVA

Introduction: Adjuvant treatment with aromatase inhibitors (AI's) in postmenopausal women (PMW) with early breast cancer (BC) can be associated with decreased bone mineral density (BMD) and increase risk of osteoporosis and fractures. Previous studies showed that the addition of Zoledronic (ZA) acid to frontline AI's treatment reduced bone loss. Our study was designed to evaluate the efficacy and safety of ZA in preventing AI's bone loss in PMW with early BC receiving Letrozole therapy after Tamoxifen.

Patients / Methods: An open-label, randomized phase II study, enrolled PMW with stage I-III hormone receptor positive BC previously treated with Tamoxifen for the last 2.5 years (with BMD T score > -2.5). Patients were randomized to receive Letrozole +/- ZA. Treatment arm patients received 4 mg intravenous ZA every 6 months for 2 years. All patients were evaluated on months 1,6,12,18,24,30,36 with blood chemistry and BMD, and were supplemented with vitamin D and calcium.

Results: Sixty one PMW were screened. Fifty eight patients were evaluable, 26 randomized to receive ZA and 32 to the control group. All patients are alive one had ipsilateral BC recurrence. Median age is 58.9(46.5-83.6) years. Median follow-up is 15.6(0.7-41.9) months, 13 patients had 4 BMD evaluations, 24 had 3 and 39 had 2. A comparison between groups and between time points was performed by one-way Analysis of Variance with repeated measures using the Mixed model. At this point in time a significant interaction between groups and time trend was found, in favor of ZA treated group in lumbar T score ($p=0.0422$). While in the control group a significant decline in lumbar BMD was noticed ($p= (0.0009)$), in the treatment group BMD did not change over time ($p= 0.9783$). Adverse events with ZA were mild, with musculoskeletal pain within 2 days of infusion as the most common toxicity. No ONJ or serious renal events reported.

Conclusions: Our study reports significant benefit in BMD when Zoledronic Acid is added to letrozole after switching from Tamoxifen. Letrozole-induced bone loss increases with time and longer follow-up is needed to evaluate the real magnitude of ZA protection effects; further investigation is warranted.

Abstract Code: 243

FULVESTRANT IN HEAVILY PRETREATED METASTATIC BREAST CANCER: IS IT STILL EFFECTIVE AS A VERY ADVANCED LINE OF TREATMENT?

(1) * DR. SAFRA TAMAR (1) DR. GREENBERG JULIA (1) PROF. RON ILAN G (1) PROF. BEN-YOSEF RAMI (1) PROF. INBAR MOSHE (1) DR. SARID DAVID (1) DR. YAAL-HAHOSHEN NEORA (1) DEPARTMENT OF ONCOLOGY, TEL AVIV SOURASKY MEDICAL CENTER, SACKLER FACULTY OF MEDICINE, TEL AVIV UNIVERSITY, RAMAT AVIV, ISRAEL

Introduction: Over 75% of postmenopausal patients with metastatic breast cancer have hormone receptor-positive tumors. Endocrine therapy, with its more favorable toxicity profile than chemotherapy, is the preferred treatment modality for these patients. **OBJECTIVES:** To assess our experience with fulvestrant, an antiestrogen, in an advanced phase of treatment, after progression on the classical anti-estrogen (tamoxifen) and aromatase inhibitors.

Patients / Methods: The study group comprised 46 patients with metastatic breast cancer treated with fulvestrant during the years 2002-2006. Fulvestrant was given monthly until disease progression or unacceptable toxicity.

Results: The median number of fulvestrant cycles was 4.14 (range 1-32). Four patients are still on the treatment. The reasons for treatment discontinuation include disease progression (n=40), refusal (n=1), and allergic reaction (n=1). Ten patients (22%) achieved partial response and 22 (47%) had stable disease. Fourteen (30%) had disease progression with a response rate of 22% and a clinical benefit of 67%, and 14 (30%) had stable disease for > 6 months. Twenty-five patients (54%) are still alive, 4 (9%) without and 21 (45%) with disease progression. With a median follow-up of 15 months (range 1-30.1), the median time to progression was estimated to be 4 months (95% confidence interval 3.1-4.9), and the estimated overall survival 20.1 (95% CI 13.6 to upper limit; not reached yet). The 1 year estimated survival is 67%.

Conclusions: In terms of late-phase administration, fulvestrant still appears to have a good clinical effect, with a time to progression of 4 months and a clinical benefit > 60%, notably accompanied by only very mild toxicity. Irrespective of the line of treatment the patients received, the 4 month time to progression was constant and the medication was still working effectively in a very late line of treatment in metastatic breast cancer. Fulvestrant offers clinical benefit with very mild toxicity in a very heavily pretreated population and the medication is recommended, even in patients who received many lines of chemotherapy

Abstract Code: 245

AN EARLY EXPERIENCE WITH TRASTUZUMAB (H)-CONTAINING REGIMENS FOR THE TREATMENT OF METASTATIC BREAST CANCER PATIENTS

(1) * DR. SALAH AZZAM (2) DR. SALIM NIDAL (3) DR. MERLE IRIT (4) DR. HAMBURGER TAMAR (5) DR. GALINSKY DALIA (6) DR. KATZ DANIELLA (7) DR. UZIALY BIATRIS (8) PROF. PERETZ TAMAR
(1) SHARETT INSTITUTE OF ONCOLOGY, HADASSAH UNIVERSITY HOSPITAL, JERUSALEM, ISRAEL
(2) SHARETT INSTITUTE OF ONCOLOGY, HADASSAH UNIVERSITY HOSPITAL, JERUSALEM, ISRAEL
(3) SHARETT INSTITUTE OF ONCOLOGY, HADASSAH UNIVERSITY HOSPITAL, JERUSALEM, ISRAEL
(4) SHARETT INSTITUTE OF ONCOLOGY, HADASSAH UNIVERSITY HOSPITAL, JERUSALEM, ISRAEL
(5) SHARETT INSTITUTE OF ONCOLOGY, HADASSAH UNIVERSITY HOSPITAL, JERUSALEM, ISRAEL
(6) SHARETT INSTITUTE OF ONCOLOGY, HADASSAH UNIVERSITY HOSPITAL, JERUSALEM, ISRAEL
(7) SHARETT INSTITUTE OF ONCOLOGY, HADASSAH UNIVERSITY HOSPITAL, JERUSALEM, ISRAEL
(8) SHARETT INSTITUTE OF ONCOLOGY, HADASSAH UNIVERSITY HOSPITAL, JERUSALEM, ISRAEL

Introduction: H was introduced in the late 90's for the treatment of MBC. The optimal combination and Schedule has been explored along the years. We report our experience in the early introduction of H to the treatment repertoire of MBC.

Patients / Methods: From 6/1999 to 5/2003 seventy three Her-2 + metastatic breast cancer (MBC) patients were included in our retrospective analysis.. The median age at diagnosis was 47 years (range 29-70). 53% were hormone receptor positive. All patients received prior adjuvant therapy (24% of them hormone therapy only) and 56% received one or more prior chemotherapy (CT) lines for metastatic disease. 72% of patients in the present cohort received H + Navelbine, and 25% with Taxanes. 29% received the combination of H+CT as first line chemotherapy, 42% as second line and 29% as 3-5th line of treatment. Twenty seven % of the patients received another line of chemotherapy with H after failing the initial treatment of H+CT.

Results: The overall response rate was 51% (CR 15% and 36% PR) and disease stabilization in 18% with a clinical benefit in 69% of the patients. There was no difference in response rate whether H was combined with Taxanes or Navelbine. Median survival from the presentation of metastatic disease was 49 months and was affected only by Her-2 status (IHC +2 vs. +3 or positive FISH) favoring patients with +3 or Fish positive. Median survival did not differ according to the type of chemotherapy, whether H+CT was administered as first or more advanced line or ER status. Further response was observed in patients receiving a second combination of H+CT. Median duration of Trastuzumab therapy was 9 months (range 1-70 months).

Conclusions: Trastuzumab-containing therapies in Her-2 positive MBC show a significant activity even in heavily pretreated women. In our retrospective analysis, Navelbine and Taxanes showed similar response rates and survival. The contribution of H to chemotherapy after failure of initial regimen with H should be explored in randomized studies

Abstract Code: 247

PRELIMINARY RESULTS OF A PHASE 1/2 OF A COMBINATION OF ERBITUX AND TAXANE FOR "TRIPLE NEGATIVE" METASTATIC BREAST CANCER PATIENTS

(1) * DR. NECHUSHTAN HOVAV (1) MRS. STAINBERG HANI (1) PROF. PERETZ TAMAR
(1) ONCOLOGY DEPARTMENT HADASSAH HEBREW UNIVERSTIY MEDICAL CENTER

Introduction: Introduction: Breast cancer is composed of at least 5 subtypes. One of them the basal cell subtype. A marker for this subtype is triple negativity for ER PR and Her2. currently there is no biologic therapy available for this subtype. over 50% of this kind of tumors express EGFR. Cetuximab is a humanized antiEGFR IgG1 antibody. In colon cancer there are also high percentage of EGFR expression and addition of Cetuximab to chemotherapy results in renewed sensitivity to treatments. We therefore hypothesized that in a similar manner addition of Cetuximab to taxanes which are among the most potent anti breast cancer drugs will result in increased effectiveness in this subset of breast cancer patients.

Patients / Methods: From January 2007 until October 2008 we treated 12 breast cancer patients with either Paclitaxel 80 mg/m², (10 patients) or Docetaxel (30 mg mg/m²) (2 patients) with Cetuximab weekly. Patients had at least one pathology sample of breast cancer with triple negative components, metastatic disease and up to two prior chemotherapy lines in the metastatic settings..

Results: Patient characteristics (median)- age 60 (31-69) years, prior taxane therapy 9/11 pt's, Toxicity Dermatologic toxicity (grade 2 8/11 grade 3 1/11) nail disease grade 2 8/10 evaluable patients fatigue grade 3- 1/11 pt response is evaluable for 11/12 patients. including clinical response(mainly substantial pain control(6) decrease in tumor markers and roentgonologic response altogether 8/11 patients . Including tumor marker normalization and nearly a roentgoenologic CR in a young patient previously treated with taxol in the adjuvant settings and two chemotherapy lines in the metstatic adjuvant settings. 3 patients developed brain metastasis during treatments.

Conclusions: To our knowledge this is the first trial of weekly taxane cetuximab in breast cancer. Administration of taxane-cetuximab weekly therapy for triple negative breast cancer patients is possible. Toxicity is the cumulated expected toxicity of each of the agents – special care should be taken for nail disease which occurred in most of the patients. Some impressive clinical responses were obtained even in taxane pretreated patients. Trial is ongoing

Abstract Code: 249

DIFFERENT SCHEDULES OF GRANULOCYTE GROWTH FACTOR (G-CSF) FOR BREAST CANCER PATIENTS RECEIVING ADJUVANT DOSE DENSE CHEMOTHERAPY (DDC): A PROSPECTIVE NON-RANDOMIZED STUDY

(1) * DR. HENDLER DANIEL (1) DR. RIZEL SHULAMITH (1) DR. YERUSHALMI RINAT (1) DR. NEIMAN VICTORIA (1) DR. BONILLA LUISA (2) MR. BRAUNSTEIN RONY (1) PROF. SULKES AARON (1) DR. STEMMER SALOMON
(1) INSTITUTE OF ONCOLOGY, DAVIDOFF CENTER, RABIN MEDICAL CENTER, PETACH TIKVA, ISRAEL (2) INDEPENDENT STATISTICAL CONSULTANT

Introduction: This prospective, non-randomized study summarizes four different schedules of G-CSF given at our institution for breast cancer patients receiving adjuvant dose dense chemotherapy (DDC) regarding febrile neutropenia, hospitalization events, treatment delays and costs.

Patients / Methods: 191 consecutive patients were enrolled to receive adjuvant DDC (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m² Q14D x 4) with four G-CSF schedules: filgrastim 300 mcg days 3-10 (n=84 [44%] group A); days 3-7 (n=22 [11%] group B); days 5, 7, 9 and 11 (n=34 [18%] group C), or pegfilgrastim, 6 mg on day 2 (n=51 [27%] group D).

Results: Twelve patients were hospitalized due to thirteen episodes of febrile neutropenia, three patients in group A, three in group B and six in group D. No statistically significant difference was observed among the four groups or when compiling groups AD (long-term schedules) versus BC (short-term schedules). A statistically significant difference regarding febrile neutropenia was observed when comparing groups D and C (P=.041). No statistically significant differences were observed with regard to treatment delays and other hematological toxicities. Average overall G-CSF cost per patient in groups AD was 8500 USD versus 4400 USD in groups BC.

Conclusions: We found that all schedules did not differ with regard to dose intensity, febrile neutropenia and hospitalization rate, but there was a trend in favor of the shorter schedule. A larger, prospective randomized trial should be done to evaluate shorter versus standard filgrastim and pegfilgrastim schedules with regard of clinical outcomes, hematological and non-hematological toxicities and impact in overall costs.

Abstract Code: 250

DECLINE IN PULMONARY FUNCTION IN PATIENTS WITH BREAST CANCER RECEIVING DOSE-DENSE CHEMOTHERAPY: A PROSPECTIVE STUDY

(1) * DR. YERUSHALMI RINAT (2) PROF. KRAMER MORDECHAI (3) DR. RIZEL SHULAMITH (4) PROF. SULKES AARON (5) PROF. GELMON KAREN (6) MRS. GRANOT TAL (7) DR. NEIMAN VICTORIA (8) DR. STEMMER SALOMON

(1) ONCOLOGY INSTITUTE, DAVIDOFF CENTER, BEILINSON CAMPUS, PETACH TIKVA (2) PULMONOLOGY UNIT, BEILINSON CAMPUS, PETACH TIKVA (3) ONCOLOGY INSTITUTE, DAVIDOFF CENTER, BEILINSON CAMPUS, PETACH TIKVA (4) ONCOLOGY INSTITUTE, DAVIDOFF CENTER, BEILINSON CAMPUS, PETACH TIKVA (5) MEDICAL ONCOLOGY, BC CANCER AGENCY, VANCOUVER (6) ONCOLOGY INSTITUTE, DAVIDOFF CENTER, BEILINSON CAMPUS, PETACH TIKVA (7) ONCOLOGY INSTITUTE, DAVIDOFF CENTER, BEILINSON CAMPUS, PETACH TIKVA (8) ONCOLOGY INSTITUTE, DAVIDOFF CENTER, BEILINSON CAMPUS, PETACH TIKVA

Introduction: Prompted by complaints of dyspnea in breast cancer patients receiving adjuvant dose-dense chemotherapy (DDC), we sought to evaluate the possible association of DDC with pulmonary dysfunction.

Patients / Methods: 34 consecutive patients receiving adjuvant DDC were enrolled. The chemotherapy regimen consisted of IV doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² q 14 days X4 (AC) with growth-factor support followed by weekly IV paclitaxel 80 mg/m² x12. The following parameters were prospectively measured before and after the AC protocol (P1, P2) and at completion of paclitaxel treatment (P3): presence of dyspnea, blood pressure, pulse rate, hemoglobin, erythrocyte-sedimentation-rate, C-reactive protein level, cardiac ejection fraction, and pulmonary function. Repeated measures analysis was used to evaluate differences among the time points, and paired t-test was used to evaluate differences between consecutive time points.

Results: Results: Although only 5 patients (15%) complained of dyspnea, there was a significant decrease in mean carbon monoxide diffusing capacity (DLCO), in all patients from P1 (21 ml/min/mmHg) to P3 (14 ml/min/mmHg), and in 29 of 32 patients (90.6%) from P1 to P2 (15 ml/min/mmHg) (P<0.001).

Conclusions: Conclusions: DDC is associated with a statistical significant reduction in DLCO. Awareness of this potential toxicity may be important in women with preexisting lung disease.

Abstract Code: 251

Fistula formation in a breast cancer patient receiving bevacizumab [Avastin]

(1) * KUCHUK IRINA (1) CATANE RAPHAEL (2) APTER SARAH (1) WEITZEN RONY (1) ADERKA DAN
(1) WOLF IDO (1) MODIANO TAMI (1) KAUFMAN BELLA
(1) ONCOLOGY DIVISION, SHEBA MC (2) RADIOLOGY, SHEBA MC

Fistula formation is a known complication of bevacizumab therapy in colorectal (Wolf et al), ovarian and head and neck tumors. We report here the first case of such fistula formation in a patient with breast cancer. A 33 y/o pt, was diagnosed with locally advanced left breast cancer. She received neoadjuvant AC>T chemotherapy, followed by lumpectomy with ALND with 2/10 lymph nodes involved. She was irradiated to the breast, axilla and supraclavicular region. Seven months after completion of radiotherapy extensive local recurrence in her left breast and axilla was diagnosed, radical mastectomy with axillary dissection performed. One month later, recurrence was noted in the axillary region with mediastinal lymph nodes. Systemic therapy with vinorelbine was initiated with progression of disease in 6 weeks. Chemotherapy was changed to docetaxel and bevacizumab (10mg biweekly). Under this combination the disease remained stable for 9 months, until progression at the axillary region. 4 weeks after discontinuation of bevacizumab, discharge from a chest wall, and left shoulder pain appeared. On physical examination an ulcerated tumor in the axilla and a chest wall nodule with clear discharge were noticed [fig 1 or 2]. 5 days later, when fever (38.5-39) growing yellowish discharge from the chest wall nodule and increasing pain of the left shoulder worsened antibiotic with amoxicillin-clavulanic acid for a week was initiated with no improvement and the patient then was hospitalized. On examination there was an ulcerated tumor with purulent discharge, redness and tenderness in the axilla and CT scan revealed tumor infiltration of the brachial plexus, anterior and axillary chest wall with connected collection of 3X5 cm in diameter within chest wall tumor with skin involvement - a fistula. The collection underwent surgical drainage - 500ml purulent fluid with staph aureus culture and was treated with antibiotic according to sensitivity until improvement. The patient now is afebrile, although the fistula is still present.

Conclusion: As expected, bevacizumab may predispose the formation of fistulae, in breast cancer patients as in colorectal, ovarian and head and neck patients, particularly in areas with local recurrence and previous radiotherapy.

Abstract Code: 252

(18)F-FDG (PET/CT) IMAGING IN TREATMENT PLANNING FOR LOCALLY ADVANCED AND RECURRENT BREAST CANCER

(1) * DR. BEN-DAVID MERAV (2) DR. TATIANA RABIN (3) DR. ZVI SYMON (4) DR. BELLA KAUFMAN (5) DR. PFEFER RAPHAEL

(1) RADIATION ONCOLOGY DEPARTMENT, ONCOLOGY, SHEBA MEDICAL CENTER (2) RADIATION ONCOLOGY DEPARTMENT, ONCOLOGY, SHEBA MEDICAL CENTER (3) RADIATION ONCOLOGY DEPARTMENT, ONCOLOGY SHEBA MEDICAL CENTER (4) THE BREAST UNIT, ONCOLOGY, SHEBA MEDICAL CENTER (5) RADIATION ONCOLOGY DEPARTMENT, ONCOLOGY UNIT, SHEBA MEDICAL CENTER

Introduction: PET/CT studies are increasingly used for staging breast cancer(BC). The information provided by these studies can be incorporated into radiotherapy treatment planning. PET/CT can provide us with accurate information about the location of positive axillary LN and the presence of positive internal mammary (IMN) nodes prior to treatment (as in neoadjuvant-chemotherapy) and change the treatment-fields accordingly.

Patients / Methods: Between 6/2007-9/2008, 20 women with stage II-IIIBC or recurrent loco-regional disease who underwent radiation-therapy in our institution had PET/CT scan at diagnosis. All scans were done with both arms above the head, which is the CT-simulation position in our department. Treatment plans were done using the information from the PET/CT by contouring pathologic LN volumes into the simulation CT datasets. Following IRB approval, we retrospectively evaluated their charts for clinical- and pathological-staging, presence and position of PET/CT +LN and treatment-fields. Differences in treatment-fields and adding LN-basins to the treatment-fields were recorded.

Results: Sixteen women had primary BC, 10-clinical stage II, 6-clinical stage III, 4 had local-regional recurrence. For the primary BC, positive IMN were demonstrated on PET/CT in 4/16 patients(25%). For the recurrences, positive IMN were seen in 2/4(50%). All PET/CT positive IMN received at least 95% dose to the IMN volume. This area would not have been included in the treatment fields in the recurrence cases, as there was no clinical evidence for these nodes or enlarged nodes on the contrast enhanced CT scan. For primary BC, two had medial tumor with clinical-pathological negative axilla, and therefore treated to the breast and IMN only, as a result of the +IMN seen with PET/CT. All other had clinically +axilla or > 4+veLN and therefore, as per-our institution policy, treated to the axilla, supraclavicular- and infraclavicular-area and IMN. All 4 with PET/CT +IMN received full dose as mentioned above. 2/16 could not receive IMN irradiation due to V20 restriction. Size and extent of the positive axillary nodes at diagnosis changed the treatment-fields in 8/20 patients(40%). In toto, 12/20(60%)patients had changes in treatment-fields due to PET/CT scan.

Conclusions: PET/CT information can be incorporate into the treatment planning in locally-advanced and loco-regional BC for accurate dosing of positive LN.

Abstract Code: 306

ONCOTYPE DX, ST. GALLEN RISK GROUP AND ADJUVANT!ONLINE NOMOGRAM AS PROGNOSTIC PREDICTOR.

(1) * LEITZIN LARISA (1) SIKORSKY NATALIA (1) LEVIOV MICHELLE (1) GRIKSHTAS EDUARD (1) STEINER MARIANA
(1) LIN MEDICAL CENTER: DEPARTMENT OF ONCOLOGY; HAIFA; ISRAEL.

Introduction: With introduction of Oncotype Dx in clinical practice we compared its prognostic prediction to the previous methods commonly used, St. Gallen risk group and Adjuvant!online nomogram and analyze its impact on clinical decision on adjuvant therapy in early breast cancer.

Patients / Methods: Surgical specimens of 100 women with intermediate and selected low risk early breast cancer (by St Gallen criteria) were examined by Oncotype Dx method. The risk category definition obtained was compared with St. Gallen prognostic subgroups. In addition, the recurrence scores obtained by Oncotype Dx were compared with those obtained by using the Adjuvant!online nomograms.

Results: By Oncotype Dx, 63% of patients were defined as low risk, 27% intermediate and 10% high risk. In 39% of cases definition of risk group by St. Gallen risk category and by Oncotype Dx was similar. In 48% of patients St. Gallen risk classification allocated patients in worse risk group and in 13% in better prognostic group than Oncotype Dx. Only in 15% of patients 10 years recurrence rate by Oncotype Dx and by Adjuvant!online were similar. In 83% 10 years recurrence rate by Oncotype Dx was lower than by Adjuvant!online (by 6-44%, mean 18, median 16), and in 2% Oncotype recurrence rate was higher than this calculated by Adjuvant!online nomogram. Oncotype Dx results were considered in treatment decision on adjuvant therapy in this particular group of patients. Initial treatment plan coincided with treatment decision based on Oncotype Dx results 76% of cases (hormonal therapy in 63%; chemotherapy in 13%). 16% patients, initially planned to hormonal therapy received chemotherapy and 8% initially scheduled to chemotherapy received hormonal therapy.

Conclusions: Oncotype Dx allocates early breast cancer patients in lower risk group than other classification methods. The use of Oncotype Dx risk group in treatment decision strategy may avoid unnecessary chemotherapy.

Abstract Code: 307

FUNCTIONAL VARIANT OF KLOTHO MODIFIES BREAST CANCER RISK AMONG BRCA1 MUTATIONS CARRIERS

(1) * WOLF IDO (2) LAITMAN YAEL (1) RUBINEK TAMI (1) ABRAMOVITZ LILACH (2) FRIEDMAN EITAN (1) KAUFMAN BELLA
(1) ONCOLOGY INSTITUTE, SHEBA MEDICAL CENTER (2) SUSANNE LEVY GERTNER
ONCOGENETICS UNIT, SHEBA MEDICAL CENTER

Introduction: Klotho is a transmembrane protein which can be shed and act as a circulating hormone. We have recently identified klotho as a putative tumor suppressor in breast cancer (Wolf et al, Oncogene 2008). A single nucleotide polymorphism (SNP) in the klotho gene, results in an amino acid substitution, F352V, which is associated with altered activity of klotho. Germ-line mutations in BRCA1 and BRCA2 substantially increase lifetime risk of breast and ovarian cancers. Yet, penetrance of deleterious BRCA1 and BRCA2 mutations is incomplete even among carriers of identical mutations. As klotho is a potential tumor suppressor, we hypothesized that it may also modify the penetrance of BRCA1 or BRCA2 mutations.

Patients / Methods: The presence of F352V variant was evaluated using exon-specific polymerase chain reaction followed by restriction enzyme analysis, in a cohort of 826 Ashkenazi Jewish women consisting of 236 non-carriers (healthy: 109, breast cancer: 94, ovarian cancer: 33), 340 BRCA1 (185delAG, 5382insC) carriers (healthy: 138, breast cancer: 142, ovarian cancer: 60) and 248 BRCA2 (6174delT) carriers (healthy: 101, breast cancer: 116, ovarian cancer: 31).

Results: Similar distribution of the F352V variant was noted in non-carriers and BRCA1 carriers (FF, wild-type 78%; FV, heterozygous 19%; VV, recessive 3%). However, adjusted for age, FV status among BRCA1 carriers was associated with significantly increased breast cancer risk (HR 1.8, 95% CI 1.24-2.61, p=0.002). Moreover, age at diagnosis was 59 for non-BRCA1 carriers regardless of klotho genotype, 53 for BRCA1-FF and only 45 for BRCA1-FV status (p<0.0001 for BRCA1-FF vs. BRCA1-FV). The KLOTHO gene is located on chromosome 13q12, 616kb upstream of the BRCA2 gene. F352V was over-represented among BRCA2 carriers: FF 25%, FV 50% and VV 25% and analysis of an additional marker, D13S171, indicated linkage disequilibrium between F352V and BRCA2 6174delT mutation. Studies in breast cancer cells revealed reduced growth inhibitory activity of klotho F352V variant compared to wild type klotho.

Conclusions: These data suggest klotho F352V variant as a risk modifier for breast cancer among BRCA1 mutation carriers. If validated in additional cohorts, the presence of the F352V klotho variant may serve as a predictor of cancer risk among BRCA1 mutation carriers.

Abstract Code: 408

THE IMPORTANCE OF FERTILITY PRESERVATION IN WOMEN WITH EARLY BREAST CANCER

(1) * DR. AGBARYA ABED (2) PROF. LINN SHAI
(1) ONCOLOGY DEPARTMENT-RAMBAM HEALTH CARE CAMPUS (2) EPIDEMIOLOGY SCHOOL-
HAIFA UNIVERSITY

Introduction: Young women with breast cancer often seek advice about whether treatment will affect their fertility. We sought to gain a better understanding of women's attitudes about fertility and how these concerns affect decision making.

Patients / Methods: We developed a survey about fertility issues for young women with a history of early-stage breast cancer. The survey was completed by a direct interview with the patients

Results: Eighty four eligible respondents completed the survey. Mean age at breast cancer diagnosis was 34.7 years. Fifty seven percent of women were Jewish; 71% were married; 75% had studied more than 12 years. Stages at diagnosis were as follows: I, 51%; II, 38%; III, 11%. Seventy seven percent of women were within 6 months of diagnosis. Forty nine percent recalled substantial concern at diagnosis about becoming infertile with treatment. In multivariate logistic regression, greater concern about infertility was associated with wish for children ($P = .0008$), number of children less than 3 ($P = 0.001$), education more than 12 years ($P = 0.004$) and moderate or high level of fear from treatment ($P = 0.004$). only 5 women reported that infertility concerns influenced treatment decisions. Seventy-nine percent of women reported discussing fertility concerns with their doctors; and 14% underwent a medical procedure for fertility preservation.

Conclusions: Fertility after treatment is a major concern for young women with breast cancer. There is a need to communicate with and educate young patients regarding fertility issues at diagnosis and a need for future research directed at Preserving fertility for young breast cancer survivors.

Abstract Code: 412

THE INFLUENCE OF NARROW MARGINS IN BREAST CANCER SURGERY ON PROBABILITY OF RECURRENCE AND DEATH

(1) * DR. MEIROVITZ AMICHAY (2) DR. RENNERT HEDY (1) PROF. PERETZ TAMAR (2) DR. RENNERT GAD

(1) ONCOLOGY DEP.-HADASSAH-HEBREW UNIVERSITY MEDICAL CENTER, EIN KEREM JERUSALEM ISRAEL (2) DEPARTMENT OF COMMUNITY MEDICINE AND EPIDEMIOLOGY, CARMEL MEDICAL CENTER AND TECHNION, NATIONAL BREAST AND COLORECTAL CANCER DETECTION PROGRAMS, MINISTRY OF HEALTH AND ISRAEL CANCER ASSOCIATION, HAIFA, ISRAEL

Introduction: Narrow margins are commonly reported after breast cancer surgery and the safe distance from the tumor to the edge of the pathological specimen is continuously debated.

Patients / Methods: The database of the National Israeli Breast Cancer Detection Program was used to evaluate the relationship between distance of tumor from specimen margins and recurrence rate and overall mortality over time. This was separately evaluated in different age and stage sub-groups. Analysis was restricted to incident cases, diagnosed between 2003 and 2008 with single invasive breast cancer of any histology who did not undergo mastectomy as their therapeutic procedure. Recurrence was defined as any re-operation 6 months or more after first lumpectomy. All Cause mortality was reliably available for Clalit members only.

Results: Altogether 9,058 cases complied with the entry criteria. Of them, 23.6% were under age 50 and 22.9% at age 70 or over. Overall, 41.2% of cases with margin information had narrow margins (touching or up to 2 m³m). Of the cases with touching margins, only 52.3% were re-operated, most of them (83.9%) within 6 weeks after the first lumpectomy. Of the cases with narrow margins of 1-2 m³m, only 17.7% were re-operated. After a total of 321,618 months of follow-up (mean of 2.47 years of follow-up) recurrences were noted in 234 women (2.6%) and deaths in 393 women (4.3%). Recurrence rates and deaths were both diagnosed significantly more commonly in women who had touching margins in their first open surgery, regardless of their reoperation status. Compared to a recurrence rate over the study follow-up period of 1.2% among women with wide margins, the rate among women with 1-2 m³m margins were 2.2-3.7%, and among women with touching margins were 0.8-4.4% if re-operated, but 7.5% if not re-operated (p=0.0001).

Conclusions: A substantial number of all newly diagnosed breast cancer cases are diagnosed with narrow margins after their first operation but only a minority of them are re-operated. Recurrence rate was higher in women with touching margins and highest in those who did not undergo reoperation.

Abstract Code: 603

THE DISCREPANCY BETWEEN RESULTS OF HER2 RECEPTORS IN NEEDLE BIOPSY AND SURGICAL SPECIMEN OF BREAST CANCER

(1) * DR. SIKORSKY NATALYA (2) DR. LEITZIN LARISA (3) DR. RUBINOV RAFAEL (4) DR. LEVIOV MISHEL (5) DR. GRIKSHTAS EDUARD (6) DR. SHTAINER MARIANA
(1) ONCOLOGY DEPARTMENT LIN CLINIC HAIFA (2) ONCOLOGY DEPARTMENT LIN CLINIC HAIFA (3) ONCOLOGY DEPARTMENT LIN CLINIC HAIFA (4) ONCOLOGY DEPARTMENT LIN CLINIC HAIFA (5) ONCOLOGY DEPARTMENT LIN CLINIC HAIFA (6) ONCOLOGY DEPARTMENT LIN CLINIC HAIFA

Introduction: Her2 and hormone receptors are important prognostic and predicting factors in breast cancer and are essential for treatment recommendation.

Patients / Methods: There is an update of our previous study . From January 2006 to March 2008 610 breast cancer patients were referred to from Carmel Hospital to Oncology Department at Lin Medical Center for further therapy. We reviewed all their pathological reports and excluded patients whom did not have needle biopsy or had final operation after neoadjuvant therapy. The final analysis included the results of 240 breast cancer patients with immunohistochemical results of Her2 receptors in both needle biopsy and surgery specimens

Results: In 216 patients no differences between Her2 receptors results in biopsy and surgery specimen were found: 192 patients (88%) were Her2 negative and 36 (12%) were Her2 positive +3. In 24 patients we found discrepancy between the Her2 results in the two specimens. 22 patients were reported Her2 positive in the needle biopsy and turned out to be Her2 negative in the surgical specimen and in 2 cases Her2 was reported negative in biopsy and positive in surgery specimen.

Conclusions: In 10% of patients discrepancy was found between the Her2 receptors results in needle biopsy and surgery specimens, usually reporting positivity in the needle biopsy which turned out to be false. Probably this is due to technical issue of testing the receptors on small sample size, However this possibility should be taken under consideration in patients in whom neoadjuvant Herceptin therapy is planned. FISH examination of Her2 receptors in needle biopsy specimen should be considered in this group of patients.

Abstract Code: 605

ASSESSING THE YIELD OF ANALYZABLE METASTATIC TUMOUR IN PATIENTS WITH METASTATIC BREAST CANCER (MBC) UNDERGOING; TARGETED COMPUTED TOMOGRAPHY (CT) GUIDED BONE METASTASIS (BM) BIOPSY AND ILIAC CREST BONE MARROW ASPIRATE AND TREPINE

(1) * DR. FREEDMAN ORIT (1) DR. BROOM REUBEN (1) DR. AMIR EITAN (2) MR. HAWTHORN THOMAS (3) DR. BARTH DAVID (2) DR. DONE SUSAN (4) DR. GIANFELICE DAVID (1) DR. CLEMONS MARK

(1) MEDICAL ONCOLOGY, PRINCESS MARGARET HOSPITAL, TORONTO, CANADA (2) PATHOLOGY, TORONTO GENERAL HOSPITAL, TORONTO, CANADA (3) HEMATOLOGY, PRINCESS MARGARET HOSPITAL, TORONTO, CANADA (4) RADIOLOGY, TORONTO GENERAL HOSPITAL, TORONTO, CANADA

Introduction: Malignant cells are found in the bone marrow of up to one-third of patients with early stage breast cancer, and almost three-quarters of patients with BM. We sought to evaluate the yield of analysable malignant tissue retrieved from bone marrow sampling for immunohistochemistry/immunocytochemistry (IHC/ICC), histomorphology and gene-expression profile analysis compared to bone samples taken from a CT guided biopsy of a BM evident on imaging.

Patients / Methods: Patients with known BM from breast cancer underwent a CT guided targeted BM biopsy (BM-CT) followed by a routine bone marrow aspirate (BMA) and trephine biopsy (BMT) from the iliac crest. Samples were sent for; morphology assessment by histology/cytology, IHC/ICC including estrogen-receptor (ER) and progesterone-receptor (PR) assays, histomorphology and gene-expression profiling. The IHC/ICC results were compared to those from the primary specimens.

Results: 10 patients underwent all three sampling procedures. 3 patients had analyzable malignant cells present in all of their specimens. One patient had analyzable malignant cells only in the CT guided biopsy specimen, whereas 3 patients had analyzable specimens only from their BM aspirate/trephine. The yield of malignant cells suitable for IHC/ICC was greater from BM aspirate/trephine specimens (6 versus 4).

Conclusions: The proportion of analyzable cells from both a CT guided biopsy and BM aspirate/trephine is substantial. Caution must be used in interpreting any IHC result from bony samples, since these samples must be decalcified prior to processing, and this process may increase false negative values. Given the minimal invasiveness of bone marrow aspirate and trephine, this procedure may be ideal to obtain tumour tissue for patients with metastatic disease that is otherwise difficult to sample. Histomorphology and gene-expression profile results are awaited.

Abstract Code: 608

THE PROGNOSTIC IMPORTANCE OF VARIOUS CLINICAL, PATHOLOGICAL, AND IMMUNOHISTOCHEMICAL PARAMETERS IN TAMOXIFEN-TREATED PATIENTS WITH EARLY BREAST CANCER.

(1) * DR. GRINBERG VLADISLAV (1) DR. MERMERSHTAIN WILMOSH (1) DR. LAZAREV IRENA (1) PROF. ARIAD SAMUEL (1) DR. GEFFEN DAVID B

(1) DEPARTMENT OF ONCOLOGY, SOROKA UNIVERSITY MEDICAL CENTER AND FACULTY OF HEALTH SCIENCES, BEN-GURION UNIVERSITY OF THE NEGEV, BEER-SHEVA, ISRAEL

Introduction: Adjuvant tamoxifen reduces the annual odds of death for women with early breast cancer by approximately 15% over 10 – 15 years. Since some patients experience disease progression during or after treatment with tamoxifen, it is important to identify factors that predict poor outcome and according to reduce mortality by adding chemotherapy. The primary objective of this study was to assess the prognostic importance of various clinical, pathological, and immunohistochemical parameters in tamoxifen-treated patients with early-breast cancer.

Patients / Methods: This was a single-institution, retrospective clinicopathological study on patients with hormone-receptor positive, early-breast cancer diagnosed during the years 1993-1998 that were treated with adjuvant tamoxifen. The following parameters were studied: age, menopausal status, tumor size and location, lymph node status, pathologic grade, and immunohistochemistry for estrogen and progesterone receptors, Her/2neu, Ki67, E-cadherin and cathepsin-D. Disease-free-survival (DFS) and overall-survival (OS) were calculated with the use of Cox-proportional hazard, and logistic-regression models. 211 patients with histological diagnosis of estrogen receptor-positive, invasive-breast cancer treated with adjuvant-tamoxifen were included. Median age -57yrs (range 29-89yrs); menopausal status – pre-36(17%), peri-15(7.1%), post-160(76%); node-positive- 83(40%); progesterone receptor-positive- 120(80%); low-grade- 33(20%), intermediate-grade- 79(49%), high-grade- 48(31%); Her2/neu-positive- 19(9%); adjuvant/neoadjuvant chemotherapy- 101(48%), adjuvant radiotherapy- 152(73%); disease status – AWOD- 164(82%), DWD/DWOD- 31(15%), AWD- 6(3%).

Results: In Cox multivariate analysis, the only variables associated with longer OS were tumor size ($p<0.001$), lymph-node-status ($p<0.001$), location ($p<0.001$), and grade ($p=0.007$), and with DFS were tumor size ($p<0.001$), location ($p=0.01$), and lymph-node-status ($p=0.03$). In multivariate logistic regression analysis, the only variables associated with longer OS were menopausal status ($p<0.001$), grade ($p<0.001$), and progesterone-receptor status ($p<0.001$), and with DFS was tumor size ($p<0.001$).

Conclusions: This retrospective, single-institution experience validates: a) the prognostic importance of classic clinicopathological parameters including the status of menopause, tumor size and location, lymph-node, grade and progesterone-receptor, and b) The limited prognostic value of various immunohistochemical parameters commonly-used in practice.

Abstract Code: 908

THE RELATION BETWEEN HEPARANASE EXPRESSION AND THE PROGNOSIS OF YOUNG BREAST CANCER PATIENTS

(1) * DR. SHULMAN KATHERINA (2) DR. GOLDBERG HADASSAH (3) PROF. BEN-IZHAK OFER (4) DR. ILAN NETA (5) PROF. VLODAVSKY ISRAEL

(1) ONCOLOGY DEPARTMENT, RAMBAM MC (2) ONCOLOGY DEPARTMENT, NAHARYA MC (3) PATHOLOGY DEPARTMENT, RAMBAM MC (4) CANCER AND VASCULAR BIOLOGY RESEARCH CENTER, TECHNION, HAIFA (5) CANCER AND VASCULAR BIOLOGY RESEARCH CENTER, TECHNION, HAIFA

Introduction: Young patients, fewer than 45 years old, with breast cancer are characterized by poor prognosis due to aggressive behavior of the tumor and the absence of efficient screening programs. Heparanase is an endoglycosidase that preferentially expressed in human tumor and its over-expression in tumor cells confers an invasive phenotype in experimental models. Heparanase upregulation correlates with increased tumor vascularity and poor post-operative survival of cancer patients.

Patients / Methods: The aim of this study was to evaluate the relation between heparanase expression in breast cancer cells and clinical parameters of young breast cancer patients. 116 cases of young breast cancer patients were diagnosed at Rambam Medical Centre between the years 1992 and 2002; 61 of which fulfill the study criteria. Heparanase expression was evaluated by immunohistochemical staining applying anti-heparanase antibodies (Ab733 and Ab3964), and lymphatic vessels density was evaluated following staining with the D2-40 monoclonal antibody which specifically decorate lymphatic endothelial cells.

Results: In multivariate analysis, there was no significant correlation between heparanase staining in the tumor tissue and the following parameters: tumor size (T-stage), regional lymph node involvement (N-stage), estrogen and progesterone receptor status, differentiation and the stage of the tumor. Statistically significant correlation was found between heparanase staining in the surrounding tissue between poorly and moderately differentiated tumors (65.2% vs. 31.8%) $p=0.0025$. There was also a statistically significant correlation between the number of lymph vessels in the tumor and heparanase staining ($p=0.039$).

Conclusions: A concordance between heparanase staining intensity in the tumor microenvironment and breast cancer differentiation, also correlation with lymphatic vessels in the tumor support an importance of a heparanase molecule in cancer process and need for further evaluation.

Abstract Code: 1908

IMPROVING CANCER THERAPY BY DOCETAXEL AND GRANULOCYTE COLONY-STIMULATING FACTOR: CLINICAL VALIDATION OF A PHYSIOLOGICALLY-BASED IN SILICO MODEL FOR PREDICTING DRUG SAFETY IN METASTATIC BREAST CANCER PATIENTS .

(1) MR. VAINAS ODED (2) PROF. ARIAD SAMUEL (2) DR. MERMERSHTAIN WILMOSH (1) DR. VAINSTEIN VLADIMIR (1) MRS. BLOCH NAAMAH (1) MRS. ASHKENAZI AMIT (1) DR. KLEIMAN MARINA (1) DR. BEN-AV RADEL (3) DR. MUKHERJEE ABHIK (3) DR. CHAN STEPHEN (1) * PROF. AGUR ZVIA

(1) OPTIMATA LTD, RAMAT-GAN, (2) DEPARTMENT OF ONCOLOGY, SOROKA UNIVERSITY MEDICAL CENTER, BEER SHEVA, ISRAEL, (3) DEPARTMENT OF ONCOLOGY, NOTTINGHAM CITY HOSPITAL, UK

Introduction: Neutropenia is the dose-limiting toxicity of the 3-weekly docetaxel (DOC) treatment schedule. A physiologically-based mathematical model of granulopoiesis was developed for predicting chemotherapy-induced neutropenia.

Patients / Methods: Weekly blood counts were collected from 38 MBC patients, treated by DOC, 67-100 mg/m², Q21D, N=18, and 23-35 mg/m², Q7D, N=20. These were randomly divided into a training (N=12), and a validation set (N=26). DOC's three-compartment pharmacokinetics (PK) and pharmacodynamics (PD), described as direct killing of neutrophil progenitors were modeled, PD parameters being adjusted by the training set data. Kinetics and dynamics of G-CSF were modeled. The PK/PD models were simulated in conjunction with the granulopoiesis model with baseline neutrophil counts and individual DOC schedule of each patient in the validation set. Neutrophil counts and neutropenia grade that were predicted by the model were compared to the patients' counts at the corresponding time-points, using a Pearson correlation test (r). Average population parameters were evaluated and embedded in the validated model, and different DOC and G-CSF combination schedules were simulated.

Results: The model was validated by correctly predicting grade 4 neutropenia in 81% of the patients (21/26) and by showing highly significant precision in predicting the neutrophil profiles ($r = 0.68, 0.63$, in time windows of ± 12 hrs and ± 6 hrs, respectively) and nadir timing ($r = 0.99$). Model analysis confirms clinical results, suggesting smaller toxicity of the once-weekly DOC regimen, as compared to the tri-weekly regimen, and predicts that DOC regimens, intensified above the conventional dose of 33 mg/m²/week, predicted a crucial timing for G-CSF support. Applications of G-CSF, at a dose of 60 μ g/day, for three consecutive days, starting on day six post-DOC for the bi- and tri- weekly regimens and day four post-DOC for the weekly regimen, result in a clinically manageable neutropenia. In contrast, application of G-CSF, one day post DOC, may result in a fast, serious, neutropenic response.

Conclusions: The timing and magnitude of individual neutropenic response can be accurately predicted by the granulopoiesis/DOC model, incorporating mean population parameters. The model suggested an improved intensified DOC/G-CSF regimen, achieving maximal dose intensity, while maintaining manageable neutropenia, when G-CSF is applied six days post-DOC.

Abstract: 244

SUPERIOR PATHOLOGICAL COMPLETE RESPONSE TO NEO-ADJUVANT CHEMOTHERAPY IN BREAST CANCER AMONGST WOMEN WITH BRCA1/2 MUTATIONS

(1) * PALUCH-SHIMON SHANI (2) PAPA MOSHE Z (3) FRIEDMAN EITAN (2) SHABTAI MOSHE (4) YOSEPOVICH ADY (1) MODIANO TAMI (1) GOLDFARB ALBERTO (1) CATANE RAPHAEL (1) KAUFMAN BELLA

(1) DIVISION OF ONCOLOGY, SHEBA MEDICAL CENTRE (2) DEPARTMENT OF SURGERY, SHEBA MEDICAL CENTRE (3) ONCOGENETICS UNIT, SHEBA MEDICAL CENTRE (4) DEPARTMENT OF PATHOLOGY, SHEBA MEDICAL CENTRE

Background: Germline mutations in BRCA1 and BRCA2 occur in ~ 11% of Jewish Ashkenazi women with breast cancer. BRCA1/2 proteins are key players in the repair mechanisms of double-strand DNA breaks induced by DNA-damaging agents. Hence, inactivating mutations in BRCA1/2 genes have been postulated to result in increased chemo-sensitivity in women with breast cancer who carry these germline mutations. Neo-adjuvant therapy provides the opportunity for in vivo assessment of this notion, assessing chemotherapy (CT) sensitivity via pathological complete response (pCR) rates in breast cancer patients. This study assessed the pCR amongst women with BRCA1/2 mutations compared to those who are BRCA1/2 mutation negative.

Methods: Retrospective evaluation of response to neo-adjuvant CT amongst consecutive breast cancer patients who had all undergone genetic testing at the Oncogenetics unit, Sheba Medical Centre to define their BRCA1/2 mutational status. pCR was defined as absence of residual invasive carcinoma in the breast and axillary lymph nodes. Only women who received anthracycline based therapy were included. Women who had received concurrent trastuzumab in the neo-adjuvant setting were excluded. Statistical analysis included Fisher's exact test for categorical variables, and student t-test for continuous variables.

Results: 75 women were identified who had received neo-adjuvant CT and who had undergone genetic testing. 61 were BRCA non-carriers and 14 harbored BRCA1/2 mutations (5 BRCA1 and 9 BRCA2 mutation carriers). There were no statistically significant differences between the BRCA1/2 positive and BRCA1/2 negative groups with regard to mean age, grade 3 histology, hormone receptor status or HER2/neu over-expression, and clinical TNM staging. Seven women received anthracycline based CT and 68 received an anthracycline and taxane regimen. No statistically significant differences existed between the two groups with regards to chemotherapy treatment protocol. Amongst women with a BRCA1/2 mutation 50% had a pCR compared with only 21% in BRCA-negative women, $p=0.035$.

Conclusions: Women with BRCA1/2 mutations demonstrated a higher pCR compared with women who were BRCA negative. Prospectively designed studies are needed to optimize choice of chemotherapy agents in BRCA1/2

Abstract: 248

BEVACIZUMAB PLUS PACLITAXEL: A SERVICE PROTOCOL FOR METASTATIC BREAST CANCER

(1) * GREENBERG JULIA (2) JIVELIOUK IRENA (3) INBAR MOSHE
(1) TEL AVIV SOURASKY MEDICAL CENTER (2) TEL AVIV SOURASKY MEDICAL CENTER (3) TEL AVIV SOURASKY MEDICAL CENTER

Background: Paclitaxel-Bevacizumab bio-chemotherapy combinations have been recently reported to be highly active in the first line for metastatic breast cancer (Miller et al, NEJM 2007). The aim of this study was to evaluate the efficacy of this new approach as a service regimen, out of a clinical trial.

Protocol: Eligibility criteria were: Her2 negative, measurable/evaluable metastatic breast cancer; no previous chemotherapy for metastatic disease, no previous exposure to bevacizumab; previous exposure to taxanes as part of adjuvant therapy was permitted; adequate organs reserve and functions; good performance status (PS 0-2); no contra-indications for bevacizumab administration; signing an informed consent for chemotherapy. Bevacizumab (B) 10mg/kg/d on days 1&15 and paclitaxel (P) 90 mg/m²/d on days 1,8,15 q4w were administered until progression or intolerance or life-threatening toxicity. Patients: 18 patients (F=17, M=1) at a median age of 47y (range 31-75y). Of the 17 women, 9 were pre-menopausal. Three presented with metastatic disease and 16 had either early or locally advanced disease at presentation and developed metastases. All had IDC. Three had triple negative tumors, and 14 had at least one HR positive. Systemic adjuvant/neoadjuvant therapy included chemotherapy (AC, TXTR, CAF, CMF, CNF, ET, taxol) in 12 patients, tamoxifen in 9 patients. First line hormonotherapy for metastatic disease was given to all but 2 patients. Sites of metastases prior to administration of B+P were mostly bone (15 pts), liver (9 pts), and lung (8).

Results: 17 the patients got at least 2 cycles of B+P and were evaluable for response and toxicity. Neuropathy was observed in 8 patients, neutropenic fever in 1, and dermatomyositis in 1. Clinical benefit response was impressive in 12/17 patients. Significant PR was observed in 15/17 patients, SD in 1/17 and PD in 1/17. The overall response rate was 88%, and the overall disease-control rate was 94%. Median time to progression was >6mo (range 2 to >11mo).

Conclusions: B+P as first line service therapy for metastatic breast cancer is associated with high rate of disease control for a significant period of time, and thus should be considered in all HER2 negative cases.

Abstract Code: 246

PRELIMINARY RESULTS OF A PHASE 1/2 OF A COMBINATION OF ERBITUX AND TAXANE FOR "TRIPLE NEGATIVE" METASTATIC BREAST CANCER PATIENTS

(1) * DR. NECHUSHTAN HOVAV (1) MRS. STAINBERG HANI (1) PROF. PERETZ TAMAR
(1) ONCOLOGY DEPARTMENT HADASSAH HEBREW UNIVERSTIY MEDICAL CENTER

Introduction: Introduction: Breast cancer is composed of at least 5 subtypes. One of them the basal cell subtype. A marker for this subtype is triple negativity for ER PR and Her2. currently there is no biologic therapy available for this subtype. over 50% of this kind of tumors express EGFR. Cetuximab is a humanized antiEGFR IgG1 antibody. In colon cancer there are also high percentage of EGFR expression and addition of Cetuximab to chemotherapy results in renewed sensitivity to treatments. We therefore hypothesized that in a similar manner addition of Cetuximab to taxanes which are among the most potent anti breast cancer drugs will result in increased effectiveness in this subset of breast cancer patients.

Patients / Methods: From January 2007 until October 2008 we treated 12 breast cancer patients with either Paclitaxel 80 mg/m², (10 patients) or Docetaxel (30 mg mg/m²) (2 patients) with Cetuximab weekly. Patients had at least one pathology sample of breast cancer with triple negative components, metastatic disease and up to two prior chemotherapy lines in the metastatic settings..

Results: Patient characteristics (median)- age 60 (31-69) years, prior taxane therapy 9/11 pt's, Toxicity Dermatologic toxicity (grade 2 8/11 grade 3 1/11) nail disease grade 2 8/10 evaluable patients fatigue grade 3- 1/11 pt response is evaluable for 11/12 patients. including clinical response(mainly substantial pain control(6) decrease in tumor markers and roentgonologic response altogether 8/11 patients . Including tumor marker normalization and nearly a roentgoenologic CR in a young patient previously treated with taxol in the adjuvant settings and two chemotherapy lines in the metstatic adjuvant settings. 3 patients developed brain metastasis during treatments.

Conclusions: To our knowledge this is the first trial of weekly taxane cetuximab in breast cancer. Administration of taxane-cetuximab weekly therapy for triple negative breast cancer patients is possible .Toxicity is the cumulated expected toxicity of each of the agents – special care should be taken for nail disease which occurred in most of the patients. Some impressive clinical responses were obtained even in taxane pretreated patients. Trial is ongoing.