

# Central nervous system progression among patients with metastatic breast cancer responding to trastuzumab treatment

E. Shmueli\*, N. Wigler, M. Inbar

*Department of Oncology, Sourasky Medical Center, 6 Weizmann St, Tel-Aviv 64239, Israel*

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## Abstract

Central nervous system (CNS) metastases from breast cancer are common and can present as the first or solitary site of disease progression. The CNS has been reported to act as a sanctuary site that denies access to many chemotherapeutic agents. We present here, a series of 10 metastatic breast cancer patients who developed CNS metastases after an initial response to trastuzumab treatment. Forty one patients with metastatic HER2-overexpressing breast cancer, without evidence of CNS involvement prior to the initiation of trastuzumab treatment, were followed during trastuzumab treatment. A neurological evaluation was performed in those patients who developed neurological signs or symptoms during the course of treatment. The clinical course and pattern of CNS involvement in these patients are discussed. Thirty two patients (78%) showed an initial response to trastuzumab treatment. Ten (31%) of the responding patients developed either isolated CNS relapse or concurrent CNS and systemic progression at a median of 43 weeks after the initiation of trastuzumab treatment. Trastuzumab as a single agent was continued following control of brain symptoms in three patients, two showed signs of systemic disease progression at 11 and 15 weeks following the diagnosis of CNS metastases, respectively. In two other patients, trastuzumab in combination with weekly chemotherapy was continued for more than 20 weeks after CNS relapse without evidence of disease progression. The incidence of CNS involvement in our group of patients was higher than expected. With more successful and prolonged systemic anti-tumour effects achieved by novel drug combinations, the risk of developing CNS metastases might be even greater. Evaluation of prophylactic cranial irradiation strategies might be studied for high-risk patients.

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## 1. Introduction

Trastuzumab (Herceptin<sup>TM</sup>) is a recombinant humanised monoclonal antibody directed against the epidermal growth factor receptor, erbB2 (HER2). This receptor is overexpressed in 25–30% of breast cancer patients [1]. The combination of trastuzumab and chemotherapy has yielded an overall response rate of up to 71% [2–4] and is gaining wide acceptance worldwide for use in the treatment of metastatic breast cancer.

Central nervous system (CNS) metastases from breast cancer are not rare. In fact, breast cancer is the second most common source of brain metastases among cancer patients. CNS metastases can present as the first or

solitary site of disease progression, while systemic disease is well controlled. The possibility of sanctuary sites in the CNS of patients receiving chemotherapy due to poor penetration of drugs through the blood–brain barrier (BBB) has been suggested [5]. The extent to which trastuzumab crosses the BBB in humans is still unknown.

A more successful and prolonged systemic anti-tumour effect might be accompanied by a greater risk for the development of CNS metastases. We present here, a series of 10 patients with metastatic breast cancer who were treated with trastuzumab and developed CNS metastases after an initial response to treatment.

## 2. Patients and methods

Forty seven consecutive patients with metastatic HER2-overexpressing breast cancer were treated with

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\* Corresponding author. Tel.: +972-3-6973494; fax: +972-3-6974828.

E-mail address: einshmu@hotmail.com (E. Shmueli).

trastuzumab at the Tel-Aviv Sourasky Medical centre in Israel from December 1998 to November 2002. Trastuzumab was given weekly, usually in combination with weekly taxanes or vinorelbine. Trastuzumab was continued as single agent therapy when chemotherapy-associated toxicity developed. Data for six patients who had confirmed CNS involvement prior to the initiation of trastuzumab are excluded from this report.

The clinical course of patients responding to trastuzumab treatment was reviewed. Those patients whose disease subsequently progressed were classified according to the site of progression: systemic, CNS or both. CNS progression included brain metastases demonstrated on computerised tomography (CT) scan and/or magnetic resonance imaging (MRI).

A neurological evaluation was performed in patients who developed signs or symptoms of neurological involvement during the course of treatment. The patterns of CNS involvement will be discussed in this paper.

### 3. Results

Of the forty one patients who were evaluated, 32 (78%) showed an initial response to trastuzumab treatment, usually given in combination with weekly taxanes or vinorelbine. Response was defined as regression of an index lesion on imaging and/or physical examination and serum marker decline. Ten responding patients (10/32, 31%) developed CNS metastasis while on trastuzumab treatment. Their characteristics are shown in Table 1.

Four patients had concurrent CNS and systemic progression and the other six had isolated CNS relapse. The mean time interval between the initiation of trastuzumab

treatment and the diagnosis of brain metastases was 43 weeks (range 8–81 weeks).

Imaging studies of all ten patients revealed that the metastases were widespread, involving both the cerebral hemispheres and the cerebellum, and were accompanied by a surrounding oedema. One patient had impending herniation. None of the lesions showed signs of haemorrhage.

All ten patients were treated with steroids and whole brain irradiation, 3Gy×5 per week to a total dose of 30 Gy. The CNS symptoms disappeared after this treatment in eight patients, but recurred in seven patients after a short period of time (i.e. 4–15 weeks).

In three patients who had isolated CNS escape, single agent trastuzumab was continued following control of neurological symptoms by whole brain irradiation. In two of them, the disease progressed systemically at 11 and 15 weeks following the diagnosis of CNS metastases and trastuzumab therapy was stopped. In two other patients, trastuzumab in combination with weekly chemotherapy was continued after CNS relapse, and they received more than 20 weeks of additional trastuzumab without evidence of brain relapse or other systemic progression.

### 4. Discussion

Clinically overt CNS metastases are found in 10–15% of breast cancer patients [6] and in up to 30% of patients at autopsy [7]. Such metastatic spread is usually associated with a poor prognosis. CNS involvement is almost always associated with morbidity, and is detected because of neurological signs and symptoms [8].

In this study, 41 patients without CNS involvement prior to the initiation of trastuzumab treatment were

Table 1  
Patients' characteristics

| No  | Age (years) | Stage of primary | ER&PR <sup>a</sup> status |                 | DFI <sup>b</sup> (months) | Sites of metastases           | Trastuzumab (line of treatment) | Response duration <sup>c</sup> (weeks) |
|-----|-------------|------------------|---------------------------|-----------------|---------------------------|-------------------------------|---------------------------------|--|
| 1.  | 50          | T2N0             | +                         | UN <sup>d</sup> | 33                        | Supra, lung, chest wall       | Third                           | 66                                     |
| 2.  | 47          | T1N1             | +                         | —               | 78                        | Liver, bone, lung, chest wall | Second                          | 64                                     |
| 3.  | 64          | T3N2Bil          | —                         | —               | 26                        | Axillary LN, lung, bone       | Third                           | 18                                     |
| 4.  | 49          | T2N1             | UN                        | UN              | 33                        | Liver, bone                   | Fourth                          | 20                                     |
| 5.  | 55          | T2N2             | UN                        | UN              | 36                        | Liver                         | Fifth                           | 49                                     |
| 6.  | 64          | T2N1M1           | —                         | —               | —                         | Bone                          | Second                          | 61                                     |
| 7.  | 43          | T2N0             | +                         | —               | 26                        | Lung, bone                    | Second                          | 8                                      |
| 8.  | 55          | T1N1             | +                         | —               | 52                        | Liver, bone                   | First                           | 81                                     |
| 9.  | 28          | T1N0             | +                         | +               | 11                        | Liver, bone                   | Second                          | 51                                     |
| 10. | 58          | T1N0             | —                         | —               | 37                        | Liver, lung                   | Third                           | 60                                     |

LN, lymph nodes; Bil, bilateral.

<sup>a</sup> ER—Oestrogen receptor; PR, progesterone receptor.

<sup>b</sup> DFI—disease-free interval from diagnosis to first relapse (in months).

<sup>c</sup> Response duration—time interval between initiation of trastuzumab treatment to diagnosis of central nervous system (CNS) involvement (in weeks).

<sup>d</sup> UN—unknown receptor status.

followed and 32 (78%) responded to trastuzumab. Of these responding patients, 10 (31%) developed either isolated CNS relapse or concurrent CNS and systemic progression while on trastuzumab treatment. Crivellari and colleagues described similar rates of CNS involvement in patients with advanced and metastatic breast cancer responding to epirubicin and docetaxel treatment [9]. A recent report by Bendell and colleagues showed CNS metastases in 34% of metastatic breast cancer patients treated with trastuzumab at the Dana-Farber Cancer Institute [10].

Despite the small numbers of patients in the current report, the incidence of CNS involvement in this cohort is higher than expected. They also had aggressive and advanced disease, which had progressed following several (from one to four) lines of chemotherapeutic regimens. Nevertheless, they all responded to trastuzumab treatment as evaluated by objective parameters. Notably, a comparison between this group of the responding patients with the non-responders showed that CNS progression was more prevalent in these patients than in the non-responders. This might explain the longer survival rates observed in the responding patients and is a common finding in ovarian cancer [11].

The clinical presentation leading to CNS dissemination was quite similar in all ten patients. Headaches were the most common neurological symptom indicative of CNS involvement at diagnosis. Other less common symptoms were gait disturbances and dizziness. Interestingly, imaging studies showed widespread metastatic lesions involving both the hemispheres and the cerebellum accompanied by substantial oedema in all patients, but one. None of the patients had single or isolated regional CNS metastases, and none of the lesions showed signs of haemorrhage.

We suspect that CNS involvement was probably present, but asymptomatic, in some of the patients prior to trastuzumab treatment, but development of neurological signs and symptoms clearly points towards disease progression.

The phenomenon of the disease progressing in the CNS, while systemic disease is responding to treatment has been previously described in breast cancer patients receiving various chemotherapeutic regimens [9,12,13]. The CNS was reported as the first region of metastatic disease in up to 20% of metastatic breast cancer patients who had achieved a complete or partial response to chemotherapy [9,12]. Moreover, brain metastases as the first site of relapse were reported to be more prevalent in breast cancer patients receiving adjuvant chemotherapy compared with those that did not receive adjuvant chemotherapy [14–16].

The CNS has been regarded as a sanctuary site in patients receiving chemotherapy. It is not known whether trastuzumab crosses the BBB in humans. In a recent case report, the level of trastuzumab in the cerebro-spinal

fluid of a patient with meningeal spread was 300-fold lower than serum levels after an intravenous infusion, suggesting a low penetration of trastuzumab across the BBB despite possible disruption of this barrier due to the spread of the disease [17].

In conclusion, the more successful and prolonged systemic anti-tumour effect, that is now being achieved with novel drug combinations, might result in a higher risk of developing CNS metastases. Since CNS metastases are sometimes the sole site of clinical progression, and as they are frequently disabling and associated with a poor survival, future investigation into prophylactic cranial irradiation strategies in high-risk patients is warranted.

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