CASE REPORT

Can maintenance trastuzumab be stopped in patients with HER2-positive metastatic breast cancer?

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Accepted 9 May 2015

SUMMARY

Trastuzumab has significantly improved the median survival of patients with HER2-positive breast cancer. In metastatic disease, maintenance trastuzumab is usually given after tumour response has been achieved with the combination of chemotherapy and trastuzumab, with the aim of prolonging time to disease progression. We report a case where a durable complete response (CR) was achieved without maintenance trastuzumab. In the absence of consensus guidelines, it is difficult to recommend which HER2-positive patients with metastatic breast cancer after CR will benefit from withdrawing maintenance trastuzumab therapy and when this could be considered.

BACKGROUND

Primary metastatic breast cancer (MBC), defined as the presence of distant metastases within 3 months of the initial diagnosis of breast cancer, is rare and comprises 3–10% of all breast cancers.[1] The advent of trastuzumab, a humanised monoclonal antibody against the HER2 protein, has revolutionised and greatly improved the natural history and survival of patients with HER2-positive MBC. Prolonged CR from MBC is frequently observed while patients are on extended trastuzumab therapy.[2] However, a few reports exist of patients who achieved a sustained CR without subsequent maintenance trastuzumab. What is not known is whether there is a subgroup of patients with HER2-positive MBC who achieve sustained CR, where discontinuation of maintenance trastuzumab could be considered.

CASE PRESENTATION

A 70-year-old woman presented to The Queen Elizabeth Hospital with a self-detected left (L) breast lump. She had a background history of hypertension, vitamin B_{12} deficiency and a ventriculoperitoneal shunt for normal pressure hydrocephalus 6 years earlier. She had no family history of breast cancer but had been using hormone replacement therapy for 5 years prior to the diagnosis of breast cancer. Mammography and breast ultrasound confirmed the presence of a suspicious 30–40 mm lesion located in the left upper outer quadrant of the breast associated with (L) axillary lymphadenopathy. Core biopsy of the breast and axillary lymph node (LN) confirmed malignancy. CT staging showed extensive axillary lymphadenopathy in addition to numerous small (1–2 mm) indeterminate bilateral parenchymal lung nodules.

The patient underwent (L) mastectomy and axillary LN dissection. Histology revealed a 70 mm, grade 3, invasive carcinoma of no specific type, which was oestrogen and progesterone receptor negative. A high level of HER2 gene amplification was demonstrated by chromogenic in situ hybridisation (CISH) with >10 HER2 gene copy number per 40 cells detected. All 33 LN analysed were positive for metastatic involvement. The patient was then referred for systemic therapy. In view of the indeterminate nature of the numerous lung nodules evident on the preoperative CT, a repeat CT of the chest/abdomen/pelvis was performed, which showed mediastinal and hilar lymphadenopathy, an increase in number and size of the numerous pulmonary nodules, and multiple hypodensities within the liver, all consistent with metastatic disease (figures 1 and 2). Palliative chemotherapy was started with paclitaxel 80 mg/m^2 weekly, and trastuzumab 4 mg/kg loading dose followed by 2 mg/kg weekly. In total, the patient had only five doses of weekly paclitaxel over a 3-month period. Omission of paclitaxel was required on three occasions, due to the toxicities, of grade 2 diarrhoea or fatigue. Weekly trastuzumab was given regularly with no treatment delays. A restaging CT scan prior to week 8 of trastuzumab revealed marked radiological response with near complete resolution of pulmonary and liver metastases. In view of the significant radiological response to treatment and difficulty tolerating paclitaxel, treatment was changed to 3-weekly trastuzumab monotherapy. However, a subsequent gated blood pool scan indicated a

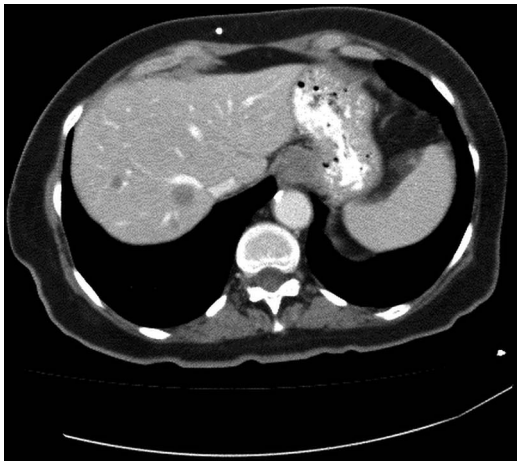

Figure 1 Baseline CT of metastatic liver lesions.

To cite: Hsieh A, Pittman K, Patterson WK, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2014-207750

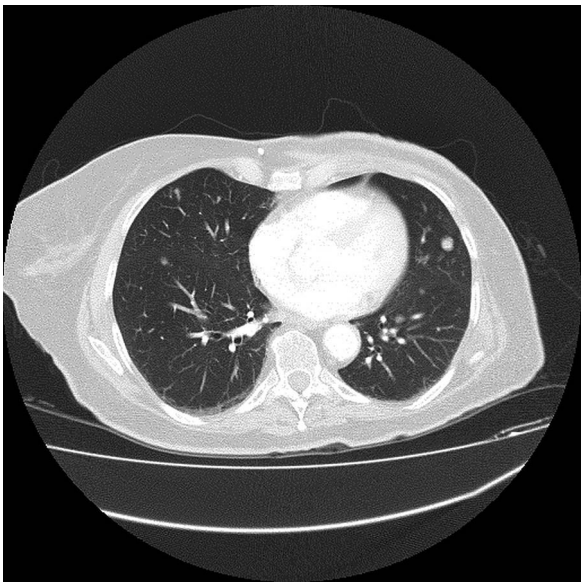

Figure 2 Baseline CT of metastatic lung lesion.

decline in left ventricular ejection fraction (LVEF) from a baseline of 70% to 50%. As a result, trastuzumab was not administered for the next 6 weeks. Despite this, CT restaging 2 months later showed complete radiological response with no evidence of metastatic disease. LVEF remained depressed on repeat gated heart pool scan at 50%, and the decision was made to permanently cease trastuzumab after discussion with the patient. The total cumulative dose of trastuzumab administered was 1170 mg. On serial follow-up since ceasing treatment over 6.5 years, the patient has remained progression-free (figures 3 and 4).

DISCUSSION

Despite the advent of many new-targeted therapies, the average survival after diagnosis of MBC is approximately 2 years.[3] Patients with HER2-positive breast cancer previously had a poorer prognosis. However, this has significantly improved since the development and routine use of trastuzumab. The combination of trastuzumab and a taxane in the first-line treatment of MBC results in an overall response rate (RR) of 49–73%.[4–8] CR rates achieved from the combination of trastuzumab and chemotherapy have been reported to be between 7 and 17% and long-term survivors are increasingly being recognised.[9–12] Following combination treatment with trastuzumab and chemotherapy, trastuzumab is traditionally continued until disease progression with many patients remaining on maintenance trastuzumab for many years.[12–14]

The case presented here is of a patient who achieved a durable CR to trastuzumab-based therapy despite receiving only a short course of treatment and no maintenance therapy. While this is an unusual outcome and not considered standard care, it does illustrate that there is a group of patients who have exquisitely sensitive tumours and respond rapidly to trastuzumab-based therapy. This case raises a number of questions regarding the management of HER2-positive MBC. Can we predict in advance which patients will achieve durable control of their disease with trastuzumab-based therapy? Can trastuzumab maintenance treatment safely be stopped? In which patients and when? And are there any guidelines available to aid clinicians in making these decisions?

The US cohort study, registHER, recently identified 244 long-term survivors from the 1001 patients with HER2-positive MBC entered on the registry. Seventy-one per cent of long-term survivors had achieved a CR to first-line therapy, and the median progression-free survival (PFS) was 37 months. Long-term survivors were more likely to present with de novo MBC, have hormone receptor (HR) positive disease, have bone or local disease (no visceral disease), and have received a taxane and trastuzumab as their first-line therapy.[15] A small retrospective study identified 11 patients who achieved a durable CR (lasting ≥36 months) out of a total of 120 (9%) with HER2-positive MBC; these patients were more likely to have HR-negative disease and liver only metastases.[11] These results, which fail to define a consistent subgroup based on clinical factors, suggest that those with durable CR likely represent a distinct molecular subgroup, and molecular analysis of these tumour samples will be important.

A number of potential biomarkers and imaging techniques have been assessed in an attempt to predict patients who will achieve the greatest benefit from trastuzumab. The degree of

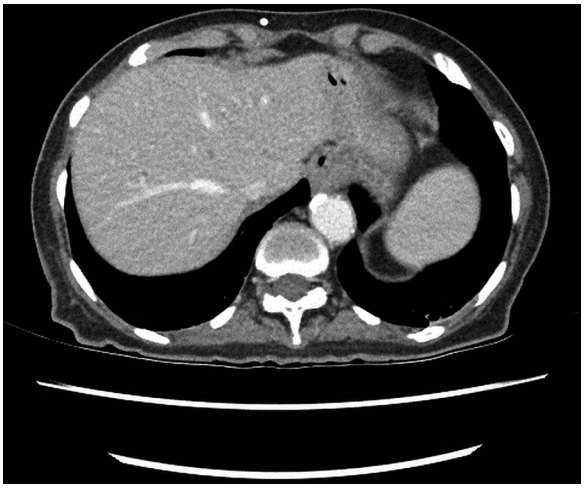

Figure 3 Follow-up CT of liver—no metastases.

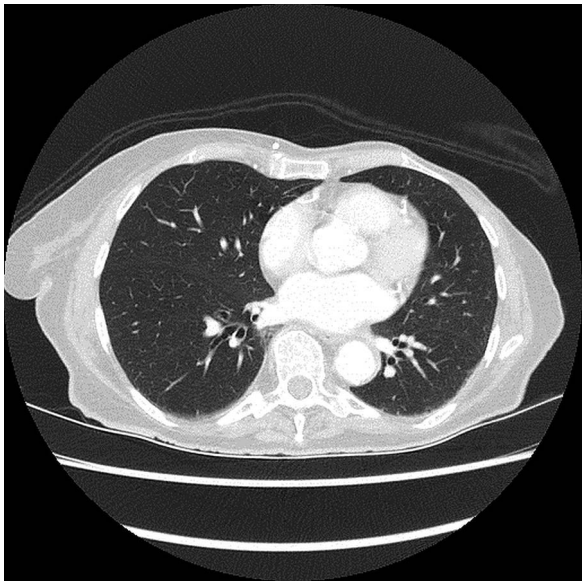

Figure 4 Follow-up CT of lung—no metastases.

HER 2 gene amplification has been associated with response to trastuzumab with high HER2 gene copy number associated with increased rates of pathological CR (pCR) following neoadjuvant treatment as well as improved CR and progression-free survival in metastatic disease, when compared to those with low HER2 gene copy number.[16–18] Interestingly, high levels of HER2 gene amplification are also associated with HR-negative disease and grade 3 tumours, as in this case.[19] HER2 enriched tumours, as assessed using the PAM50 intrinsic molecular subtyping, also achieve higher pCR rates to neoadjuvant therapy compared to the other PAM50 molecular subtypes, and in metastatic disease, those with HER2 enriched tumours were more likely to persist on single agent trastuzumab or lapatinib.[16 20] In addition, 18F-fluorodeoxyglucose positron emission tomography (PET)/CT to look for 'metabolic responders', characterised by reduction in SUVmax <2.1 in the primary tumour as early as 2–6 weeks after trastuzumab administration in the neoadjuvant setting, may identify patients with an increased likelihood of pCR to trastuzumab-based therapy.[21–23] Currently, none of these methods are used in clinical decision-making and future confirmatory studies will be required to determine the utility of these biomarkers and the role of PET in selecting patients who may be suitable to cease trastuzumab maintenance.

Historically, chemotherapy for most 'solid' cancers was not considered a curative approach. Since the introduction of anti-HER2 therapy, we see a proportion of patients who have prolonged clinical CR. Therefore, in those patients with ongoing durable CR can maintenance trastuzumab safely be stopped and when? Some investigators have attempted to define this. A retrospective study from two institutions included 84 HER2-positive patients with MBC and found 15% achieved a CR to trastuzumab and 9% remained in durable CR. One institution ceased maintenance trastuzumab after 2 years while the other withdrew trastuzumab after at least 5 years of maintenance therapy. A higher proportion of patients with durable CR were observed in the institution that administered maintenance trastuzumab for the longer duration of 5 years as opposed to 2 years (11% vs 6%). This occurred despite the frequency of CR rates achieved in the two institutions being similar at 15–16% post completion of combination therapy with chemotherapy and trastuzumab. Furthermore, the duration of PFS was also longer in the institution administering 5 years of maintenance trastuzumab (7–10.2 years) compared with the institution administering 2 years maintenance trastuzumab (3.1–3.7 years).[9] Although the study is not a prospective study and is of relatively small numbers, these findings suggest the duration of maintenance trastuzumab administered may be important in altering the natural course of HER2-positive MBC.

At present, there is a lack of internationally recognised consensus guidelines from any of the recognised cancer organisations available to assist in the decision to cease maintenance trastuzumab.[12] The current American Society of Clinical Oncology (ASCO) guidelines conclude that adequate data are not available to provide a statement on when to stop administering trastuzumab.[24] Currently, most clinicians do not stop maintenance trastuzumab unless contraindicated.[10 13] This case report, however, illustrates that in some circumstances no detrimental effect is seen after stopping trastuzumab and that there is likely to be a subgroup of patients where this is appropriate.

Currently, there are also no biomarkers available to predict those patients likely to achieve a durable CR following trastuzumab-based therapy and, therefore, when to consider ceasing maintenance trastuzumab. Potential predictive profiles may include high HER2 gene amplification, or HER2 enriched tumours on molecular subtyping, but future studies will be required to better define this group. In the meantime, for those patients who have remained in durable CR for a number of years on maintenance trastuzumab, any decision to cease trastuzumab will need to be considered carefully and most would recommend follow-up to involve an 'active surveillance' protocol. In the future, increasing numbers of patients will be on dual HER2 blockade, which will further increase the cost of maintenance therapy and the length of maintenance therapy will seriously need to be considered.

Learning points

- Combination therapy with chemotherapy and trastuzumab is beneficial in treating patients with HER2-positive metastatic breast cancer.
- Durable complete response can be achieved.
- The optimal duration of maintenance trastuzumab prior to considering stopping is yet to be defined.
- Predictive biomarkers or robust functional imaging is required, together with guidelines, to assist future decision-making.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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