A case of breast cancer with multiple lung metastases: complete response achieved after trastuzumab and weekly paclitaxel therapy and sustained over 8 years after withdrawal of these drugs

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Abstract We report a case of breast cancer with multiple metastases that achieved a complete response (CR) after trastuzumab and weekly paclitaxel (PTX) therapy and sustained CR for over 8 years after withdrawal of these drugs. The patient was a 64-year-old postmenopausal woman with a non-contributory medical history. In September 2001, she underwent a pectoral muscle-conserving mastectomy with axillary dissection for a right-sided breast cancer. The pathological diagnosis was papillotubular carcinoma, $n = 9/34$, nuclear grade 3, ly1, v0, estrogen receptor (–), progesterone receptor (–), and human epidermal growth factor receptor type 2 (3+) (pT2N2aM0-stageIIIA). Postoperative adjuvant therapy was performed using six cycles of cyclophosphamide, epirubicin, and fluorouracil. Subsequently, oral tegafur-uracil was administered, but multiple lung metastases developed in October 2002. The patient began treatment with trastuzumab and weekly PTX and achieved CR 9 months later in July 2003.

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Thus, trastuzumab and weekly PTX therapy was discontinued as per the patient's request. The treatment was changed to oral doxifluridine and a complete response had been sustained as of August 2007. Since the patient requested drug withdrawal, doxifluridine treatment was discontinued thereafter. However, there has been no recurrence even without treatment.

Keywords Breast cancer · Lung metastasis ·
Trastuzumab · Complete response

Introduction

Trastuzumab is an important drug for treatment of advanced or recurrent breast cancer positive for human epidermal growth factor receptor type 2 (HER2). Long-term clinical CR is frequently achieved by this treatment. If CR is achieved, the standard procedure is to continue the treatment. However, there are no clear criteria for continuation or completion of treatment. Thus, such decisions are made based on criteria that differ by physician and institution.

In this study, we treated a case of HER2-positive breast cancer with multiple lung metastases using trastuzumab and weekly paclitaxel (PTX) and achieved CR. The patient sustained CR for over 8 years after withdrawal of these drugs. We report this case and include a brief literature review.

Case report

The patient was a 64-year-old postmenopausal woman with a non-contributory medical history. In September 2001, she

underwent a pectoral muscle-conserving mastectomy with axillary dissection for a right-sided breast cancer. The pathological diagnosis was papillotubular carcinoma, *n*+ (9/34), nuclear grade 3, ly1, v0, estrogen receptor (ER) negative, progesterone receptor (PgR) negative (enzyme immunoassay: ER ≤ 5.0 fmol/mg of protein and PgR ≤ 5.0 fmol/mg of protein), and HER2 3+ [pT2N2aM0-stage IIIA (UICC)] (Fig. 1). Postoperative adjuvant therapy was performed using six cycles of CEF [cyclophosphamide: 75 mg/m² (day 1–14), epirubicin: 60 mg/m² (day 1 and 8), and fluorouracil 500 mg/m² (day 1 and 8), every 4 weeks]. Subsequently, oral tegafur-uracil (300 mg/day) was administered, but multiple lung metastases developed in October 2002 (Fig. 2a, b). Trastuzumab was used because our patient had HER2-positive breast cancer, multiple lung metastases, and a short-time interval until recurrence. Thus, the first-line treatment involved trastuzumab (initial administration: 4 mg/kg and second administration and onward: 2 mg/kg, every week) plus

weekly PTX [80 mg/m² (day 1, 8, and 15), every 4 weeks]. Nine months later in July 2003, imaging revealed no previous metastatic lung lesions or new metastatic lesions, and CR was achieved (Fig. 3a, b). The tumor markers (CEA and CA 15-3) were within normal limits from the preoperative stage until the time of recurrence. Our plan was to continue trastuzumab and weekly PTX after CR. However, the patient did not want to continue treatment because of the burden of outpatient visits and medical costs. We strongly recommended the patient to continue trastuzumab therapy even if chemotherapy was discontinued, but the patient declined trastuzumab monotherapy for the same reasons as the above. Since there was a high risk for recurrence if the treatment was completely discontinued, we could not approve such a request. Therefore, we discontinued trastuzumab plus weekly PTX but managed to obtain the patient's agreement to receive an oral anticancer drug, doxifluridine (600 mg/day), because of its ease of use. A complete response had been maintained as of August 2007 with the use of doxifluridine. Since the patient made a strong request for drug withdrawal, all treatment was discontinued thereafter. There has been no recurrence as of March 2012.

Fig. 1 HER2 3+ in HercepTest®

Discussion

It is often difficult to cure metastatic breast cancer and recurrent breast cancer, except for some local recurrences. The 10-year survival after chemotherapy is approximately 5 % [1, 2]. Thus, improvement of QOL and extension of survival are the objectives of treatment for metastatic breast cancer and recurrent breast cancer.

Approximately 20–30 % of breast cancer cases show HER2 protein overexpression [3], and HER2-positive breast cancer has a poor prognosis [3, 4]. However, the

Fig. 2 The patient developed multiple lung metastases 1 year and 1 month postoperatively in October 2001 (a chest X-ray, b chest CT)

Fig. 3 Imaging revealed no metastatic lung lesions, and CR was achieved in July 2003 (9 months after beginning trastuzumab and weekly PTX therapy) (**a** chest X-ray, **b** chest CT)

molecularly targeted drug trastuzumab has greatly improved the prognosis of these types of patients [5, 6].

A randomized clinical trial compared first-line trastuzumab plus docetaxel versus docetaxel alone for HER2-positive metastatic breast cancer. Trastuzumab plus docetaxel was significantly better than docetaxel alone in extending the overall survival (OS) (median 31.2 vs. 22.7 months) [5]. Another study compared trastuzumab plus paclitaxel and paclitaxel alone for HER2-positive metastatic breast cancer. The results showed that compared to paclitaxel alone, trastuzumab plus paclitaxel had a higher response rate (41 vs. 17 %), a longer duration of response (median 9.1 vs. 6.1 months), and a longer time to disease progression (median: 10.5 vs. 4.5 months) [6]. Thus, trastuzumab has become an important drug to treat HER2-positive advanced breast cancer and recurrent breast cancer. In general, a combination of trastuzumab and chemotherapy is recommended. However, high response rates of 35 and 15 % have been achieved with trastuzumab monotherapy as the first-line treatment and second-line treatment or beyond, respectively [7]. Thus, trastuzumab monotherapy can be considered depending on the patient's recurrence status.

Trastuzumab was approved in 1998 in the US and in 2001 in Japan. Since then, it has been used to treat HER2-positive metastatic breast cancer and recurrent breast cancer. In recent years, there have been reports on long-term CR in cases with metastatic or recurrent breast cancer after the use of trastuzumab [8–15]. According to these reports, the biomarkers were hormone receptor negative and HER2 positive in all cases except for one [15]. These cases required 3–7 months to achieve CR. In the patient in our study, the biomarkers were also hormone receptor negative and HER2 positive, and the patient required 9 months to achieve CR (Table 1).

A phase II trial examined a combination of neoadjuvant chemotherapy with trastuzumab for HER2-positive early breast cancer. Subpopulation analysis revealed that the pathological complete response rate was significantly higher in the hormone receptor negative group compared to the hormone receptor positive group (54.2 vs. 29.7 %, $p = 0.02$) [16]. The cases with long-term CR after using trastuzumab were mostly hormone receptor negative. The reason is thought to be that sensitivity to chemotherapy and trastuzumab is higher for HER2-positive metastatic or recurrent breast cancer cases that are hormone receptor negative.

The optimal length of time has not yet been determined for continuation of treatment after CR. In most past cases, trastuzumab has been continued after consideration of the risk of recurrence if it is discontinued. Ohta et al. [10] used trastuzumab to achieve pathological CR in lung metastasis cases, and it was discontinued thereafter. They reported on cases that had no recurrence at the time of their report, at least 2 years after its discontinuation.

If CR is achieved in cases with metastatic or recurrent breast cancer, in principal, trastuzumab and chemotherapy should be continued because there is no predictive factor that identifies recurrence risk. However, side effects are a major problem associated with continuation of chemotherapy. It is necessary to determine the pros and cons of discontinuing treatment after consideration of the condition of the disease, complaints regarding adverse events, and QOL. If patients have already achieved CR, one option is to temporarily discontinue chemotherapy and restart it if recurrence occurs.

Trastuzumab is highly effective against HER2-positive breast cancer, has no major side effect of long-term administration except cardiotoxicity, and allows the patient

Table 1 Metastatic breast cancer and recurrent breast cancer cases with long-term CR

Authors	Year of publication	Biomarker	Organ with metastasis	Duration until CR	Treatment that resulted in CR	Treatment after CR	Recurrence after CR
Eichbaum et al. [8]	2005	HR (–), HER2 (+)	Liver	4 months	T	Unknown	None
Tsutani et al. [9]	2006	HR (–), HER2 (+)	Breast, lymph node, and lung	6 months	T	T	None
Ohta et al. [10]	2001	HR (–), HER2 (+)	Lung	7 months	T	None	None
Morohashi et al. [11]	2007	HR (+/–), HER2 (+)	Liver	5 months	T + CAP	T + CAP	None
Tonini et al. [12]	2003	HR unknown, HER2 (+)	Chest wall (skin)	2 months	T	T	None
Syrios et al. [13]	2010	HR (–), HER2 (+)	Liver	6 months	T + VNR + GEM	T	None
Beda et al. [14]	2007	HR (–), HER2 (+)	Liver	4 months	T + PTX	T (3 years)	Brain metastasis 2 months after treatment discontinuation
Shigematsu et al. [15]	2011	HR (+), HER2 (+)	Lymph node	3 months	T + PTX	T + PTX (1 year) → T	None
Our case	2012	HR (–), HER2 (+)	Lung	9 months	T + PTX	Doxifluridine (4 years)	None

HR hormone receptor, HER2 human epidermal growth factor receptor type 2, T trastuzumab, CAP capecitabine, VNR vinorelbine, GEM gemcitabine, PTX paclitaxel

to maintain a high QOL. Therefore, trastuzumab should be continued even when chemotherapy is discontinued.

In our patient, chemotherapy and trastuzumab were discontinued at the patient's strong request, but there has been no recurrence up to the present. However, if long-term CR is achieved in cases with HER2-positive metastatic or recurrent breast cancer, in principal, trastuzumab and chemotherapy should be continued. Thus, our policy is to recommend the continuation of trastuzumab and chemotherapy to such patients in the future.

Conclusion

We reported the case of a patient with breast cancer with multiple metastases who achieved CR after trastuzumab and weekly PTX therapy and sustained CR for over 8 years after withdrawal of these drugs.

Conflict of interest The authors declare that they have no conflict of interest.

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