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.

242 Poster

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

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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.

243 Poster

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

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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.

244 Poster

PI3KCA Mutations in HER2-Positive Breast Carcinomas Treated with Trastuzumab

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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.

245 Poster

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

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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,

HER2, KRT19, EGFR, EpCAM and/or ELF3. Analysis of additional samples is ongoing, as is the analysis of further mesenchymal markers for RT-PCR.

Conclusions: Using both epithelial and mesenchymal markers can increase the yield of CTC/DTC from advanced breast cancer patients, representing a more sensitive means of identifying patients with an increased risk of recurrence, and monitoring patient response to systemic therapy. Analysis of the EMT status of these cells may also add benefit in predicting treatment outcomes and therefore optimising treatment regimes.

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246 Poster

Is Hepatic Arterial Infusion Chemotherapy Truly Ineffective for Liver Metastasis From Breast Cancer?

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Background: Liver metastasis from breast cancer (BCLM) is generally considered to be a prognostic factor and the median survival time after a diagnosis of BCLM is reported about 12-24 months. When BCLM is detected, patients usually undergo treatment by systemic chemotherapy (SCx) and metastases eventually spread throughout the body.

Oncologists do not recommend hepatic arterial infusion chemotherapy (HAIC) because there has been no definite evidence of a survival benefit, while there are severe toxicities associated with the treatment. However, good local control for BCLM by HAIC has also been reported.

This retrospective study aimed to evaluate the efficacy and safety of HAIC for BCLM for the patients who failed first/second line SCx based on anthracycline and taxane-based chemotherapy.

Material and Methods: From September 2002 to September 2011 at our hospital, 49 female patients with BCLC were treated by HAIC after failure of anthracycline- and taxane-based chemotherapy. The patients received 5-fluorouracil at 500 mg/body each week, Mitomycin C at 4 mg/body once every 2 weeks, and Epirubicin at 40 mg/body once every 4 weeks, via an implantable port-catheter system placed by an interventional radiological procedure.

We evaluated the survival (Kaplan-Meier method), response of the BCLM (RECIST v1.1), and the toxicity of the treatment (CTCAE v4.0).

Results: The median age of the 49 patients was 55 years (range 30−80y). The disease-free survival time from the primary surgery was 36 months (0–288months) excluding one stage 4 patient who did not undergo an operation.

The objective response rate (CR+PR; ORR) of the liver metastasis was 69% (34/49) and the disease control rate (CR+PR+SD; DCR) was 82% (40/49). The median survival from the diagnosis of BCLM was 28.5 months (95% CI = 20−35 months), the survival time after HAIC was 13 months (95% CI = 7−16 months), and the hepatic progression free survival was 7.5 months (95% CI = 4−11).

Complications($\geqslant$Grade 3) occurred in 13 patients (liver dysfunction in 3, myelosuppression in 9, and gastric ulcer in 1). Catheter-related events occurred in 1 patient (a pseudoaneurysm in a peripheral hepatic artery without symptoms) with no need for additional treatment.

Conclusion: Although they were treated after failure of anthracycline- and taxane-based chemotherapy, all patients had a good ORR and DCR, and the survival time was good. These results suggest that the HAIC prolongs the survival of patients with BCLM who failed to respond to anthracycline- and taxane-based chemotherapy, without inducing any major toxicities.

247 Poster

Fulvestrant in the Treatment of Metastatic Breast Cancer (MBC). A Retrospective Analysis of the Results From Two Centers in Northern Greece

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Introduction: Fulvestrant, an estrogen receptor downregulator, is currently approved for the treatment of advanced breast cancer in post-menopausal women. As it has a unique mechanism of action it does not display cross-resistance with other endocrine treatments (tamoxifen and aromatase inhibitors [AI]) and therefore has been used after the failure of tamoxifen, AI or both. In the present study, we retrospectively analyzed the progression free survival of MBC patients treated with fulvestrant in two centers form Northern Greece (Oct 2004 till Nov 2010). Patients were analyzed according to line of treatment and to whether they received fulvestrant as 'treatment' or as 'consolidation' (i.e. after chemotherapy, without previous evidence of progression).

Patients: A total number of 169 eligible patients were identified. All patients were postmenopausal (younger patients had ovarian ablation) and had received at least one line of previous endocrine treatment either in the adjuvant or in the metastatic setting. Fulvestrant was delivered intramusculary in the standard dose (250 mg every 28 days, n = 14), a loading dose scheme (initial dose of 500 mg at day 0 and 250 mg fulvestrant on day 14 and 28 and every 28 days thereafter, n = 72) or at a high dose (500 mg fulvestrant on days 0, 14 and 28 and every 28 days thereafter, n = 83).

Results: Median progression-free survival (PFS) was 6 months (95% CI: 5−8 months). Line of treatment differentiated statistically significantly outcome (p = 0.0001), with median PFS for 1st line 12 months (95% CI: 8−20 months), for 2nd line 6 months (95% CI: 5−10 months) and for 3rd line and above 5 months (95% PFS 3−6 months).

Regarding type of therapy, 55% of the patients received fulvestrant as 'consolidation' and 45% as 'treatment'. Consolidation was much more common in the 1st line (62%), a finding indicating that oncologists tend to treat 1st line patients with chemotherapy rather than endocrine therapy. Fulvestrant as 'treatment' resulted in longer PFS (9 vs 5 months), however this did not reach statistical significance (p = 0.18). In first-line patients when fulvestrant was given as 'consolidation' it resulted in a median PFS of 8 months vs 22 months when it was given as 'treatment' (p = 0.012). However, this may be attributed a selection bias, as patients with more aggressive disease were more likely to receive first-line chemotherapy and to continue with fulvestrant as 'consolidation'.

Conclusion: Fulvestrant is an effective hormonal treatment for post-menopausal MBC women. Earlier incorporation into the therapeutic strategy may result in better outcome for these patients.

248 Poster

Long Term Treatment with an All-oral Metronomic Schedule of Vinorelbine (VRL) and Capecitabine (CAPE) in Metastatic Breast Cancer (BC) Patients (pts). Preliminary Results of Toxicity and Efficacy of the VICTOR-2 Study

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Background: Previous data of the VICTOR-1 study (BCRT, 2010) established that the recommended dose of metronomic oral VRL in combination with fixed daily (500 $\times$ 3 mg) continuous doses of CAPE is 40 mg thrice a week. These data suggested that the combination is feasible with very low toxicity, thus no G3−4 events were reported. Due to the small number of the pts treated in the Phase I part of the study (N = 12), no conclusion could be done about efficacy and long-term toxicity. Aim of the present analysis is the evaluation of efficacy and toxicity in a group of pts who received the metronomic treatment with VRL 40 mg thrice a week plus CAPE 500 mg $\times$3 daily, for a period longer than 6 months.

Materials and Methods: Of the 31 pts actually enrolled in the Phase II part of the VICTOR study, 9 received VRL+CAPE for more than 6 months. Median age was 75 (47−84), all pts but 2 had a PS >80, 8/9 had $\geqslant$3 metastatic sites, 8 were HR+. Median DFI was 38 months (0–120). Five pts (55%) had already been treated with previous chemotherapy, mainly containing anthracyclines and/or taxanes. A cycle was arbitrary considered to be composed by 3 weeks. Median number of the cycles received is 18 (12−23). Partial Response (PR) was obtained in 5/9 pts (55.5%), the others obtained SD >24 weeks, for an overall CB (OR+SD >24 weeks) of 100%. Median TTP is not yet reached, thus considering that all pts but 2 are still responding to the metronomic therapy. Only 1 patient experienced disease progression after 16 months; the second one refused to continue therapy. In 164 cycles delivered, we observed 10 (6%) G3 events (6 related to VRL) and 2 (1%) G4 events, all of them related to VRL. G3−4 toxicities were mainly hematological (leukopenia/neutropenia: 6 events).

Conclusion: These data, obtained during a very long treatment period, confirm that the all-oral metronomic schedule of VRL+CAPE is feasible, with a very low incidence of G3−4 events. The efficacy of the metronomic schedule of these two drugs is very promising. The Phase II study is still ongoing.