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Management of Human Epidermal Growth Factor Receptor-2(HER2) Positive Breast Cancer Patients at University Hospitals of Leicester

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Background: The HER2 protein is overexpressed in upto 30% of breast cancers. This is correlated with more aggressive breast cancer and poor prognosis. Trastuzumab (Herceptin; Genentech) is a recombinant humanized monoclonal antibody against the HER2 receptor and is the only FDA-approved targeted agent for treatment of HER2 over-expressing breast cancer. Phase II and III clinical trials performed in women with metastatic breast cancers that overexpress HER2 have shown trastuzumab to have clinical activity when used as monotherapy, while also improving survival when used as a first line therapy in combination with chemotherapy. NICE guidelines recommends use of trastuzumab in combination with chemotherapy. However, evidence is lacking to guide use of this as single agent therapy in adjuvant setting in breast cancer patients having significant medical comorbidities. The aim of our retrospective audit was to study the management of patients who were HER2 positive and to identify patients who could have benefited with trastuzumab as single agent.

Methods: The data was collected on patients who presented with invasive breast cancer between January 2007 and April 2010. Information was obtained using electronic databases and case notes. Patients with HER2 + receptor status were identified and analysed. Number of patients who received trastuzumab and patients who did not receive trastuzumab were identified and assessed.

Results: A total of 2124 female patients with invasive breast carcinoma were identified. 234 patients (11.01%) were HER2 positive out of which 162 (69.2%) received chemotherapy and trastuzumab, 7 (0.02%) patients had chemotherapy but did not receive trastuzumab (4 with advanced metastatic cancer, 3 had cardiac toxicity). 65 (27.8%) patients did not get chemotherapy because of comorbidities. Out of these however, 3 patients did receive trastuzumab as single agent therapy. Out of the 65 patients who did not receive chemotherapy, 59 patients had ductal cancer, 3 had lobular cancer and 3 had mixed ductal and lobular cancer features. 27 (41.5%) of these 65 patients had grade 3, 22 (33.8%) had grade 2, and 2 (0.03%) had grade 1 cancer. The mean Nottingham Prognostic Index in this group was 4.12. 35 (53.8%) of these patients were estrogen receptor (ER) +ve, while 30 (46.1%) were ER −ve. 9 (13.8%) of these patients had vascular invasion.

Discussion: In our study, we identified that about 29% of our HER2 +ve patients have not received trastuzumab as they were not 'fit' to have chemotherapy. These patients are known to have aggressive tumours and have a poor prognosis. Evidence based guidelines are lacking to manage this unique subset of patients who are HER2 positive but cannot have chemotherapy due to medical comorbidities or significant side effects. Further studies regarding the efficacy and toxicity of single agent trastuzumab in the adjuvant setting are needed.

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Is Angiogenesis in Inflammatory Breast Cancer a Prognostic Finding?

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Background: With combined modality treatment, five-year overall survival rates for inflammatory breast cancer range from about 30 to 70 percent. Emerging data shows that inflammatory breast cancer (IBC) is angiogenic, thereby making angiogenesis a potential attractive therapeutic target. By elucidating the biologic characteristics of IBC, new targeted treatment options may become available**.** The aim of this study is to confirm the angiogenic phenotype of inflammatory breast cancer compared to non-inflammatory primary resectable breast cancer and to investigate the response to neoadjuvant chemotherapy in patients with inflammatory breast cancer.

Material and Methods: Core needle biopsies from the primary tumor and samples obtained from the surgical specimen will be analyzed in 25 patients with IBC and compared to 25 patients with primary resectable non-IBC. Microvessel density and angiogenic factors such as vascular endothelial growth factor (VEGF)-A, VEGF-C, VEGF-D, fibroblast growth factor-2 (FGF-2), will be assessed as well as CD31 and CD34 mediated endothelial cell-cell interactions. Moreover, derivatives of hypoxia (e.g. carbonic anhydrase IX, hypoxia inducible factor alpha) will be analyzed. Results will be correlated with response to neo-adjuvant chemotherapy and clinical outcome.

Conclusions. We will investigate whether inflammatory breast cancer has a higher expression of angiogenic factors, thereby facilitating further research into drugs that potentially target angiogenesis and may inhibit tumor growth in inflammatory breast cancer.

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Developing New Generation of Effective Anti-breast Cancer Drugs Based on the Anti-HIF-1a Mechanism − A Novel High-throughput Screening System for Rapidly Selecting Potent Anti-breast Cancer Compounds

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Background: One characteristic of fast-growing breast cancer (BCa) is the development of intratumoral hypoxia, whose existence correlates to a more malignant phenotype and worse diagnosis. Adaptation to the hypoxic environment is critical for BCa cell survival and growth. The hypoxic BCa cells in tumors modify gene expression in order to obtain a blood supply and prevent cellular damage; the main mediator of the hypoxia response is hypoxia-inducible factor-1 or HIF-1. HIF-1 activity is mainly dependent on the level of HIF-1a protein, the inducible and regulatory subunit of the HIF-1 dimer complex. The activation of HIF-1a stimulates a group of downstream genes including VEGF that are responsible for tumor angiogenesis and malignant progression; therefore, targeting and inhibiting the activity of HIF-1a should provide an effective strategy to suppress BCa growth, angiogenesis, and metastasis.

Material and Methods: To screen for effective anti-HIF-1a compounds, human BCa cells that have been stably transfected with VEGF-Luc (a chimeric construct containing a VEGF promoter fused to a reporter gene luciferase) were treated with or without candidate compounds, followed by incubation in the hypoxic conditions. As the HIF-1a-mediated VEGF transactivation is reflected in the increased luciferase activity, the potential anti-HIF-1a effect of the compound is identified by its significant reduction of luciferase activity compared to the untreated control group (which will result in high luciferase activity due to the HIF-1a-mediated VEGF transactivation). The screen procedure has been developed as a 96-well platform as a high-throughput screening system.

Results: In our pilot screening of 120 plus compounds, more than a dozen of the positive anti-HIF-1a compounds have been identified by this screening system. The positive compounds were validated and confirmed by Western blot and VEGF ELISA assay for anti-HIF-1a abilities. One such lead compound (PG-928310) and its synthetic derivative (CJ-III-60), demonstrated 70% and 82% inhibition, respectively, on BCa-induced angiogenesis compared to the control, as well as their powerful abilities of anti-breast tumor growth.

Conclusions: This technology has the potential to make a significant impact in the translational drug discovery and development. This novel high-throughput screening system can rapidly identify anti-HIF-1a compounds and lead to clinical application of new drugs for treatment of breast cancer patients.

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Efficacy and Safety of Lapatinib Treatment in Trastuzumab Pretreated Patients with HER2 Positive Metastatic Breast Cancer − An Analysis of IntERB Registry in the Czech Republic

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Background: Lapatinib is an oral dual tyrosin kinase inhibitor of EGFRand HER2. In the Czech Republic is currently available for treatment for patients with HER2 positive metastatic breast cancer that progressed during trastuzumabtreatment. We evaluated effectiveness, safety and tolerability of lapatinib treatment using data from IntERB registry that has been initiated and run by Czech Society for Oncology and Institute of Biostatistics and Analyses at Masaryk University, Brno, Czech Republic.

Materials and Methods: An analysis included 213 patients with HER2 positive metastatic breast cancer treated from January 2007 to September. Median age was 56 years (range 23−78). Lapatinib was mostly administered orally 1250 mg/day with capecitabine (2000 mg/m^2 D1−14), 16 patients received lapatinib in monotherapy. All patients had experienced progression during prior trastuzumab based therapy. Median ejection fraction of LV before lapatinib treatment was 60% (range 48−90%, evaluated in 172 patients).