Possible Radiation Sensitisation by Trastuzumab Leading to Radiation-Induced Myelitis

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Key Words

Breast cancer · Chemotherapy · External beam radiotherapy · Trastuzumab · Radiosensitisation

Summary

Background: Trastuzumab is used as adjuvant treatment in patients with HER2-positive breast cancers and has been shown to reduce the chance of recurrence by up to 50%. However, experience with it given with radiotherapy is limited and there is in vitro evidence of a radiosensitisation effect. We describe the first case of trastuzumab-associated radiation-induced myelitis. **Case Report:** This patient received a calculated dose of 28 Gy to the spinal cord when receiving adjuvant radiotherapy to the chest wall and supraclavicular and axillary lymph nodes. This is well below the accepted radiation tolerance of the spinal cord (50–60 Gy) but she developed radiation-induced myelitis of her spinal cord with characteristic magnetic resonance imaging changes. We postulate that trastuzumab given concurrently with radiation may have acted as a radiosensitiser and that normal repair mechanisms in the acute stage were affected by trastuzumab blockage of epidermal growth factor receptors, resulting in demyelination at a lower dose of radiation than normally seen. **Conclusions:** Concomitant radiotherapy and adjuvant trastuzumab treatment should be given with caution and consideration made of delaying trastuzumab until after radiotherapy has been completed. As longer-term data become available for patients who received trastuzumab and radiation, it will become clearer whether there is a significant interaction on organs such as the heart and spinal cord in the radiation field.

Schlüsselwörter

Brustkrebs · Chemotherapie · Externe Bestrahlung · Trastuzumab · Radiosensibilisierung

Zusammenfassung

Hintergrund: Trastuzumab wird zur adjuvanten Behandlung von Patientinnen mit HER2-positivem Mammakarzinom eingesetzt. Es hat sich gezeigt, dass Trastuzumab die Rückfallrate um bis zu 50% reduziert. Es gibt jedoch nur begrenzte Erfahrungen mit Trastuzumab, wenn zusammen mit einer Radiotherapie verabreicht, und In-vitro-Hinweise deuten auf einen Radiosensibilisierungseffekt. Wir beschreiben den ersten Fall einer Trastuzumab-assoziierten bestrahlungsinduzierten Myelitis. **Fallbericht:** Die Patientin erhielt eine adjuvante Radiotherapie der Brustwand und der supraklavikulären und axillären Lymphknoten, die Wirbelsäule erhielt dabei eine kalkulierte Dosis von 28 Gy. Diese Bestrahlung lag weit unterhalb der akzeptierten Toleranzgrenze für Bestrahlungen der Wirbelsäule (50–60 Gy), dennoch entwickelte die Patientin eine bestrahlungsinduzierte Myelitis der Wirbelsäule mit den charakteristischen Veränderungen der Magnetresonanzbilder. Wir postulieren, dass die Trastuzumab-Gabe gleichzeitig mit einer Bestrahlung zu einer Radiosensibilisierung geführt hat und dass normale Reparaturmechanismen in der akuten Phase durch die Blockade von epidermalen Wachstumsfaktorrezeptoren beeinflusst wurden. Dies führte zu einer Demyelinisierung schon bei einer geringeren Strahlungs-dosis, als sonst üblicherweise zu beobachten ist. **Schlussfolgerungen:** Radiotherapie mit gleichzeitiger adjuvanter Behandlung mit Trastuzumab sollte mit Vorsicht verabreicht werden. Es sollte erwogen werden, die Trastuzumab-Gabe auf einen Zeitpunkt zu verschieben, wenn die Radiotherapie abgeschlossen ist. Sobald längerfristige Daten über Patientinnen verfügbar werden, die Trastuzumab und Bestrahlung erhalten haben, wird deutlicher werden, ob es eine signifikante Interaktion im Bezug auf Organe wie Herz und Wirbelsäule im Bestrahlungsfeld gibt.

Introduction

We describe the first case to our knowledge of trastuzumab-associated radiation-induced myelopathy. Whilst trastuzumab has been shown in HER2-positive cancer to reduce recurrence by 50% and death by 30% [1], information on its interaction with radiotherapy is limited. We report a case from our centre that may have implications on timing and planning of radiotherapy when trastuzumab is being used.

Case Report

A 66-year-old lady was found to have a suspicious area on a routine mammogram in May 2006 and, after biopsy, was found to have two carcinomas in her right breast. She underwent mastectomy and axillary node sampling in July. Pathology showed two carcinomas. The larger was 20 mm grade 1 with deep margins clear by less than 1 mm, and the second lesion was 17 mm, also grade 1 with clear margins. One of the 4 nodes sampled contained a micrometastasis (smaller than 2 mm). Oestrogen receptor status was positive and HER-2 status was reported as positive on immunohistochemistry on the sample.

She was reviewed in the oncology clinic, and adjuvant chemotherapy and trastuzumab (Herceptin®, Roche Pharma AG, Grenzach-Whylen, Germany) was advised. She was entered into the ongoing Trial of Accelerated Chemotherapy 2 (TACT2) and received 4 cycles of epirubicin and 4 cycles of capecitabine from September to December 2006, which was tolerated well apart from grade 2 diarrhoea. This necessitated a dose reduction of capecitabine for her last 2 cycles of capecitabine.

She started adjuvant trastuzumab on 9 January 2007 on completion of her chemotherapy. She was initially planned for a total of 17 doses given every 3 weeks (first dose 8 mg/kg and subsequent doses 6 mg/kg).

In February 2007 she commenced 4 weeks of adjuvant radiotherapy concurrent with trastuzumab. The treatment field included her right chest wall and axillary and supraclavicular lymph nodes in view of the close margin and positive lymph node on axillary sampling. Whilst the significance of a micrometastasis on sentinel biopsy is uncertain, a recent retrospective review has shown worse prognosis than truly node negative and it is our policy to treat these patients as node positive [2]. The radiotherapy was thus given with 4 fields, with 2 glancing fields to the chest wall and a matched supraclavicular field which extended from midline to humeral head, and the lower border was matched to the top of the glancing fields and extended to the level of the fifth thoracic vertebra. A posterior axillary field was used to bring the dose up to the axilla nodes. The total dose was 45 Gy in 20 fractions over 4 weeks, with the supraclavicular field prescribed to 1.5 cm depth using 6-MV photons.

A routine audit in pathology on HER2 samples was undertaken in April 2007. The initial immunohistochemistry result for this patient was felt to be indeterminate and the sample was analysed by fluorescence in situ hybridisation (FISH) test for gene amplification. This was negative for HER-2 receptor amplification and trastuzumab treatment was stopped on 3 April after a total of 4 doses.

The patient remained well until late June 2007 when she was readmitted to hospital with a 2-week history of urinary retention and leg weakness resulting in multiple falls and difficulty in walking. Examination showed reduced power in leg and knee flexion and extension (4 out of 5 of the Medical Research Council (MRC) scale), brisk reflexes in both lower limbs and extensor plantar responses. Magnetic resonance imaging (MRI) of the spine showed a patchy hyperintense signal within the cord, most marked on the right side at C7 to T1 and anteriorly within the cord from T3 to T5 (fig. 1). The area of cord signal abnormality closely corresponded with the fatty marrow signal change in those vertebra within the radiation treatment field. This ended inferiorly at the upper margin of T5 (fig. 2, arrow). No contrast enhancement was demonstrated following gadolinium. The rest of the spine was normal. The MRI of the spine also showed changes at the right lung apex and computed tomography of the chest confirmed marked radiation fibrosis in the upper zone of the right lung.

The patient was reviewed by the neurology service, who confirmed that the neurological and neuroradiological signs were consistent with radiation-induced myelitis affecting the cervical and upper thoracic cord. She was started on intravenous methylprednisolone 1 g for 3 days starting 29 June 2007 and then a reducing course of oral steroids. Her neurological symptoms and signs resolved over 5 days and she was discharged home. She has remained well subsequently. A repeat MRI in December 2007 showed improved appearances in the spinal cord.

The radiation prescription was reviewed and it was confirmed that a standard technique was used and that there were no dosimetry errors. This technique had never previously resulted in myelopathy. The calculated dose to the spinal cord was 28 Gy in 2-Gy equivalent fractions, when the plan was reconstructed using a phantom model.

Discussion

We describe the first case to our knowledge of trastuzumab-associated radiation-induced myelopathy. The calculated dose to the cord of 28 Gy is well below the accepted radiation tolerance of the spinal cord (50–60 Gy in 2-Gy fractions) [3]. It is accepted that some people are more sensitive to radiation (Ataxia Telangiectasia, Gardner's syndrome, Nijmegen Breakage syndrome) [4], but this patient is not known to have any predisposing factors.

Fig. 1. Axial T2-weighted imaging at **a** the cervicothoracic junction and **b** the T4 level showing myelopathic cord signal changes, predominantly right-sided at the cervicothoracic junction, and bilateral and anterior in the upper thoracic region.

Fig. 2. Sagittal T2-weighted imaging demonstrating a multifocal intrinsic high cord signal from the cervical region to T5 (arrowheads). The cord signal abnormality extends inferiorly to the lower margin of the radiation changes within the vertebral marrow at T5 (arrow).

This raises the possibility that trastuzumab acted as a radiation sensitizer in her case. Experience of trastuzumab given concurrently with radiotherapy is limited; the HERceptin Adjuvant (HERA) study started trastuzumab only once the standard radiotherapy [5] and chemotherapy (mainly anthracycline based) was completed. The other large study of adjuvant trastuzumab (National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31) [6] allowed concurrent tras-

tuzumab and radiotherapy though the radiation techniques used were not reported and, being a North American study, the radiotherapy is likely to have been conformal with a lower radiation exposure of the spinal cord. In this case, only three doses of trastuzumab were given as the tumour was subsequently found to be HER negative on FISH amplification and the initial pathology was incorrect.

There is evidence that epidermal growth factor (EGF) receptors are important in the spinal cord development and growth [7, 8]. There is also in vitro evidence that trastuzumab can have a synergistic effect with radiotherapy on oesophageal and breast carcinomas with HER-2 overexpression [9, 10]. We postulate that the concurrent trastuzumab given with radiation may have acted as a radiosensitizer, resulting in a lower threshold for radiation-induced myelitis of the portion of the spinal cord that was in the radiation field. The spinal cord is known to have two types of radiation-induced injury, an acute form resulting in demyelination and a later form with glial atrophy [11]. It is possible that the normal repair mechanisms in the acute stage were affected by trastuzumab blockage of EGF receptors, resulting in demyelination at a lower dose of radiation than normally seen.

As a result of this event, we have altered our current practice to avoid giving trastuzumab concurrently with radiotherapy. We have also altered our standard radiation plan to minimise the dose to the cord by rotating the gantry 10 degrees away from the cord on the supraclavicular field. As longer-term data becomes available for patients who received trastuzumab and radiation, it will become clearer whether there is a significant interaction on organs such as the heart and spinal cord in the radiation field.

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