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SHORT COMMUNICATION

Extended survival of a HER-2-positive metastatic breast cancer patient with brain metastases also treated with intrathecal trastuzumab

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In 1991, a 38-year-old woman underwent a left mastectomy (Patey's procedure) for stage IIA breast cancer. The histological diagnosis was ductal infiltrating carcinoma, estrogen receptor (ER) and progesterone receptor (PgR) negative, the grading and the HER-2 status unknown. She received six courses of adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate and 5-fluorouracil) i.v. on days 1, 8 every 4 weeks. In September 1998 a modest increase of CA15-3 was detected and a chest and abdomen CT scan visualized three liver and one lung lesions. A biopsy of one liver lesion diagnosed metastasis of breast cancer ER and PgR negative, HER-2 3+ by immunohistochemistry (IHC). At that time trastuzumab was not approved in Italy and the patient received a first line chemotherapy with paclitaxel and doxorubicin given every 3 weeks, obtaining, after six courses, a complete remission (CR) that was consolidated with weekly trastuzumab and paclitaxel [1]. Six months later, paclitaxel was stopped and trastuzumab continued. In July 2002, the patient complained of headaches, dizziness and gait disorder and multiple brain metastases were diagnosed by MRI without evidence of other lesions (PET-CT scan negative). Whole brain radiotherapy (30 Gy in 10 fractions) was administered using 4 MV photons produced by a linear accelerator with trastuzumab on a 3-weekly schedule obtaining a partial remission (PR) of the brain lesions. In April 2003, two new brain lesions in the cerebellar lobes were diagnosed by MRI without systemic progression. The patient underwent stereotaxic radio-surgery (22 Gy) and temozolamide was added to trastuzumab. After eight courses, a CR was documented by MRI and only temozolamide was discontinued. About 8 months later a new brain lesion in the left cerebellar lobe close to the meningeal layer was diagnosed without other metastases. Temozolamide was re-started along with trastuzumab, but progression of the brain lesions was documented after 3 months. Weekly cisplatin plus capecitabine were combined to trastuzumab but her neurological conditions began to deteriorate with gait apraxia and progressive dementia due to an increase of the brain lesions but also due to the development of late effects of radiation therapy such as confluent lesions involving much of the periventricular white matter and cerebral atrophy on MRI (Fig. 1). Corticosteroids were initiated. Since the liver and lung lesions never re-appeared, this disease was considered sensitive to trastuzumab, which due to its molecular weight does not seem to pass the blood-brain barrier although, recently, it has been reported that trastuzumab levels in the cerebrospinal fluid can increase under conditions that alter the blood-brain barrier such as meningeal carcinomatosis or radiotherapy [2] Therefore, in June 2005, following the suggestion of Doctor D. J. Slamon an Ommaya ventricular catheter was inserted and intrathecal injections of trastuzumab (12.5 mg every 3 weeks) were initiated combined with intravenous trastuzumab that had never been stopped since 1999. No tumour cells were found in the cerebrospinal fluid. A

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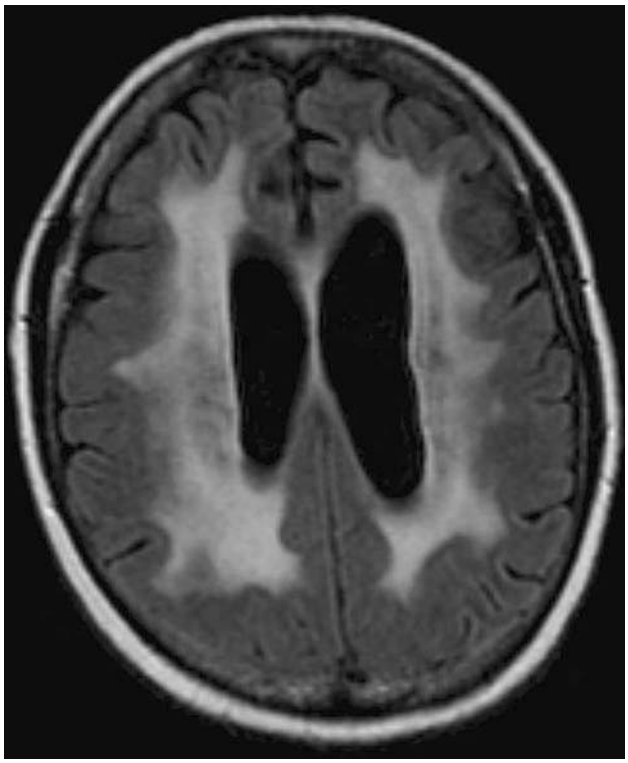

Fig. 1 Periventricular white matter lesions and cerebral atrophy

stabilization of the brain lesions was obtained and corticosteroids were gradually stopped. The patient's neurological condition improved although she requires assistance in walking and her mental status remains impaired. The treatment was continued for 19 months and 23 intrathecal injections were administered without major side effects. In February 2007, an increase of one lesion in the right cerebellar lobe and a new lesion in the right temporal lobe in contiguity to the tentorium were shown by MRI together with the stable white matter lesions. Trastuzumab was stopped and the patient was enrolled in an international extended access protocol to receive lapatinib plus capecitabine [3]. A PR has been obtained with a further slight improvement of neurological condition. In July 2008 she is still on treatment.

Discussion

Patients with HER-2 overexpressing metastatic breast cancer treated with trastuzumab and chemotherapy develop central nervous system (CNS) metastases with an incidence that varies from 28 to 42% [4–6] and for about half the patients [7, 8], they represent the only disease progression site. This progression does not result from a loss of HER-2 over-expression but may be related, among other causes, to poor trastuzumab penetration into the brain. In patients with CNS progression continuing trastuzumab in combination with alternative chemotherapeutic agents seems to prolong survival [9, 10]. In our patient a stabilization of CNS metastases was obtained for 19 months with 3 weekly intrathecal trastuzumab in combination with systemic trastuzumab with a good clinical tolerance. The efficacy of intracerebral microinfusion of trastuzumab was shown in animal models. A human breast cancer cell line transfected to over-express HER-2 was transplanted by intracerebral injection into the cerebrum of athymic rats which, were then treated with saline, trastuzumab, or an isotype-matched control MAb systemically or by intracerebral microinfusion (IMC). Trastuzumab by IMC significantly increased the median survival in this model [11]. In some clinical reports, patients with meningeal carcinomatosis received weekly intrathecal trastuzumab, at a higher dose than in our patient and in combination with intravenous chemotherapy [12–14] or intrathecal methotrexate [15]. To our knowledge, the best schedule and dose of intrathecal trastuzumab is largely unknown.

Furthermore, in our patient we observed late effects of irradiation. These side effects are observed mostly in young patients with primary CNS tumours who can survive long enough to see them, and can be correlated with total radiation dose, fractionation schemes, volume of the brain irradiated, age at the time of treatment, and use of associated chemotherapeutic agents [16]. Several patterns of white matter alteration, diffuse cerebral atrophy, radiation-induced vasculopathy, mineralizing microangiopathy, and focal areas of radiation necrosis are reported. In an attempt to better define patients who can respond to trastuzumab we retrospectively evaluated in 45 HER-2-positive metastatic breast cancer patients the EGFR, pMAPK, pAkt and PTEN status by IHC [17]. Our patient was PTEN positive (Nagata score) and pAkt negative, markers that seem to be predictive of response to trastuzumab [18].

In conclusion, we report a very unusual case of HER-2 over-expressing metastatic breast cancer. The patient obtained a CR of lung and liver metastases with an anthracycline and taxane-based regimen. After 10 years these lesions never recurred and she is still alive 72 months since the diagnosis of brain metastases treated with radiotherapy, radiosurgery, several combinations of chemotherapy and trastuzumab, intrathecal and systemic trastuzumab and the dual tyrosine kinase inhibitor lapatinib plus capecitabine.

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