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Anti-Tumour Treatment

A systematic review of trastuzumab and lapatinib in the treatment of women with brain metastases from HER2-positive breast cancer

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ABSTRACT

Patients with HER2-positive breast cancer are living still longer and increasingly experiencing brain metastases. Current HER2-targeted therapies have limited potential to cross the blood–brain-barrier. We performed a systematic review to investigate data on HER2-targeting therapies in the treatment of brain metastases in breast cancer. We searched PUBMED for all human studies published 1998–2012 using the following search terms: breast neoplasm/cancer, human epidermal growth factor receptor 2/HER2, ErbB2, trastuzumab, lapatinib, brain/cerebral neoplasm/metastases and blood–brain barrier. We identified few and mostly small clinical studies. Study designs were very heterogeneous making comparisons on endpoints difficult. Overall survival for patients treated with trastuzumab varied from 8 to 25 months and 5.5 to 11 months for patients receiving lapatinib. The majority of studies were retrospective thus possibly biasing data. Only three studies were identified comparing trastuzumab to lapatinib. Conclusively, no solid data exist on how to treat patients with HER2-positive disease and brain metastases. Although continuous HER2-blockade is recommended by international consensus guidelines, it is still not evident which HER2-targeting agent should be preferred when brain metastases occur. The choice of chemotherapy to accompany the blockade is not obvious and we do not know if dual is better than single blockade. Further clinical trials are urgently needed.

Introduction

Metastatic brain tumours are the most common cerebral neoplasm in adults[1] and breast cancer is the second leading cause of metastases to the brain[2,3] Only lung cancer gives rise to brain metastasis (BM) more often than breast cancer.[4] The incidence of BM in patients with breast cancer is reported to be up to 36% in autopsy data[5,6] and diagnosed in 6–16% of patients.[7–9] Factors predicting development of BM in patients with breast cancer include negative hormone receptor status, young age (<40 years), active extra cranial disease, and low performance status.[9–12] Overexpression of human epidermal growth factor receptor 2 (HER2) has shown to be an independent factor for development of BM.[13,14] The current treatment of patients with breast cancer and BM involves surgery, radiation therapy, chemotherapy and biological agents. While current standard of treating HER2-positive patients with trastuzumab in the metastatic setting is highly effective in delaying time to central nervous system (CNS) metastases,[15,16] standard treatment after diagnosis of BM is not established. This systematic review focuses on the current literature on the treatment of HER2-positive breast cancers with metastases to the brain. Focus is on the use of trastuzumab and lapatinib, both biological therapies directed against HER2.

Methods

We searched PUBMED for all human studies published 1998–2012 using the following search terms: breast neoplasm/cancer, human epidermal growth factor receptor 2/HER2, ErbB2, trastuzumab, lapatinib, brain/cerebral neoplasm/metastases and blood–brain barrier. Preclinical studies, reviews and letters to the editor were excluded. Full articles were obtained and references were checked for additional material when appropriate. In addition, abstracts from annual meetings of the American Society of

Abbreviations: ASCO, American Society of Clinical Oncology; BBB, blood brain barrier; BM, brain metastases; CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FDA, Food and Drug Administration; HER, human epidermal growth factor receptor; MBC, metastatic breast cancer; OS, overall survival; PFS, progression free survival; PR, partial response; PS, performance status; SD, stable disease; TTP, time to progression; WBRT, whole brain radiation therapy.

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Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium 2009–2011 were retrieved for relevant abstracts using the same search terms. The reference list was updated in August 2012.

The authors independently surveyed the literature. In case of uncertainty or disagreement, the complete paper was analyzed and a decision was reached by consensus. The designs of the studies were divided into "randomized controlled trial", "prospective study" (a priori fixed selection criteria), or retrospective study (register data, medical charts, etc.).

A total of 52 papers were identified. The following criteria were then applied: original studies reporting $\geqslant$15 patients, papers in English, studies focusing primarily on solid metastases excluding studies only on leptomeningeal carcinomatosis, studies reporting systemic treatment with trastuzumab or lapatinib excluding intrathecal treatment. Two papers were not included as differences in overall survival between trastuzumab and non-trastuzumab treated patients could not be determined. Conclusively, 18 papers on trastuzumab, 5 papers on lapatinib, and 3 studies comparing trastuzumab and lapatinib were included in the review (Fig. 1).

Background

HER2 is overexpressed in approximately 20% of breast cancers.[17] Several studies have shown, that BM are a frequent complication to HER2-overexpressing breast cancer[9,13,18,19] and up to 37% of patients with HER2-positive breast cancer relapse due to intracranial disease, despite control of the peripheral tumours.[8,20–22] Multifactorial effects of HER2-overexpression are likely to account for the increased risk of brain metastases.[15] Several possible explanations have been proposed. One is that HER2-positive disease is a more aggressive subtype of breast cancer with a general trend to spread to organs outside the breast.[18] Another suggestion has been a preferential homing of HER2-overexpressing cells to CNS tissue[23] although this hypothesis has not been confirmed in clinical studies. Finally, the higher incidence of BM may simply reflect the fact that patients with HER2-positive breast cancer treated with trastuzumab live longer due to extra cranial disease control and therefore, more often will experience involvement of the CNS.[15,24]

The median survival after diagnosis of BM in breast cancer patients is between three and sixteen months,[25,26] with a one year survival of approximately 20%.[27] Current treatment of BM relies primarily on whole brain radiation therapy (WBRT), chemotherapeutics and surgery. WBRT is considered a golden standard and has a proven efficacy superior to other treatment modalities. The treatment is usually given as 30 gray in ten fractions.[28]

Overview of current approved HER2 directed-therapies

Since its approval by FDA in 1998, trastuzumab (Herceptin®) (Genentech Inc. San Francisco, CA, USA; Hoffmann-La Roche Ltd., Basel, Switzerland), a humanized anti-HER2 monoclonal antibody directed against the extracellular domain of HER2, has been the standard of care for HER2-positive primary breast cancer and first-line metastatic breast cancer (MBC). In the adjuvant setting trastuzumab, has been approved in combination with chemotherapy or as single agent after anthracycline-based therapy. In this setting, adding of trastuzumab reduces the risk of recurrence by approximately 50%.[29]

In MBC trastuzumab has been approved in combination with chemotherapy or as single agent after prior chemotherapy for MBC. In the pivotal trial by Slamon et al. 469 women with HER2-positive MBC were randomized to first-line chemotherapy (doxorubicin + cyclophosphamide or paclitaxel) ± trastuzumab. Adding trastuzumab to the chemotherapeutic regimens significantly increased response rate (RR) from 32% to 50%, increased median duration of response (6–9 months) and overall survival (OS) (20–25 months).[30] The optimal combination of trastuzumab plus chemotherapy has been an area of intensive clinical investigation. In general, vinorelbine and taxane-containing regimens seem to be the most active with RR ranging from 45% to 86% with a median duration of time to progression of 7–17 months. The activity of single agent trastuzumab has been moderate with RR ranging from 15% to 26% for a median duration of 9 months.[31]

Lapatinib (Tyverb®, GW572016) (GlaxoSmithKline, Middlesex, UK) is a dual tyrosine kinase inhibitor of both HER1 and HER2. The use of lapatinib in combination with capecitabine in the second-line treatment of patients with HER2-positive MBC previously treated with trastuzumab, anthracyclines and taxane therapy has been established.[32,33] Lapatinib has been approved by FDA in 2007 in this setting. Furthermore, the compound has been approved for treatment of postmenopausal women with hormone receptor positive, HER2-positive breast cancer in combination with an aromatase inhibitor.[34]

As of June 8th 2012, Pertuzumab (2C4, Omnitarg®) (Genentech Inc. San Francisco, CA, USA) was approved by the US Food and Drug Administration (FDA) for use as first-line therapy in HER2-positive MBC in combination with trastuzumab and docetaxel. Pertuzumab is a monoclonal antibody that sterically blocks dimerisation of HER2 with HER1, 3 and 4. The drug inhibits signalling from HER2/HER1 and HER2/HER3 heterodimers.[35]

Studies on trastuzumab

Eighteen studies on treatment of BM with trastuzumab were included and are listed in Table 1. None of these were randomised trials. Except for one, all studies were retrospective and even in the one prospective study, data on the diagnosis, treatment and response of CNS metastases were collected retrospectively.[21] The number of participants in the trials ranged from 16 to 377 with the majority of the trials including fewer than one hundred patients.

Some trials included patients with MBC in general, also including patients with metastases to the central nervous system. In these publications the subgroups of patients with BM were described separately. The remaining studies focused on patients with BM exclusively, including only patients with disease progression to the brain. In general all patients enrolled had been exposed to multiple lines of chemotherapy prior to diagnosis of BM. However, study designs were quite heterogenic. Some studies compared patients who received trastuzumab before, during or after the diagnosis of BM to patients who either never received trastuzumab or to patients who had discontinued trastuzumab prior to BM diagnosis,[16,21,36–43] some compared HER2-positive patient to HER2-negative[44,45] and finally some studies did not have a comparator group.[23,46–50] Information on duration and timing of trastuzumab was unevenly reported. However, four studies did report duration of previous trastuzumab and found the mean treatment time prior to BM diagnosis to be 6–20 months (range 0–88).[37,39,43,48]

Performance status (PS) was reported in nine studies. Five studies only included patients in good PS (Eastern Cooperative Oncology Group (ECOG) 0–2)[21,36,45,46,48] and two studies included 54% and 37%, respectively, in ECOG PS $\leqslant$2.[41,42] Finally two studies included 34% and 50% of patients in Karnofsky performance status <70, respectively.[38,47]

OS was reported as time from BM diagnosis to death in all studies. Results varied from 8 to 25 months for the groups defined as having received trastuzumab versus 2–9 months for the control groups of patients not receiving trastuzumab after diagnosis of BM. However, among the control groups some patients had been treated with trastuzumab for metastatic disease prior to development of BM.[36,40,41] The study reporting the highest OS