Predicting pathological complete response in breast cancer early

Baseline staging with $[^{18}F]$-fluorodeoxyglucose ($[^{18}F]$-FDG) PET-CT scans can enable better patient selection before randomisation in neoadjuvant trials by excluding those patients with occult distant metastases and poor prognosis. A second potential role for PET-CT is its ability to provide an early prediction of pathological complete response to neoadjuvant treatment. During the past decade, several single-institution studies have shown a correlation between early changes in $[^{18}F]$-FDG primary tumour uptake (change in the standardised uptake value [ΔSUV]) after one or two courses of chemotherapy and the extent of pathological response at completion of treatment. However, the ability to implement $[^{18}F]$-FDG PET-CT as a surrogate marker for treatment efficacy has remained unclear because of substantial heterogeneity across studies, and also because breast cancer was assessed as a single entity. Breast cancer actually comprises various phenotypes with different responses to chemotherapy, treatment options, and prognoses. We therefore suggested that the clinical aims of early $[^{18}F]$-FDG monitoring and the criteria used to predict efficacy should be established for separate subgroups: oestrogen receptor-positive and HER2-negative breast cancer, HER2-positive breast cancer, and triple-negative breast cancer. In these three subtypes, Humbert and colleagues reported that the change in breast tumour SUV, after the first course of neoadjuvant chemotherapy, was predictive of pathological complete response in the HER2-positive subgroup.

In the neoadjuvant setting, patients with HER2-positive breast cancer receive trastuzumab plus chemotherapy. Recent studies have shown that dual inhibition of HER2 (trastuzumab plus lapatinib or trastuzumab plus pertuzumab) improves the proportion of patients achieving a pathological complete response. Another approach has used bevacizumab together with trastuzumab and chemotherapy. However, these treatment strategies might also entail increased side-effects, hence the importance of patient selection.

In The Lancet Oncology, Bruno Coudert and colleagues report the results of the multicentre AVATAHERXER study, in which they assessed the benefit of adding bevacizumab to the standard treatment regimen when patients with HER2-positive breast cancer are predicted to be poor responders to trastuzumab plus docetaxel according to $[^{18}F]$-FDG PET early assessment. Of 142 patients, 69 were predicted to be responders to standard therapy according to the change in $[^{18}F]$-FDG uptake after one treatment cycle. In these patients, pathological complete responses were noted in 37 (53.6%, 95% CI 41.2–65.7) patients. Of the 73 patients predicted to be poor responders, pathological complete responses were noted in six (24.0%, 9.4–45.1) of the 25 patients randomly allocated to standard treatment.
alone and 21 (43.8%; 29.5–58.8) of the 48 patients who also received bevacizumab in their treatment regimen.

These results are encouraging. However, although pathological complete response is a strong predictor of patient outcome, when pathological complete response is increased by a new treatment it does not necessarily lead to improved patient survival. The GeparQuinto study7 showed that, in patients with triple-negative breast cancer, the addition of bevacizumab to an anthracycline–taxane-based neoadjuvant chemotherapy increased the proportion of patients achieving a pathological complete response but did not affect disease-free or overall survival. Whether or not the increase in pathological complete response recorded with bevacizumab in the AVATAXHER study will translate into a survival benefit remains to be seen with longer follow-up. However, at present, it is clear that PET early assessment can identify non-responders to neoadjuvant docetaxel plus trastuzumab therapy.

The positive predictive value for ΔSUVmax to predict pathological complete response was 52.9% (95% CI 40.6–64.9) and the negative predictive value was 75.0% (53.3–90.2), which leaves room for further improvement.5 Indeed, whether or not the change in SUVmax is the optimum approach for earlier response assessment in the specific subgroup of HER2-positive breast cancer remains uncertain. We recently reported that the absolute value of SUVmax measured after two courses of chemotherapy was more predictive of pathological complete response than was ΔSUVmax.9 We also showed that, during response assessment with PET, additional analysis of lymph nodes would further improve PET-based prediction in patients with the HER2-positive subtype.9

The interesting findings from the AVATAXHER study draw attention to the possibilities offered by 18F-FDG PET-CT in another aggressive subtype of breast cancer: triple-negative breast cancer. Triple-negative breast cancer often shows high 18F-FDG uptake at baseline and we noted that ΔSUVmax was the best PET parameter to predict pathological complete response after two courses of treatment with epirubicin and cyclophosphamide.10 Importantly, the change in tumour SUV was an indicator of event-free survival. In the 32 predicted responders, pathological complete responses were noted in 59.0% of patients and the 3-year event-free survival was 77.5%. However, in the 18 predicted non-responders, no patients had a pathological complete response and the 3-year event-free survival was 47.1%.10 On the basis of these findings, we are planning a multicentre trial using 18F-FDG PET to adapt neoadjuvant treatment in patients with triple-negative breast cancer.

With the encouraging results from AVATAXHER, the role of 18F-FDG PET in the initial management of patients with breast cancer will probably increase in the coming years. However, the wider view of 18F-FDG PET and SUV use for early tailoring of treatment in the neoadjuvant setting needs standardisation. Preparation procedures and instrumental factors can introduce slight differences in the measurement of SUV. In a given patient, the two PET examinations must be done at the same centre with the same equipment and methods. Therefore, breast oncologists and specialists in PET imaging need to create an international group to optimise PET procedures and define clear criteria of responses for each subtype of breast cancer.

David Groheux
Nuclear Medicine Department, Saint-Louis Hospital, 1 Avenue Claude Vellefaux, 75475 Paris Cedex 10, France
dgroheux@yahoo.fr
I declare no competing interests.