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CASE REPORT

Efficacy of nab-paclitaxel plus trastuzumab in a long-surviving heavily pretreated HER2-positive breast cancer patient with brain metastases

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Abstract: Brain metastases (BMs) represent a major issue in clinical practice and are associated with a significant worsening of patient's quality of life and, often, a dismal prognosis. Breast cancer (BC) is the second most common solid malignancy that metastasizes to the central nervous system. Incidence of BM varies according to the tumor subtype, with higher rates in patients with epidermal growth factor receptor 2 (HER2) overexpression and in triple negative breast cancers. The incidence of BM in HER2-positive BC patients has increased as a consequence of the success of trastuzumab-based therapy. BM represents an emerging unmet medical need and no specific treatment options exist because, until recently, nearly all randomized clinical trials in metastatic breast cancer (MBC) excluded such patients. Therefore, novel approaches in this setting are eagerly awaited. Herein, we report a lengthy progression-free survival with the combination trastuzumab/nanoparticle albumin-bound (nab)-paclitaxel in a heavily pretreated HER2-positive BC patient with BM. The long-term disease stabilization reported in the present case (>13 months) is of note for several reasons. First, the nab-paclitaxel plus trastuzumab combination, despite several previous lines of treatment, some of which were associated with known activity on BM, was the first systemic therapy not associated with central nervous system recurrence, avoiding recourse to additional locoregional treatments. Moreover, this combination was associated with long extracranial stabilization with minimal toxicity. The remarkably lengthy progression-free survival reported in our case with the nab-paclitaxel plus trastuzumab combination further confirms the efficacy and the favorable toxicity profile of this promising schedule that showed intriguing results in two phase II studies in first-line MBC and suggests a possible activity on BM. In conclusion, weekly nab-paclitaxel plus trastuzumab may represent a valuable option in the treatment of HER2-positive MBC with BM after radiotherapy and is effective and associated with a good toxicity profile, even in heavily pretreated patients.

Keywords: HER-2, breast cancer, nab-paclitaxel, brain metastases, trastuzumab, long survivor

Background

Brain metastases (BMs) represent a major issue in clinical practice and are associated with a significant worsening of a patient's quality of life and, often, a dismal prognosis.

Breast cancer (BC) is the second most common solid malignancy that metastasizes to the central nervous system (CNS), with an estimated incidence of 10%–16% during the course of the disease, reaching up to 30% on autopsy.[1,2]

The incidence of BM varies according to the tumor subtype, with higher rates in patients with overexpression of the epidermal growth factor receptor 2 (HER2) and in triple negative BC patients. The higher tendency to CNS metastatic spread among HER2-positive BC patients is largely unknown, but it is likely multifactorial: inherent

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biologic tropism for CNS of this molecular subtype, a more aggressive nature, and the ability to produce protumorigenic and prometastatic enzymes. In addition, it has been hypothesized that the incidence of BM in HER2-positive BCs has increased as a consequence of the success of trastuzumab-based therapy. Because trastuzumab does not cross the blood–brain barrier (BBB) due to its high molecular weight (180 kDa), the growing incidence of BM among patients with metastatic breast cancer (MBC) treated with trastuzumab, especially in the setting of controlled extracranial disease, has been attributed to the more frequent diagnosis of CNS involvement that would be otherwise clinically silent before death, due to the aggressive course of the disease in the pre-trastuzumab era.[1–3] Moreover, three distinct meta-analyses of the use of trastuzumab in the adjuvant setting reported a higher incidence of CNS recurrence and an increased risk of BM as first metastatic site among HER2-positive BC patients.[4–6]

BMs represent an emerging unmet medical need and no specific treatment options exist because, until recently, nearly all randomized clinical trials in MBC excluded such patients. Therefore, novel approaches in this setting are eagerly awaited.

Herein, we report a lengthy progression-free survival (PFS) with the combination trastuzumab/nanoparticle albumin-bound (nab)-paclitaxel in a heavily pretreated HER2-positive MBC patient with BMs.

Case presentation

A 31-year-old woman underwent radical left mastectomy plus ipsilateral axillary lymphadenectomy in April 2004 because of a poorly differentiated ductal carcinoma, pT2 N3(16/23) M0. The pathology review revealed a luminal B HER2-positive BC estrogen receptor (ER): 70%; progesterone receptor (PgR): 40%; ki-67 >25%; HER2: 3+ detected by immunohistochemistry. On the basis of the biological assessment, the tumor histotype, and the disease stage, she underwent adjuvant chemotherapy with fluouracil, epirubicin, and cyclophosphamide ($FEC_{(90)}$) for six cycles, followed by locoregional radiotherapy and hormonotherapy with luteinizing hormone-releasing hormone (LHRH) analog + tamoxifen. No adjuvant trastuzumab therapy was administered because of regulatory issues.

In January 2009, follow-up imaging revealed a recurrence in the lung and then she was put on first-line metastatic therapy docetaxel (75 mg/m^2 of body surface area every 21 days) plus 3-weekly trastuzumab (with a loading dose of 8 mg/kg, followed by a maintenance dose of 6 mg/kg) for 8 months. No significant cardiac adverse events were reported.

In October 2009, there was a sudden onset of headache and dizziness. Then, a brain magnetic resonance imaging (MRI) scan was performed, documenting multiple contrast-enhancing lesions disseminated in the capsular left nucleus, in the left temporal lobe, and in the right cerebellar cortical region. The metastatic spread to the brain occurred in the context of a controlled extracranial disease. On the basis of the brain progressive disease and the substantial stability of the lung lesions, in November 2009, she received brain stereotactic radiosurgery (SRS) with Cyberknife® system (Accuray Inc, Sunnyvale, CA, USA), followed by whole-brain radiotherapy, with rapid relief of the neurological symptoms. Then, trastuzumab-based therapy was continued, with stable disease.

In May 2010, a positron emission tomography–computed tomography (PET/CT) scan confirmed stability of the lung lesions, but a brain MRI revealed further progressive disease with a novel lesion in the left cerebellar tonsil, treated with SRS with Cyberknife® system. After SRS, she continued trastuzumab-based therapy beyond CNS progression.

In February 2011, a novel brain MRI scan showed CNS progressive disease, with two additional lesions in the right temporal lobe and in the right parietal lobe and recurrence of previously treated left temporal lesion, despite stable extracranial lesion. A novel SRS on the three metastatic CNS lesions was performed. Then, trastuzumab-based therapy was discontinued and in March 2011, she began treatment with lapatinib 1,250 mg daily plus capecitabine 1,000 mg/m^2 twice daily on days 1–14 every 21 days, with a CNS partial response as a maximum response. After a PFS of 9 months, she experienced bone progressive disease in the pelvis. Thus, lapatinib therapy was switched to weekly trastuzumab plus vinorelbine (at a dose of 25 mg/m^2 of body surface area once a week), which led to disease stabilization.

A CT scan in September 2012 showed extensive progressive disease with appearance of new brain, liver, bone, and lung metastases (Figure 1). A novel SRS treatment was performed on the two novel lesions in the left frontal lobe and in the right cerebellar hemisphere and, then in November 2012, it was decided to administer a novel therapeutic line with weekly nab-paclitaxel at a dose of 125 mg/m^2, continuing weekly trastuzumab beyond progression. Four courses of nab-paclitaxel/trastuzumab therapy were delivered, with evidence of a partial response in the lung lesion, with substantial stable disease (SD) in the liver and bone metastases and a minimal response in the brain nodules (Figure 2). Hence, she continued treatment for up to 14 cycles with the same schedule with substantial stable disease (Figure 3) and minimal neurological treatment-related toxicities. A complete list of all the patient's

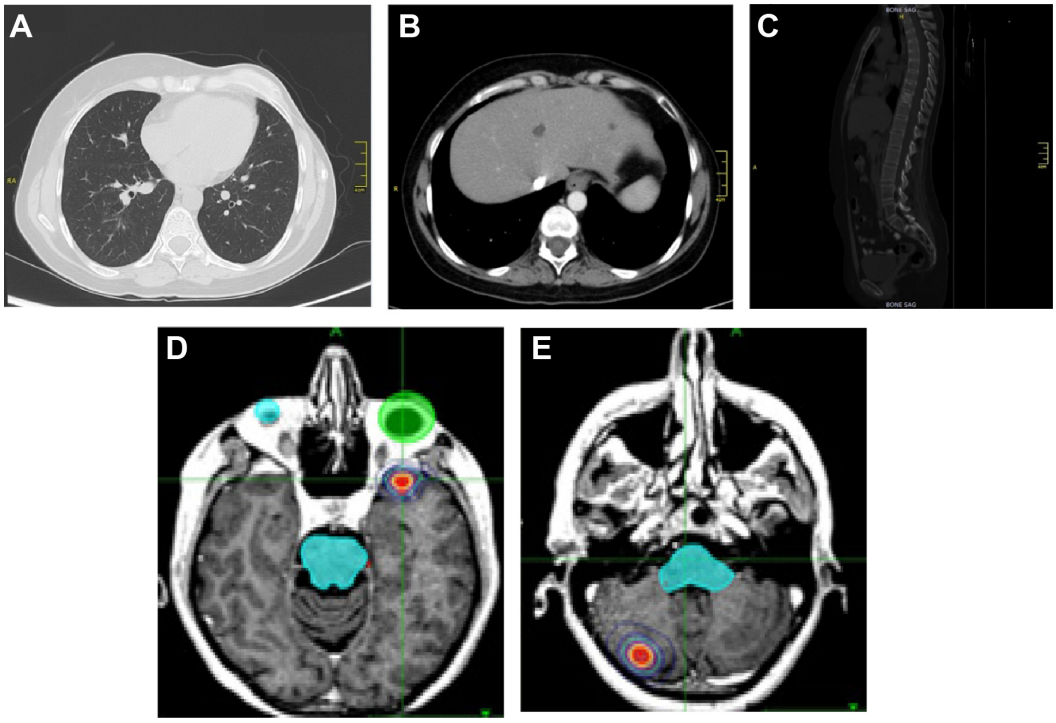

Figure 1 Lung (**A**), liver (**B**), bone (**C**), and brain (**D**, **E**) metastases before start of nab-paclitaxel/trastuzumab treatment.
Abbreviation: nab, nanoparticle albumin-bound.

treatments is reported in Figure 4. We performed a cardiological evaluation every 3 months with echocardiography, showing no cardiac dysfunction. Therefore, this combination was associated with good cardiac toxicity profile. After 13 months of substantial stable disease, she experienced further disease progression, with increase in the number and dimension of liver, brain, and pulmonary metastases, and a novel treatment was started.

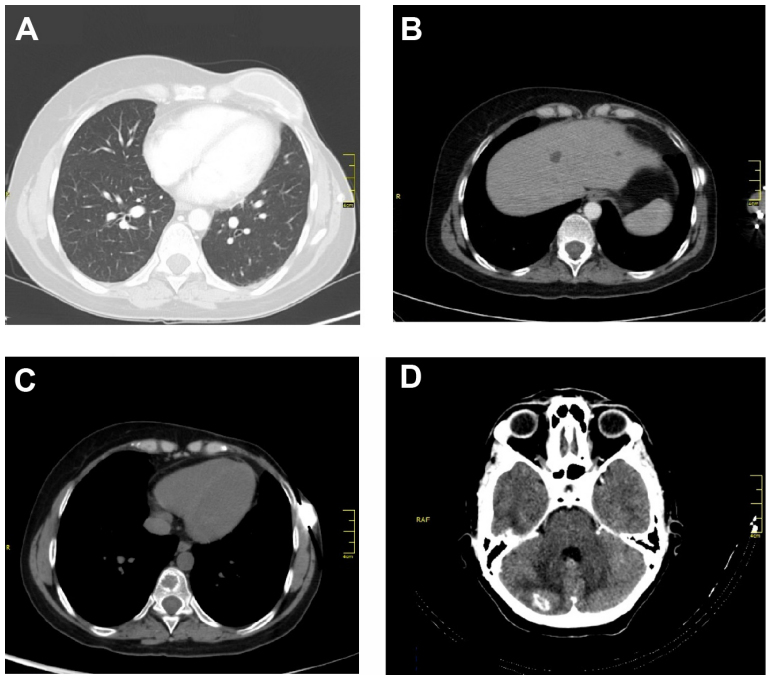

Figure 2 Lung (**A**), Liver (**B**), Bone (**C**) and Brain (**D**) lesions after four courses of nab-paclitaxel/trastuzumab combination.
Abbreviation: nab, nanoparticle albumin-bound.

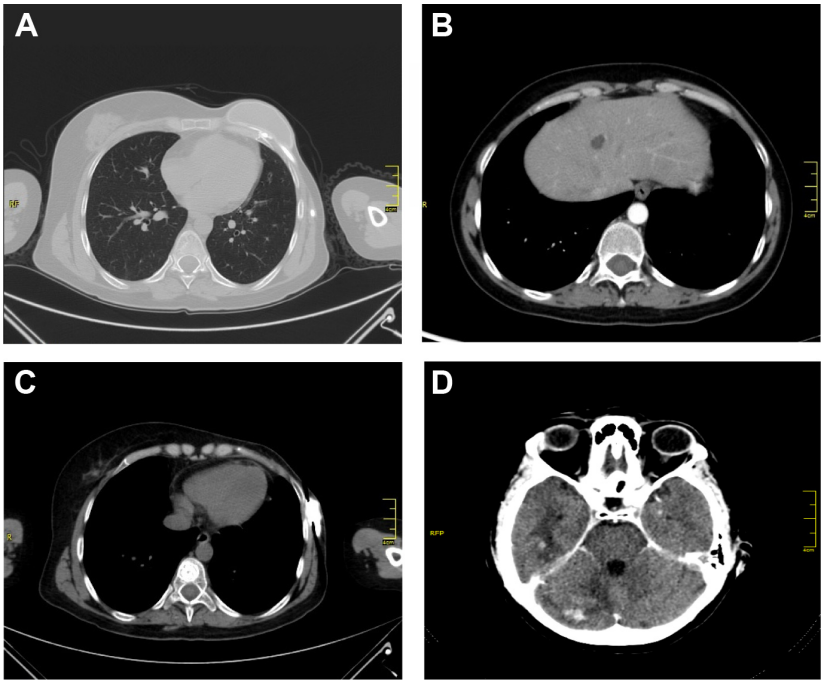

Figure 3 Lung (**A**), Liver (**B**), Bone (**C**) and Brain (**D**) lesions after nine courses of nab-paclitaxel/trastuzumab combination.
Abbreviation: nab, nanoparticle albumin-bound.

Discussion

BC is the second most common solid malignancy that metastasizes to the CNS, with an estimated incidence of 10%–16% during the course of the disease, reaching up to 30% on autopsy; however, the incidence of BM varies according to the tumor subtype, with higher rates in patients with HER2-positive and triple-negative BCs.[1,2]

Emergence of brain metastases represents one of the most life-threatening conditions in patients with HER2-positive MBC and is classically associated with a poor prognosis. Locoregional treatments, such as radiotherapy (either as whole-brain radiotherapy or as SRS), surgery or a combination of these therapies, are generally offered either for symptom palliation or with curative intent and are associated with small survival improvements.

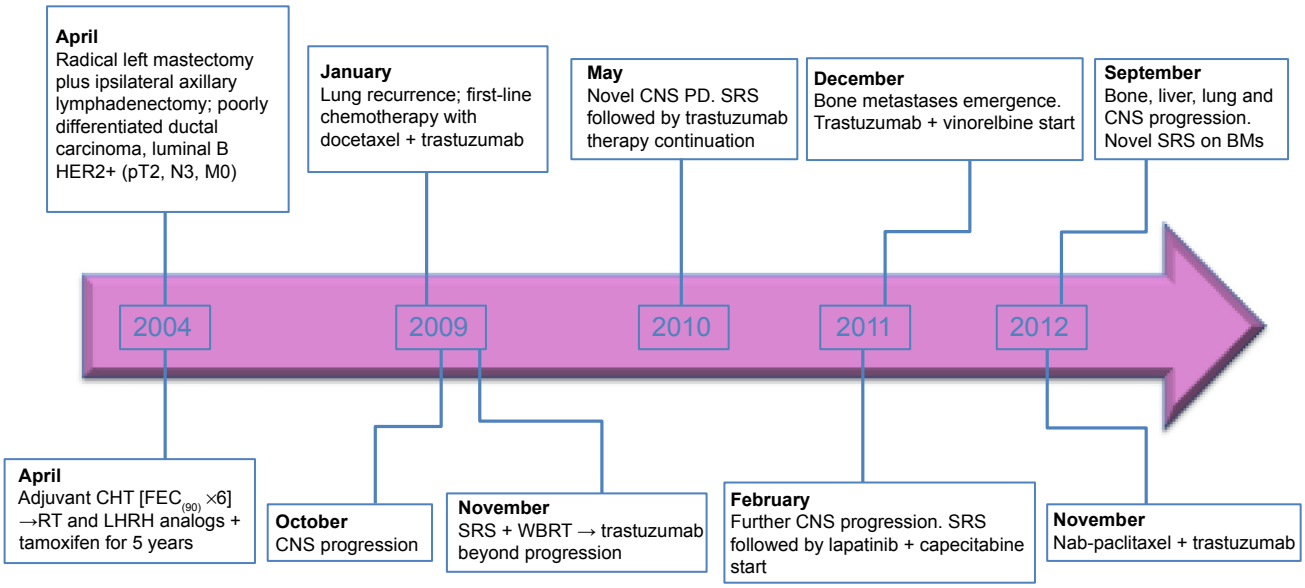

Figure 4 Timeline of patient's diagnosis and treatments.
Abbreviations: BMs, brain metastasis; CHT, chemotherapy; CNS, central nervous system; FEC, fluouracil, epirubicin, and cyclophosphamide; HER, human epidermal growth factor receptor; PD, progressive disease; SRS, stereotactic radiosurgery; nab, nanoparticle albumin-bound; LHRH, luteinizing hormone-releasing hormone; RT, radiotherapy; WBRT, whole-brain radiotherapy.

Traditionally, systemic treatments were considered mostly ineffective on BM, with only a handful of clinical responses to most standard cytotoxic drugs. These disappointing results may reflect the intrinsic increased resistance of BM, which often emerges late in the course of disease, compared with other systemic metastases, as a consequence of accumulated mutations in the metastatic tumor cells after multiple rounds of previous chemotherapies. In addition, the presence of the BBB, a multicellular vascular structure that separates the CNS from the peripheral blood circulation, prohibits an adequate brain penetration to most of the standard systemic anticancer agents, limiting their clinical efficacy, because of their chemical structure/dimensions and/or the removal by drug efflux pumps, such as the P-glycoprotein.[7,8] Brain metastases may alter the integrity of the BBB, increasing its permeability compared with that in a normal brain. However, preclinical studies support the notion that this increased permeability could not be homogeneous, with only a small subset of BM (~10%) having sufficient permeability to show a response to common cytotoxic agents, such as paclitaxel.[9] Interestingly, in a small retrospective study, a significant correlation between BC subtype and BBB disruption was reported, with HER2-positive BC tending to preserve BBB integrity compared with triple-negative and basal-like BCs.[10] In addition, the BBB permeability may be altered in patients with BM because of other perturbing factors such as radiotherapy too.[11]

Trastuzumab-based therapy is firmly established as the standard of care for patients with HER2-positive BC, demonstrating survival benefits in large, randomized clinical trials in both EBC.[12–14] Despite this impressive clinical activity, concern has been expressed that trastuzumab therapy may be associated with an increased frequency of CNS relapse.[4–6] However, retrospective studies reported that patients with HER2-overexpressing MBC who received trastuzumab after diagnosis of BM survive longer, suggesting that continuation of trastuzumab-based therapy beyond CNS progression, as shown in the present case, in patients with good performance status is beneficial in terms of survival.[15–17] From these studies, however, it is difficult to assess whether the survival benefit is attributable to systemic disease control or to an activity on BM in presence of an altered BBB.

Given its small lipophilic molecule, lapatinib can cross the BBB, and drug penetration at significant levels has been demonstrated in resected BM of patients with MBC treated with lapatinib plus capecitabine, suggesting that these drugs are capable of crossing the BBB.[18]

The long-term disease stabilization reported in the present case, for >13 months, in a heavily pretreated patient with the combination of nab-paclitaxel plus trastuzumab is of note for several reasons. First, nab-paclitaxel plus trastuzumab combination, despite several previous lines of treatment, some of which were associated with known activity on BM (ie, lapatinib plus capecitabine), was the first systemic therapy not associated with CNS recurrence, avoiding the recourse to additional locoregional treatments. Moreover, this combination was associated with long extracranial stabilization with minimal neurological toxicity. The remarkably lengthy PFS reported in our case with the nab-paclitaxel plus trastuzumab combination further confirms the efficacy and the favorable toxicity profile of this promising schedule, which showed intriguing results in two phase II studies in first-line MBC, with an ORR of 42.2%–62.5% and a median PFS of 14.5–16.6 months.[19,20] However, in these studies, patients with symptomatic BM were excluded. To date, no data were reported on a possible activity of nab-paclitaxel in the CNS. Nab-paclitaxel is a solvent-free, human albumin-stabilized formulation of paclitaxel. Its peculiar formulation allows a more rapid and deeper tissue penetration and slower elimination of nab-paclitaxel compared with solvent-based paclitaxel.[21] Our case study suggests a possible activity of this combination on BMs. In fact, the schedule in the present case was the only line of therapy not associated with further CNS recurrence, avoiding new SRS treatments. This combination reported a much longer PFS (>13 months) than previous lines of therapy.

In conclusion, weekly nab-paclitaxel plus trastuzumab may represent a valuable option in the treatment of HER2-positive MBC with BMs after radiotherapy and is effective and associated with good toxicity profile, even in heavily pretreated patients. Therefore, this option may be considered in patients with HER2-positive MBC with BM, after recurrence with standard first-line therapy, which now is represented by the trastuzumab + pertuzumab + docetaxel combination.[22] In addition, the present case further confirms the positive impact of the use of trastuzumab beyond, as emerged in the GBG 26 trial.[23]

Disclosure

The authors report no conflicts of interest in this work.

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