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EDITORIAL COMMENTARY

PET imaging of HER-2-positive tumours

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Human epidermal growth factor receptor 2 (HER-2; neu, c-erb-B2) is a transmembrane protein and a member of the erbB family of receptor tyrosine kinase proteins that amplifies the signal provided by other members of the HER family (HER-1, HER-3, and HER-4) by forming heterodimers with them. Overexpression of HER-2 increases tumorigenicity, production of vascular endothelial growth factor, angiogenesis and metastatic potential, and it also confers a survival advantage on cancer cells by making them resistant to apoptosis induced by certain proapoptotic stimuli. HER-2 is amplified and overexpressed in 20–30% of breast cancers, and is also overexpressed in other tumours, including ovarian, lung, gastric and oral cancers.

Several studies have found that breast cancers that overexpress HER-2 have a more aggressive course and are associated with a higher relapse rate and mortality rate [1]. Therefore HER-2 has great value as a prognostic indicator of patient survival, as a molecular target for therapeutic intervention and as a predictive marker of response to antineoplastic drugs. Indeed, previous studies have shown that agents that target HER-2 are remarkably effective both in the metastatic and adjuvant settings in breast cancer. Trastuzumab, a humanized monoclonal antibody, improves response rates, time to progression and even survival when used alone or added to chemotherapy in patients with stage IV disease. Moreover, in recent years several targeted agents have become available including lapatinib, a selective, reversible dual inhibitor of the epidermal growth factor receptor (EGFR; HER-1) and HER-2 [2].

However, HER-2 tumour expression can vary during treatment and can differ across metastatic lesions, and also between primary tumour and distant localization within a patient. This is well documented in breast cancer, where a change in HER-2 status has been reported in up to 38% of patients, raising questions about the validity of making decisions concerning the use of trastuzumab based on the HER-2 status of the primary tumour alone [3–5]. Furthermore, the assessment of HER-2 status is still plagued by a high rate of false-positive and false-negative results, leading to the administration of unnecessary therapies (that could be associated with side effects, such as serious cardiac toxicity), and to the termination of effective treatments, respectively [6, 7]. Therefore there is the need for methods that are able to assess the HER-2 status repeatedly, preferably in all lesions and noninvasively. HER-2 imaging through radioisotope-labelled trastuzumab-like molecules could be very useful in this setting.

Currently available HER-2 targeted ligands include full-length monoclonal antibodies, Fab fragments, $F(ab')_2$ fragments, diabodies, minibodies, Affibodies and peptides. When radiolabelling these HER-2-targeted molecules, the physical half-life of the radioisotope ideally should suit the biological half-life of the HER-2-targeting molecules to allow imaging at the optimal time-point. Thus full-length monoclonal antibodies are mostly radiolabelled with long-lived isotopes, while the smaller HER-2-targeting molecules, which have a more rapid clearance, are radiolabelled with shorter-lived isotopes. ^{111}In, ^{131}I and ^{99m}Tc have been used to label full-length HER-2 monoclonal antibodies and smaller HER-2-targeting antibody fragments, proteins and peptides for SPECT/gamma camera imaging. Moreover, full-length monoclonal antibodies have been labelled with

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^{124}I, ^{86}Y, ^{76}Br and ^{89}Zr for HER-2 PET imaging, and ^{18}F, ^{68}Ga, ^{64}Cu, ^{124}I and ^{76}Br have been used to label smaller HER-2-targeting molecules for the same purpose [8, 9]. Among the small HER-2-targeting proteins, Affibody molecules have received significant attention. They are engineered small proteins with 58 amino acid residues (about 7 kDa molecular weight) and a three-helix bundle structure, and are derived from one of the IgG-binding domains of staphylococcal protein A [10]. HER-2-binding Affibody molecules have been successfully developed and studied in conjunction with a various radiolabels for diagnostic imaging applications.

In the present issue of the *EJNMMI*, Kramer-Marek at al. report on the ability of a ^{68}Ga-DOTA Affibody molecule to detect different levels of HER-2 expression in subcutaneous human breast cancer tumours implanted in athymic nude mice. The authors observed a good correlation between PET imaging, biodistribution estimates of tracer concentration and the receptor expression [11]. These results are not unexpected, as the authors demonstrated in a previous study that ^{18}F-labelled Affibody molecules can be used successfully in the assessment of HER-2 expression in vivo and in monitoring its possible change in response to therapeutic interventions [12]. However, the use of ^{68}Ga is very attractive as it is continuously available at a reasonable cost from ^{68}Ge/^{68}Ga generators. The 270-day half-life of the parent allows the use of a generator for a long period, potentially up to 1 year or even longer; this could be of great benefit especially for centres without a cyclotron [13].

Miao et al, in their article published in this issue of the *EJNMMI*, focused on the development of a ^{18}F-labelled two-helix scaffold protein for PET imaging of HER-2-positive tumours. The authors injected ^{18}F-FBO-MUT-DS into nude mice bearing subcutaneous SKOV3 xenografts with high levels of HER-2 expression. In vivo small-animal PET showed fast tumour targeting, high tumour accumulation and good tumour to normal tissue contrast, demonstrating that the two-helix scaffold proteins are suitable for use in the development of ^{18}F-based PET probes [14]. The two-helix scaffold proteins are two-thirds the size of the three-helix anti-HER-2 Affibodies and preserve high HER-2-binding affinity. The expected advantages of smaller protein constructs include potentially lower immunogenic potential, fast clearance rate, quick tumour accumulation and relatively short in vivo biological half-life [10]. The preclinical evaluation of these tracers is a crucial phase in their development. Unfortunately, their clinical use is still limited. Indeed, few articles are available in the literature regarding the molecular imaging of HER-2-expressing tumour, with either SPECT or PET.

For instance, Baum et al. found that ^{111}In- or ^{68}Ga-labelled Affibody molecules have the potential to localize metastatic lesions in vivo, to provide qualitative information not available from conventional imaging techniques, and possibly to allow the HER-2 status of metastases not amenable to biopsy to be determined [15]. Dijkers et al. demonstrated that PET scanning after administration of ^{89}Zr-trastuzumab at appropriate doses allows visualization and quantification of uptake in HER-2-positive lesions in patients with metastatic breast cancer, even in the brain [16]. A feasibility study in a greater number of patients (Baum et al. and Dijkers et al. enrolled only 3 and 14 patients, respectively) is needed to clarify the optimal dosage and, for long-lived isotopes, the best time for image acquisition after radiotracer administration. This could be performed in patients with newly diagnosed breast cancer, in order to evaluate the HER-2 expression of primary tumours in vivo (in comparison with immunohistochemical outcome), of locoregional lymph nodes and, eventually, of synchronous metastases. A single examination could indeed offer a complete picture of the heterogeneity of HER-2 expression in metastatic breast cancer. Moreover, patients with a location suspicious of disease and found a long time after the first diagnosis of breast cancer could also be enrolled in a validation study of HER-2 PET. These patients are generally submitted to a confirmatory biopsy, that is also used to reassess hormonal receptors and HER-2 status; so, even in this case, there could be a comparison between PET data and histopathological results. Finally, this imaging modality could be useful in selecting patients who could benefit from HER-2-targeted therapies, and could also be validated in other types of cancer.

References

1. Meric-Bernstam F, Hung MC. Advances in targeting human epidermal growth factor receptor-2 signaling for cancer therapy. Clin Cancer Res. 2006;12:6326–30.
2. Alvarez RH, Valero V, Hortobagyi GN. Emerging targeted therapies for breast cancer. J Clin Oncol. 2010;28:3366–79.
3. Simmons C, Miller N, Geddie W, Gianfelice D, Oldfield M, Dranitsaris G, et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Ann Oncol. 2009;20:1499–504.
4. Zidan J, Dashkovsky I, Stayerman C, Basher W, Cozacov C, Hadary A. Comparison of HER-2 overexpression in primary breast cancer and metastatic sites and its effect on biological targeting therapy of metastatic disease. Br J Cancer. 2005;93:552–6.
5. Khasraw M, Brogi E, Seidman AD. The need to examine metastatic tissue at the time of progression of breast cancer: is re-biopsy a necessity or a luxury? Curr Oncol Rep. 2011;13:17–25.
6. Viale G. Integrating molecular profiling, histological type and other variables: defining the fingerprint of responsiveness to treatment. Breast. 2009;18:S32–6.
7. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007;25:118–45.

8. Smith TA. Towards detecting the HER-2 receptor and metabolic changes induced by HER-2 targeted therapies using medical imaging. Br J Radiol. 2010;83:638–44.
9. Dijkers EC, de Vries EG, Kosterink JG, Brouwers AH, Lub-de Hooge MN. Immunoscintigraphy as potential tool in the clinical evaluation of HER2/neu targeted therapy. Curr Pharm Des. 2008;14:3348–62.
10. Webster JM, Zhang R, Gambhir SS, Cheng Z, Syud FA. Engineered two-helix small proteins for molecular recognition. Chembiochem. 2009;10:1293–6.
11. Kramer-Marek G, Shenoy N, Seidel J, Griffiths GL, Choyke P, Capala J. 68Ga-DOTA-Affibody molecule for in vivo assessment of HER2/neu expression with PET. Eur J Nucl Med Mol Imaging. 2011. doi:10.1007/s00259-011-1810-4.
12. Kramer-Marek G, Kiesewetter DO, Capala J. Changes in HER2 expression in breast cancer xenografts after therapy can be quantified using PET and 18F-labeled Affibody molecules. J Nucl Med. 2009;50:1131–9.
13. Breeman WA, Verbruggen AM. The 68Ge/68Ga generator has high potential, but when can we use 68Ga-labelled tracers in clinical routine? Eur J Nucl Med Mol Imaging. 2007;34:978–81.
14. Miao Z, Ren G, Jiang L, Liu H, Webster JM, Zhang R, et al. A novel 18F-labeled two-helix scaffold protein for PET imaging of HER2-positive tumor. Eur J Nucl Med Mol Imaging. 2011. doi:10.1007/s00259-011-1879-9.
15. Baum RP, Prasad V, Müller D, Schuchardt C, Orlava A, Wennborg A, et al. Molecular imaging of HER2-expressing malignant tumors in breast cancer patients using synthetic 111In- or 68Ga-labeled Affibody molecules. J Nucl Med. 2010;51:892–7.
16. Dijkers EC, Oude Munnink TH, Kosterink JG, Browers AH, Jager PL, de Jong JR, et al. Biodistribution of 89Zr-trastuzumab and PET imaging of HER2-positive lesions in patients with metastatic breast cancer. Clin Pharmacol Ther. 2010;87:586–92.