Low Protein Expression of MET in ER-positive and HER2-positive Breast Cancer

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Abstract. *Aim: The mesenchymal–epithelial transition factor (MET) is a receptor tyrosine kinase that plays a key role in cell survival, growth, angiogenesis and metastasis. Because its expression is frequently altered in tumors, MET is currently under investigation as a potential target for anticancer therapy. The purpose of the present study was to determine the prognostic value of tumor MET expression levels in patients with estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-positive breast cancer, in order to strengthen the rationale for targeted therapy using MET inhibitors in this breast cancer subpopulation. Materials and Methods: We determined the expression of MET in formalin-fixed paraffin-embedded surgical specimens of ER- and HER2-positive breast cancer by immunohistochemistry. Results: Comparisons of MET expression with clinical parameters, including survival of the patients, were performed with MET expression as a dichotomized variable classified as high or low. Out of 78 tumors, 3 (3.8%) showed high MET expression. The analysis examining the association between MET and survival did not yield any statistically significant result regarding overall survival or disease-free survival. Conclusion: ER- and HER2-positive breast carcinomas do not exhibit high MET expression. This null finding, the first to be reported in the literature, is of great importance, since it indicates that this sub-group population is not proper candidate for clinical trials with MET inhibitors.*

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Selecting the optimal treatment for an individual with breast cancer seems to be a challenging task for the medical oncologist. Currently, estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status are the most relevant predictive factors for the choice of treatment modality (1, 2). *HER2* is amplified or overexpressed in approximately 20% of breast cancer cases, whilst half of them express ER (3). According to currently available data, the majority of patients with ER- and HER2-positive breast cancer should be treated with chemotherapy, trastuzumab and endocrine treatment (1, 2). However, in a significant proportion of this breast cancer sub-population, the disease progresses, highlighting the need for new targeted-agents. Knowledge of molecular biomarkers related to prognosis seems to be crucial in order to be able to devise new treatment strategies and improve the clinical outcome of ER- and HER2-positive breast cancer.

A potential candidate biomarker is the mesenchymal-epithelial transition factor (MET), a receptor tyrosine kinase which plays a significant role in cell survival, angiogenesis, growth and metastasis (4). MET and its physiological ligand, the hepatocyte growth factor (HGF) or scatter factor, are significantly overexpressed in a variety of carcinomas, including renal, lung, breast, colorectal, and head and neck cancer (4-6). Regarding breast cancer, *MET* copy number elevations were observed in 8% of early breast carcinomas and were more likely to occur in patients with triple-negative breast cancer (TNBC) (p=0.019); of note, patients with tumors harboring an elevated *MET* copy number tended to have worse 5-year recurrence-free survival (RFS) (p=0.06) (7). Additionally, our research team has independently evaluated MET expression in TNBC, showing that 52% of

tumors exhibited high MET expression and that MET was an independent prognostic factor for recurrence [adjusted hazard ratio (HR) for recurrence=3.43; 95% confidence interval (CI)=1.65 to 7.12; p=0.001] and death (adjusted HR for death=3.74; 95% CI=1.65 to 8.46; p=0.002) (3). Because of its key function in cellular processes, MET is currently under investigation as a potential target for anticancer therapy. However, to our knowledge, there are no data regarding MET expression in patients with ER- and HER2-positive breast cancer.

The purpose of the present study was to determine the prognostic value of tumor MET expression in patients with ER- and HER2-positive breast cancer in order to investigate the potential for targeted therapy using MET inhibitors in this subgroup population.

Patients and Methods

Patients. Adequate formalin-fixed, paraffin-embedded tumor blocks, clinical history, and follow-up data from 78 incident cases of pathologically-confirmed patients diagnosed with ER- and HER2-positive breast cancer were collected from the Department of Obstetrics and Gynaecology, Alexandra Hospital, Medical School, University of Athens, Greece and from the First Propaedeutic Surgical Department, Hippocrateio Hospital, University of Athens, Greece. Clinical information (including the patient's age, menopausal status, tumor size, lymph node status, and tumor grade) and primary treatment (including surgery, radiotherapy, and chemotherapy) was extracted from the medical records. Exclusion criteria were: ER- or HER2-negative status, *in situ* lesions, family history of breast cancer (so as to obtain a clear picture of sporadic cancer), ethnicity other than Greek, inadequate tissue and lack of signed informed consent.

Written informed consent was obtained by all participants in the study. The study was carried out in accordance with the Helsinki Declaration and was approved by the local Institutional Review Board.

Tumor block collection. For the current research project, the participating pathologist was asked to provide a representative formalin-fixed, paraffin-embedded tumor block from each patient. All tumor specimens were obtained at the time of surgery before adjuvant therapy. Paraffin blocks were stored at room temperature and were identified only by an identification number. A hematoxylin/eosin-stained section of each tumor block was prepared and used for pathological confirmation of invasive breast cancer. Further 4-μm sections were obtained for the immunohistochemical analysis.

Immunostaining for MET. Immunohistochemistry was performed and evaluated in an ISO certified lab at the Department of Medicine I, Medical University of Vienna, by means of a standard protocol. Briefly, tissue sections were de-paraffinized and rehydrated. To reduce non-specific background staining, slides were incubated in 0.3% H_2O_2 for 10 min. For epitope retrieval, specimens were heated for 10 min in 10 mM citrate buffer (pH 6.0) in a pressure cooker. After incubation with Ultra V Block (UltraVision LP detection system; Lab Vision Corporation, Thermo Fisher Scientific Inc., Pittsburgh, MA, USA) for 5 min at room temperature to block background staining, the tissues were incubated for 30 min at room temperature with a rabbit monoclonal antibody specific for MET (CONFIRM Anti-Total c-MET, SP44, ready-to-use; Ventana, Oro Valley, AZ, USA). Antibody binding was detected by means of the UltraVision LP detection system according to the manufacturer's recommendations (Lab Vision Corporation). Color development was performed with 3-3'-diaminobenzidine and counterstain with hematoxylin. Sections of TNBC specimens known to express MET served as external positive controls.

Expression of MET was examined by an investigator who was blinded to clinical data of the patients. At least 100 tumor cells per case were evaluated. Immunostaining was classified based on membranous staining intensity and percentage of MET-positive tumor cells. Staining intensity was scored as 0 (absent), 1 (weak) and 2 (intermediate), 3 (strong). For comparison with clinical parameters and survival, expression levels of MET were dichotomized into 'high' and 'low' expression. In order to be classified as high, tumor sections were required to have intermediate or strong membranous staining in 50% or more of invasive tumor cells. In addition to the above, the Allred score for MET expression was calculated (8).

Immunostaining for ER, progesterone receptor (PR), HER2. A centralized histological review of all cases and controls has been performed. For immunohistochemistry, the following antibodies were used: ER (ID5; Dako, Glostrup, Denmark), PR (636; Dako, Glostrup, Denmark) and HER2 (CB11; Novocastra, Newcastle upon Tyne, United Kingdom). After de-paraffinization in xylene and hydration in graded ethanol solutions, the sections of breast carcinoma tissue were subjected to pre-treatment in order to enhance antigen retrieval. The EnVision+ System-HRP (DAB) (Dako, Glostrup, Denmark) was used with primary antibodies against the following antigens: ER, PR and HER2. Immunohistochemistry was performed according to the protocols provided by the manufacturer. Regarding the immunohistochemical expression of ER and PR, both the intensity (negative, 1+ to 3+) and percentage of immunopositive cells were evaluated. Subsequently, the Allred score was calculated (8). Tumors with any detectable (≥1%) expression of ER or PR by immunohistochemistry were considered hormone receptor-positive (9).

The expression of HER2 was assessed as follows: i) negative, when no staining was documented or when membranous staining was present in fewer than 10% of tumor cells; ii) weak staining (+) when partial membranous staining was documented in more than 10% of tumor cells; iii) moderate staining (++) when weak/moderate complete membranous staining was present in more than 10% of tumor cells; and iv) strong staining when strong, complete membranous staining was observed in more than 10% of tumor cells. Cases with negative and weak HER2 staining were considered negative, whereas cases with strong HER2 staining were considered positive. In cases with moderate staining, chromogenic *in situ* hybridization was performed; subsequently these cases were considered as negative or positive.

In all cases, 10 fields (×40 magnification) were assessed and a minimum of 100 cells were evaluated in the designated areas so as to appraise the lesion as a whole.

Statistical analyses. Survival time was defined as the period between the date of surgery and death (overall survival, OS) or the period between the date of surgery and date of first local/distant recurrence or last follow-up (RFS). Patients who died before experiencing disease recurrence were censored at their date of death in the analysis.

The study protocol treated RFS as the primary end-point of our study, whereas OS was treated as a secondary end-point. The association between MET protein expression and RFS/OS was evaluated by means of two alternative analyses. Firstly, MET expression was treated as a continuous variable (Allred score); to this end, univariate Cox regression analysis was performed. Secondly, cases with high (*cf.* above) MET expression were compared to those with low MET expression, with the appropriate log-rank test; nevertheless, the fact that only three cases exhibited high MET expression substantially limited the power of statistical tests and thus the second analysis should be considered exploratory.

Finally, the associations between MET expression score with baseline clinicopathological parameters were examined with the use of non-parametric statistical tests; specifically, Spearman's rank correlation coefficient was calculated for continuous/ordinal variables, whereas the Mann–Whitney–Wilcoxon (MWW) test for independent samples or Kruskal–Wallis test was conducted regarding categorical variables. All reported *p*-values are two-sided and the level of statistical significance was set at 0.05. All analyses were performed with the use of STATA software, version 11.1 (Stata Corp., College Station, TX, USA).

Results

Seventy-eight tumor blocks were of sufficient amount and quality for sectioning. Protein expression of MET was evaluated in these 78 specimens and all further statistical analyses were performed on this patient population. Patients' characteristics are given in Table I.

We assessed tumor MET expression using standard immunohistochemistry. Immunostaining of MET was membranous and partly cytoplasmatic. Only membranous staining was used for evaluation. Out of the 78 tumors, 3 (3.8%) exhibited high MET expression.

MET Allred score was not associated with baseline parameters of patients. Specifically, regarding the associations between MET score and continuous/ordinal variables, the Spearman's rho values (*p*-values in parentheses) were: –0.06 (p=0.590) for age, –0.01 (p=0.922) for T-stage, 0.09 (p=0.453) for N-stage, –0.17 (p=0.146) for grade, –0.04 (p=0.748) for ER Allred score, 0.15 (p=0.194) for PR Allred score and 0.09 (p=0.459) for Ki-67 percentage of expression. Accordingly, concerning the categorical clinicopathological variables, MET expression score was not associated with menopausal status (p=0.191, MWW), histological type (p=0.743, MWW), contralateral breast cancer (p=0.988, MWW) and did not modify the subsequent administration of trastuzumab (p=0.850, MWW), nor the administration of radiotherapy (p=0.518, MWW) or chemotherapy (p=0.841, Kruskal-Wallis test).

The association between MET expression score and OS did not reach statistical significance (HR=1.32 per unit increase in MET expression score, 95% CI=0.91-1.90, p=0.141); neither did its association with RFS (HR=1.22 per unit increase in MET expression score, 95% CI=0.91-1.63, p=0.188). The explorative analysis treating MET expression

Table I. *Patients' characteristics.*

Characteristic	All patients, N=78 (%)
Age at diagnosis (years)	
Median (mean)	57 (57.8)
Range	31-82
Menopausal status	
Premenopausal	20 (25.6)
Postmenopausal	58 (74.4)
Tumor size	
T1	33 (42.4)
T2	35 (44.9)
T3	7 (8.9)
T4	3 (3.8)
Lymph node status	
N0	35 (44.9)
N1	19 (24.4)
N2	8 (10.2)
N3	16 (20.5)
Tumor grade	
G1	2 (2.5)
G2	30 (38.5)
G3	46 (59.0)
Histology	
Ductal	70 (89.7)
Lobular	8 (10.3)
MET Allred score	
Median (mean)	0 (1.73)
Range	0-6
ER Allred score	
Median (mean)	7 (6.46)
Range	4-8
PR Allred score	
Median (mean)	4 (3.41)
Range	0-8
Ki-67 (%)	
Median (mean)	22.5 (26.2)
Range	2-80
Chemotherapy	
No chemotherapy	1 (1.3)
Anthracyclines	7 (8.9)
Taxanes	8 (10.3)
Anthracyclines plus taxanes	58 (74.3)
CMF	4 (5.2)
Trastuzumab	
Yes	71 (91.1)
No	7 (8.9)
Radiotherapy	
Yes	53 (67.9)
No	25 (32.1)
Contralateral breast cancer	
Yes	3 (3.8)
No	75 (96.2)
Second malignancy	
Yes	0 (0)
No	78 (100)

ER=Estrogen receptor, PR=progesterone receptor, HER2=human epidermal growth factor receptor 2, CMF=cyclophosphamide/methotrexate/fluorouracil.

as a dichotomized variable (high *vs*. low) replicated the aforementioned results regarding both OS (p=0.659, log-rank test) and RFS (p=0.528, log-rank test).

Discussion

In our study, we demonstrated that ER- and HER2-positive breast carcinomas do not exhibit high MET expression. This null finding, the first to be reported in the literature, is of great importance, since it indicates that this sub-group population is not a proper candidate for clinical trials with MET inhibitors. Our finding of low MET expression in ER- and HER2-positive breast cancer is in contrast with its high expression in TNBC, found independently by our research team.

The MET expression in breast cancer reported in the literature varies between 15-28% (7, 10-14). However, these reports included all subtypes of breast cancer and were not restricted to ER- and HER2-positive breast cancer. Interestingly enough, it was noted that 52% of tumors in TNBC exhibit high MET expression and that MET is an independent prognostic factor for recurrence in these tumor types (3).

The MET signaling pathway is frequently altered in human cancer and represents an attractive target for antitumor treatment. A number of studies have shown that aberrant MET signaling caused by genetic abnormalities can induce human cancer. When endogenous MET was replaced by mutated MET in the mouse germ line, the mutations caused a variety of tumors, including carcinomas, sarcomas and lymphomas (15). Of note, when expressed in the mammary gland, they can cause basal-like breast carcinomas (16). Moreover, taking into consideration that aberrant MET is associated with progression and metastasis, and that in several types of solid tumors, including gastric, esophageal and breast cancer, amplification of MET (on chromosome 7q31) may occur (7, 18, 19), it is rational to target the *MET* signaling pathway for cancer treatment.

The clinical relevance of MET inhibitors is currently under investigation, and tivantinib and onartuzumab are the main representatives (4). Tivantinib (ARQ 197) is an oral, selective, non-adenosine triphosphate competitive MET inhibitor with promising antitumor activity (20-24). Onartuzumab (MetMAb, OA-5D5) is a one-armed monoclonal antibody developed to bind to and inhibit MET receptor tyrosine kinase. From phase I and II trials it seems that this agent is well-tolerated and has promising antitumor activity in diseases thought to be driven by aberrant MET signaling (25-27). Tivantinib, as well as onartuzumab, inhibit proliferation and induce apoptosis in cell lines derived from several types of human cancer, including small cell lung, prostate, breast, pancreatic and renal cell carcinoma, as well as glioblastoma and osteosarcoma.

The results of clinical trials evaluating MET inhibitors in breast cancer are anticipated with great interest. A phase II trial evaluating tivantinib in patients with recurrent or metastatic TNBC (ClinicalTrials.gov Identifier: NCT01575522) and a randomized phase II study examining the safety and efficacy of onartuzumab and/or bevacizumab in combination with paclitaxel in patients with metastatic TNBC (ClinicalTrials.gov Identifier: NCT01186991) are ongoing.

In conclusion, the low expression of MET in ER- and HER2-positive breast cancer indicates that this subgroup population seems not to be the best candidate for clinical trials with MET inhibitors. Despite the possible predictive value of MET status in TNBC and the clinical relevance of MET inhibitors in patients with cancer, if other studies replicate our findings, inhibition of MET does not seem to be the propar therapeutic strategy in this population and further evaluation may not be warranted.

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