mandatory in MBC patients to improve their QoL, and will result in maintaining performance status and continuing chemotherapy.

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Patterns of Care and Outcome of Locally Advanced Breast Cancer

G. Fried[1], V. Semenisty[1], Z. Regev[1], K. Drumea[1]. [1]*Rambam Health Care Campus, Oncology, Haifa, Israel*

Background: Locally advanced breast cancer (LABC) comprise 5−10% of breast cancer cases. We present a review of practice patterns and outcomes in patients with LABC treated at our institution.

Patients and Methods: We reviewed 120 consecutive patient file records treated at our institution for LABC between 1998 and 2007.Patient and disease characteristics, treatment-related data and patterns of relapse were collected.

Results: Patients' median age was 49 years (range: 28−84 years). Median tumor size at diagnosis was 7cm (range (1−11 cm). Histology showed invasive duct carcinoma in 68% and invasive lobular carcinoma in 9.3% of patients. Estrogen receptors were positive in 67% and progesterone receptors were positive in 58% of the patients. In 31% HER2/new was over-expressed and 13% of the patients were triple negative. Nineteen patients (6.3%) underwent sentinel lymph node biopsy at diagnosis. Eighty-five percent of the patients received preoperative chemotherapy (CT) and 15% received hormonotherapy (11% aromatase inhibitors and 4% tamoxifen).Primary CT was antracycline-based in 37% and anthracycline followed by taxanes in 48% of the patients. Fourteen percent of the patients received Trastuzumab before surgery.

Type of surgery: 39% of the patients underwent lumpectomy, 56% had unilateral mastectomy and 3% preferred bilateral mastectomy. Tumor size was reduced to a median of 1cm (range: 0−10 cm).

Post-treatment pathological findings: 15% of patients showed no residual tumor (pathological complete response) and 42% had negative axillary lymph nodes. All patients received adjuvant radiotherapy and patients with hormone receptors positive received adjuvant hormonal therapy. At a median follow-up of 4 years (range:1−13), 67% of the patients had no evidence of disease, 10% developed local recurrence, 31% developed distant metastasis, 2% developed secondary breast cancer and 7% developed secondary non-breast malignancy. Median survival time was 11 years (range:8−10 years) with 5-year survival rates of 76%.

Conclusions: Management of LABC at our institution is consistent with the current clinical guidelines. In our patients, local recurrence rate was low (10%) and 31% of patients developed distant metastasis. In order to improve the LABC patients' outcome, it is mandatory to increase population awareness to early tumor detection and to optimize systemic treatment strategies according to histological subtypes.

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Oral Vinorelbine (VNR) and Capecitabine (CAP) − an Acceptable and Effective Combination Chemotherapy for Early Metastatic Breast Cancer (MBC)

M. Hogg[1]. [1]*Lancashire Teaching Hospitals NHS Trust, Preston, United Kingdom*

Background: Most guidelines recommended a sequential single agent approach for MBC because of toxicity with combinations. At our centre practice is divided between doctors, providing an opportunity to compare approaches. First line taxane-capecitabine is used, but severe toxicity limits its use to fit patients. The combination of oral vinorelbine (VNR) and capecitabine (CAP) has demonstrated additive efficacy with good tolerability, providing a combination option for patients not prescribed the taxane combination due to poor performance status (PS) or patient preference. We compared toxicity and efficacy of this combination with the same agents used sequentially.

Methods: An observation study of patients with MBC treated with 1st/2nd line oral VNR and CAP combined as a doublet or given sequentially. Combination dose: VNR 60−80 mg/m^2 day 1,8 q21 plus CAP 1000 mg/m^2 bd days 1−14, q21 for a maximum of 9 cycles; sequential dose: CAP 1250 mg/m^2 bd d1−14, q21, VNR 60−80 mg/m^2 day 1,8 q21, both given until disease progression. Patients were reviewed every 3 weeks and outcome and toxicity recorded.

Results: Between Oct07 and Jan11 33 patients whose PS or preference precluded a taxane doublet received the doublet. Outcomes were compared with 30 patients who received the agents sequentially. Doublet/singlet mean age 59/57.5 yrs and median PS 2/1. Most treatment was 1st line metastatic (64%/83%). Two patients unfit for FEC received the doublet adjuvantly. Median cycles: doublet 4.5/CAP 6/VNR 5; dose delays doublet 23%/CAP 10%/VNR 20%. Severe (G3/4) toxicity was generally less frequent with the combination than either single agent. G3/4 toxicity, doublet/CAP/VNR: haematological 11%/4%/29% (no neutropenic sepsis); gastrointestinal 0%/8%/4%; dermatological 0%/13%/0%; other non-haematological 0%/0%/13%. One patient stopped treatment due to erythema multi-forme (EM) and one due to palmar-plantar erythrodysesthesia (PPE). PFS (n = 16): doublet 6 m (range 0−31 m); CAP-VNR (n = 11) 7 m (range 3−29 m), VNR-CAP (n = 2) 17 m. Response rate for doublet: 50%. No response data available for single agent.

Conclusions: All-oral combination of VNR and CAP demonstrates effectiveness and good tolerability with minimal severe toxicity. G3/4 haematological toxicity and G3 PPE were less frequent with the doublet than with single agent VNR and CAP. The low incidence of PPE has been noted in previous phase II studies. Most patients find the combination acceptable, even those with poor PS. Our findings warrant further investigation in a randomised study to challenge the standard premise of sequential single agent therapy in MBC.

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Does 'PDO' Deserve T4b Status in Early Breast Cancer?

D. Jha[1], S.V.S. Deo[1], N.K. Shukla[1], P. Khanna[1], P. Ramanathan[1]. [1]*All India Institute of Medical Sciences, Surgical Oncology, Delhi, India*

Background: Clinically apparent skin involvement (T4b) in breast cancer is a morphological criterion for staging patients in the highest non metastatic stage (stage III B) irrespective of tumor size. This heterogeneous group shows inconsistency as a prognostic variable and hence results in a non-homogenous grouping of patients with different outcomes.

Material and Methods: A retrospective analysis of prospectively maintained computerized breast cancer database in Department of Surgical Oncology, AIIMS, New Delhi was carried out from 1995–2008. Inclusion criteria for the current study were tumor size less than 5cm (T1/T2) and pathological nodal involvement less than 4 nodes (pN1). Patients who received Neoadjuvant Chemotherapy were excluded from analysis. The study group was patients with T1/T2 tumors with clinical skin involvement (Ulcer,PDO), pN1 stage taken for upfront surgery. The control group was T1T2 patients without clinical skin involvement.

Result: Total 71 patients with PDO were compared with 695 early breast cancer patients in the control group. The distribution of age, tumor size, nodal burden and Hormone receptor positivity, and adjuvant therapy was comparable in both groups. There was no statistically significant difference in recurrence rates, disease free survival, and overall survival in patients with or without PDO in the two groups.

Conclusion: Presence of PDO does not impact survival in patients with small tumors and limited nodal disease. Patients with ulcer have significantly poor outcomes. Using PDO to classify breast cancer patients with small tumors as stage III B results in a heterogeneous grouping of patients with different survival outcomes.

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Bone Marrow Micrometastases in Breast Cancer. Changes in Hematologic Parameters

M. Rodionova[1], V. Rodionov[2], O. Bogomolova[3], A. Bayramov[4]. [1]*N.N.Blokhin Cancer Research Center, Breast Cancer Department, Moscow, Russian Federation;* [2]*Ulyanovsk State University Ulyanovsk Regional Oncology Center, Medical Faculty, Ulyanovsk, Russian Federation;* [3]*Ulyanovsk Regional Oncology Center, Medical Oncology Department, Ulyanovsk, Russian Federation;* [4]*N.N. Blokhin Russian Cancer Center, Head and Neck Department, Moscow, Russian Federation*

Background: Bone marrow plays the key role in distant metastases formation and at the same time has no clinical symptoms. The purpose of the study was to define a complex of changes in hematologic parameters, associated with bone marrow micrometastases (BMMM) in breast cancer (BC) patients.

Material and Methods: Fifty patients with breast cancer treated in the Ulyanovsk regional oncology center were recruited into the trial. 37 patients (74%) had distance metastases, other 13 (74%) − locally-advanced disease. Bone marrow was obtained by biopsy from both anterior iliac crests under local anesthesia and was studied by cytological, histological and immunocytochemical (ICC) methods. The analyses was made using monoclonal antibodies against cytokeratins PAN, clone MNF 116, DAKO. Positive test was defined as detection of 1 metastatic cell per million myelokaryocytes. In ICC-positive cases we also determined tumor cell receptor status and proliferative activity with Ki-67.

Results: Nineteen (38%) of the 50 BC patients presented with BMM. The bone marrow involvement was detected more frequently (12/19) by ICC. Combinations of diagnostic techniques failed to improve detection of BMMM. Of the 12 cases with bone BMMM detected by ICC all had receptor-negative tumor cells and low Ki-67 expression. Bone metastases were discovered in half of patients free from bone marrow involvement. 26.7% of patients with non-skeletal metastases were bone marrow-positive.

Bone marrow involvement was accompanied by suppression of red cell production ($p < 0,05$) while having no effect on granulocyte or platelet counts. Anemia was found in BMMM-positive patients two times more frequently than in the control. There was a significant increase in ESR in the group with BMMM ($p < 0.001$). Mean ESR level in patients free from BMMM was 23.5 mm/h (range 17.5 to 29.5) versus 51.7 mm/h (range 44.2 to 59.2) ($p < 0.001$) in micrometastasis-positive cases. There was a statistically significant increase in tumor markers: CA 15−3 ($p = 0.003$), MCA ($p = 0.005$) and CEA ($p = 0.011$) in the group of patients with BMMM. In spite of CA 19−9 increased more often in micrometastasis-positive patients (36.8% vs. 29.0%) the difference was not statistically significant.

Conclusion: Having no clinical signs, BMMM are likely to be suspected according to the following changes in hematological parameters: significant increase in ESR and decrease in Hb levels, tumor markers increase (CA 15−3, MCA, CEA, CA 19−9) and further bone marrow biopsy is required.

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Comparison of Inpatient and Out-patient Care Needs for Metastatic Breast Cancer Patients

M. Kagzi[1], D.J. Leaning[2], D. Lee[2]. [1]*Freeman Hospital, Newcastle Upon Tyne, United Kingdom;* [2]*Freeman Hospital, Newcastle Centre for Cancer Care, Newcastle Upon Tyne, United Kingdom*

Background: Median survival in women with Metastatic Breast Cancer (MBC) is over 2 years, but many patients survive longer. MBC patients are now successfully managed with a range of systemic treatment interventions routinely in an Out Patient Clinic (OPC) setting. Knowledge of utilisation of resources is vital for the development of an efficient health system.

Materials and Methods: We reviewed the medical records of 76 MBC patients attending breast clinic at Wansbeck Hospital, UK, between August 2010 and February 2011. MBC patients represented 35% of total clinic attendances. During this period patient data collection included number of OPC and chemotherapy unit attendances along with number and frequency of chemotherapy cycles including biological agents. Hormonal treatments used since MBC diagnosis was also recorded.

Results: Median age of MBC patients attending the service was 61 years (range 39 -86 years). Their median disease free survival from time of diagnosis was 4 years (range 0−20 years). Twenty clinics were conducted during this period with a median of 4 (range 1−10) clinic attendances per patient. Out of 76 patients 28 (37%) had multiple sites of metastases, bone metastases were found in 41 (54%); lymph nodes metastases in 13 (17%); visceral metastases in 40 (53%) and brain metastases in 7 (9%) patients. During this period 35 (46%) patient were on chemotherapy. 106 one weekly chemotherapy sessions were delivered to 11 (14%) of patients, 15 two weekly sessions for 4 (5%) patients, 103 three weekly sessions for 24 (32%) patients and 3 four weekly sessions were delivered for 3 (4 %) patients. 53 (70%) patients were oestrogen receptor positive and received a median of 1 and maximum 3 endocrine treatments.

Conclusion: Our previous study from Wansbeck Hospital shows only 14% of MBC patients required inpatient care of average 4.2 days, for chemotherapy related toxicity. We demonstrate that OPC treatment comprises the bulk of MBC patient workload and a majority receive frequent systemic treatments not requiring hospital admission. Current data shows OPC and chemotherapy unit visits are important aspects of care and utilise major resources in the management of MBC patients.

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Meta Analysis to Compare Overall Survival Between Primary Metastatic Breast Cancer and Recurrent Metastatic Breast Cancer

O. Aseyev[1], A. Alanbagi[1]. [1]*Dnepropetrovsk State Medical Academy, Oncology and Medical Radiology, Dnepropetrovsk, Ukraine*

Background: The objective of this meta analysis was to determine whether differences in survival exist between women with primary metastatic and recurrent metastatic breast cancer, and also to explore the effect of other prognostic factors among survival of those patients.

Material and Methods: The data base for this meta analysis were collected from three studies, these three studies were located through search of PubMed and HINARI websites, all studies that were in English language and compared survival between primary metastatic(PMBC) and recurrent metastatic breast cancer(RMBC) were included in this meta analysis. The end point that I assessed was the survival, other factors that included in comparison were the rate of occurrence, age of patients, disease free interval (DFI), tumor size.

Result: three studies with a total of 4145 patients were included in this meta analysis, 807 patients had primary metastatic breast cancer and 3338 patients had recurrent metastatic breast cancer. There were statically non significance difference in survival in two of these studies (25.1 vs 23.3 months, $p = 0.81$ and 39 vs 30 months, $p = 0.2$ in PMBC and RMBC respectively) and statically significance difference in survival in one of them (39.2 vs 27.2, $p < 0.0001$ in PMBC and RMBC respectively) in addition that patients with primary metastatic breast cancer were older and had larger tumor size than recurrent metastatic breast cancer patients.

Conclusion: the survival of patients with PMBC and RMBC was similar in both groups in spit of the difference in clinical and histological characteristic, also DFI play an important role in survival of patients with RMBC.

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PI3KCA Mutations in HER2-Positive Breast Carcinomas Treated with Trastuzumab

A. Ferro[1], M. Barbareschi[2], L.v. Cuorvo[2], S. Girlando[2], E. Leonardi[2], R. Triolo[1], A. Caldara[1], E. Galligioni[1], P. Dalla Palma[2]. [1]*Santa Chiara Hospital, Oncology, Trento, Italy;* [2]*santa Chiara Hospital, Surgical Pathology, Trento, Italy*

Introduction: Aberrations of the components of the PI3K-AKT pathway are frequent in infiltrating breast carcinomas (IBC) and activating mutations of the *PI3KCA* gene mainly occur at hotspot in exons 9 and 20.

Material and Methods: We evaluated 123 Her2-positive IBC treated with trastuzumab at the S.Chiara Hospital of Trento, including 20 primary locally advanced IBC treated with neoadjuvant trastuzumab, 48 advanced metastatic IBC, and 55 early stage IBC treated with adjuvant trastuzumab. Genomic DNA was extracted from each paraffin-embedded tumor block using QIAamp DNA MiniKit (Qiagen Inc., Hilden, Germany). The samples were analyzed with Real-Time PCR and pyrosequencing reaction was performed according to the manufacturer's instructions PyroMark™ IDQ96 V2.0 kit (Qiagen). Pyrosequencing™ was performed using the PyroMark™ Gold Q96 reagent kit (Qiagen).

Results and Discussion: In our series *PI3KCA* gene mutations were observed in 11 % of locally advanced IBC, 10.4 % of metastatic IBC and 29% of early stage IBC. *PI3KCA* gene mutations were not associated with tumor size, grade, ER and PgR status and proliferative activity and were not predictive of response to trastuzumab treatment.

Conclusion: No statistically significant relations have been observed between status PI3K and pathological and biological parameters and response to treatment.

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Incorporating Epithelial Mesenchymal Plasticity (EMP) in the Detection and Isolation of Circulating and Disseminated Tumour Cells

N. Jacobsen[1], A. Dobrovic[2], A. Tachtsidis[3], T. Blick[3], E. Thomas[4], A. Dowling[5], D. Huang[3], N. Zeps[4], C. Saunders[1], E. Thompson[3]. [1]*The University of Western Australia, Surgery, Perth, Australia;* [2]*Peter MacCallum Cancer Centre, Pathology, Melbourne, Australia;* [3]*St Vincent's Institute of Medical Research, Invasion and Metastasis Unit, Melbourne, Australia;* [4]*St John of God Pathology, Western Australian Research Tissue Network, Perth, Australia;* [5]*St Vincent's Hospital, Oncology, Melbourne, Australia*

Background: Circulating tumour cells (CTC) in peripheral blood, and disseminated tumour cells (DTC) in bone marrow of cancer patients, represent 'seeds' that enable cancer recurrence or metastasis and are potential independent predictors of systemic relapse and death. However, current enrichment and detection methods rely on epithelial marker expression which may be lost by CTC/DTC undergoing epithelial-mesenchymal transition (EMT). This and other unresolved difficulties in detection due to low numbers prevent integration of this prognostic tool into routine clinical practice. Cells that share both epithelial and mesenchymal markers may have more aggressive properties and their detection will be an important factor in determining and monitoring treatment regimes.

Materials and Methods: To identify limitations of current widely used detection methods that rely on the expression of only epithelial markers, we undertook data-mining analysis which revealed that while mesenchymal breast cancer cell lines lose (epithelial) EpCAM expression, they gain expression of (mesenchymal) EGFR. We then developed and utilised anti-EGFR-coated immunomagnetic beads in parallel with anti-EpCAM beads to isolate CTC from peripheral blood and DTC from bone marrow of patients with advanced breast cancer and measured the expression of breast cancer markers in the isolated cells using RT-PCR.

Results: We observed CTC and DTC isolation using anti-EpCAM beads alone, or anti-EGFR beads alone. We were also able to isolate further CTC and DTC by using anti-EGRF beads after depletion with anti-EpCAM beads, demonstrating that by using this mesenchymal marker we are able to extract tumour cells that have lost or downgraded their epithelial marker expression and would be missed by current standard detection methods. RT-PCR analysis revealed that each population was positive for EPHB4,