Does trastuzumab increase the risk of isolated CNS metastases in patients with breast cancer?

Robert J Weil*

Research shows that brain metastasis of breast cancer may occur more often in women with HER2 overexpression. These patients require more aggressive surveillance to identify disease earlier, and new therapies are needed that can overcome barriers to effective CNS drug delivery.

Metastatic central nervous system (CNS) tumours represent an important health burden and portend a poor prognosis. Clinically, 10–16% of patients with breast cancer – up to 200,000 cases yearly in the US – have symptomatic brain metastases; up to 30% of autopsies in these patients show evidence of intracranial metastases.[1,2] Survival in patients with breast cancer and metastatic CNS tumours ranges from 2 to 16 months, depending on CNS involvement, the extracranial (systemic) metastatic disease present, and the treatment used; the mean 1-year survival rate is approximately 20%.[2] Traditionally, inability to control systemic disease is the limiting factor for survival.[2] As systemic therapies improve, extracranial disease control could become less influential, a point strengthened by studies of HER2-positive patients with breast cancer treated with trastuzumab.[2,3] Nearly half the patients in one study [4] died of progressive CNS disease, with a median survival of 13 months in patients treated with trastuzumab. Other studies have shown that HER2 overexpression increases the risk of developing CNS metastasis, whether symptomatic or occult, and most of the women with this type of breast cancer had controlled extracranial disease.[2]

To explore the prevalence of and predictors for CNS metastasis among women with HER2-overexpressing metastatic breast cancer receiving trastuzumab, Burstein et al. re-examined two clinical trials of first-line trastuzumab-based therapy (see opposite). In one phase III trial of 464 patients,[3] chemotherapy was used alone or with trastuzumab, while in a phase II trial of 54 patients, chemotherapy and trastuzumab were administered. In both trials, 9–10% of patients had isolated CNS metastasis as the first sign of progressive metastatic disease, accounting for 14–16% of all disease progression. CNS metastasis occurred later than progression at other sites in both treatment arms. Overall risk of initial progression within the CNS was not lowered by addition of trastuzumab to chemotherapy. *HER2* amplification was associated with a trend toward greater risk of initial CNS progression. Simultaneous CNS and other metastases were not investigated. Additionally, follow-up was limited (<8 months in both studies) and probably led to underestimation of the true incidence of CNS metastasis. These findings have been seen with other successful chemotherapeutics for systemic breast cancer.

This study highlights important pathophysiological questions. Several molecular mechanisms have been suggested to mediate the aggressive behaviour of HER2-positive breast cancers. First, increased activation of HER2 signalling enhances cell proliferation, survival, apoptosis resistance, migration and invasion.[2] Second,

*Robert Weil is Associate Director of Laboratory Research in the Brain Tumor Institute at the Cleveland Clinic Foundation, Cleveland, Ohio, USA
This article was first published in *Nature Clinical Practice Oncology* 2006 vol. 3 no. 5, and is reproduced with permission. www.nature.com/clinicalpractice
doi:10.1038/ncponc0487,

HER2 overexpression might endow tumour cells with increased metastatic aggressiveness, and increase spread to visceral sites such as the lungs and CNS.[2] Third, by enhancing patient survival, trastuzumab might permit brain metastases to develop or become symptomatic.[4] Finally, trastuzumab is likely to be ineffective against CNS metastases because of poor penetration of the blood–brain and blood–tumour barriers.[2,4,5] The Burstein paper supports this final hypothesis, since CNS metastases continue to overexpress HER2.[2,4,5]

The clinical challenges are to define new strategies for surveillance and therapy. We need to recognise occult or minimally symptomatic disease at an earlier stage – when the CNS tumour can be more easily controlled with focused radiation and surgery – and to develop preventive or novel therapeutic biologic or chemotherapeutic agents that take advantage of molecular and biological factors to overcome the critical, innate barriers to effective CNS drug delivery, such as the blood–brain and blood–tumour barriers.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld

Synopsis

HJ Burstein, G Lieberman, DJ Slamon, et al. (2005) **Isolated central nervous system metastases in patients with HER2-overexpressing advanced breast cancer treated with first-line trastuzumab-based therapy.** *Ann Oncol* 16:1772–1777

Background. The predictors for central nervous system (CNS) metastases in women with advanced breast cancer have not been well established. It has been suggested that HER2 overexpression and therapy involving trastuzumab might be associated with a high rate of CNS metastases.

Objective. To study the prevalence and timing of occurrence of isolated CNS metastases in women with HER2-positive breast cancer receiving trastuzumab in combination with chemotherapy, and to assess the contributing effects of HER2 status and trastuzumab treatment.

Design and intervention. Two clinical trials of chemotherapy in conjunction with trastuzumab as first-line treatment for HER2-positive metastatic breast cancer were reviewed for timing and sites of first progression. Sites of progression were classified as 'isolated CNS disease' (brain or leptomeningeal metastases) or 'other'. One trial was a multicentre, randomised phase III study of chemotherapy (paclitaxel or doxorubicin plus cyclophosphamide) with or without trastuzumab. The other trial was a multicentre phase II study of vinorelbine in combination with trastuzumab.

Outcome measures. A competing risks analysis using the Cox proportional hazards model, with isolated CNS disease and progression at any other sites as the two competing risks, was used to establish time to disease progression resulting from isolated brain metastases.

Results. The initial site of tumour progression was identified in all 518 patients; isolated tumour progression occurred in the CNS in 9–10% of patients receiving first-line treatment with trastuzumab and chemotherapy. Median follow-up times in the phase III study were 7 months for women receiving trastuzumab-based therapy and 4.6 months for those receiving chemotherapy alone. Risk of isolated CNS progression was similar in women receiving trastuzumab-based therapy and those receiving chemotherapy alone (hazard ratio 0.83, 95% CI 0.45–1.54), but CNS progression was a later event than progression at other sites ($P<0.0001$). Analysing outcomes according to follow-up time available, the incidence rate of isolated CNS progression was 16.1 per 100 person-years in patients receiving trastuzumab-based treatment versus 15.7 per 100 person-years in those receiving chemotherapy alone. The incidence rate of progression at other peripheral sites was 96 per 100 person-years in the trastuzumab-based arm and 188 per 100 person-years in the chemotherapy-alone arm. The effect of *HER2* gene amplification measured by fluorescence *in situ* hybridisation (FISH) was analysed for patients in the phase III study by estimating the CNS progression-free survival from the time of primary breast cancer diagnosis. Patients with FISH-positive tumours had a greater likelihood of CNS recurrence than patients with FISH-negative tumours, but the trend was of borderline statistical significance ($P=0.09$; hazard ratio 2.14, 95% CI 0.89–5.18).

Conclusions. Isolated CNS metastases can develop in patients receiving trastuzumab-based therapy for reasons such as improved peripheral tumour control, longer survival time and the lack of penetration of trastuzumab through the blood–brain barrier.

Acknowledgement: The synopsis was written by Petra Roberts, Associate Editor, *Nature Clinical Practice*