Cancer Treatment Reviews 55 (2017) 10–15

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Systematic or Meta-analysis Studies

Systematic analysis of early phase clinical studies for patients with breast cancer: Inclusion of patients with brain metastasis

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ARTICLE INFO

Article history:
Received 4 January 2017
Received in revised form 12 February 2017
Accepted 14 February 2017

Keywords:
Breast cancer
Brain metastasis
Early phase clinical trials

ABSTRACT

Purpose: This systematic review aims to better define the limitations and patterns with which patients with MBC and CNS metastasis are enrolled into early phase developmental therapeutics trials.
Methods: In June 2016, PubMed search was conducted using the following keywords: "Breast cancer". Drug-development phase 1, phase 2 or phase 1/2 trials for patients with MBC were included. Multiple-histology trials and trials without an efficacy endpoint were excluded.
Results: In total, 1474 studies were included; Inclusion criteria for 423 (29%) allowed for CNS metastasis, 770 (52%) either excluded or did not document eligibility of patients with CNS disease. Trials accruing patients with HER2-positive MBC and including targeted therapies had higher odds of allowing for patients with CNS disease (adjusted OR 1.56, 95% CI 1.08–2.2.6; $p = 0.019$ and 1.49, 95% 1.08–2.06; $p = 0.014$, respectively). There were also higher odds of accrual of patients with CNS involvement into clinical trials over time (odds ratio = 1.10, 95% CI 1.07–1.12; $p < 0.0001$).
Most published early phase clinical trials either did not clearly document or did not allow for accrual of patients with CNS disease. Early phase trials with targeted agents or enrolling HER2+ MBC had higher odds of permitting CNS metastases.

Introduction

A significant number of patients presenting with metastatic breast (MBC) will eventually develop central nervous system (CNS) metastasis as these patients have an estimated risk of CNS involvement as high as 14% [1]. Prior to improvements in targeted therapy and radiation therapy techniques, patients presenting with CNS metastasis had a median overall survival of less than 6 months [2,3]. Of note multiple intracerebral metastases at presentation limit surgical approaches and emphasizes the need for drug development [4]. Recently, the American Society of Clinical Oncology endorsed the combination of tyrosine kinase inhibitor lapatinib and capecitabine therapy HER2+ MBC in patients with asymptomatic, low-volume brain metastases who have not received radiation therapy as a first-line treatment option [5]. Despite the estimated objective intracranial response rate of 66%; approximately 50% of patients experience grade 3 or grade 4 treatment-related adverse events [6].

Conversely new-targeted therapies continue to improve clinical outcomes of patients for a subset of patients MBC without CNS lesions (i.e.; HER2 directed monoclonal antibodies and cyclin dependent kinase inhibitors) [7,8]. Patients with HER2+ primary MBC cancer have a risk of 35–50% to develop metastatic brain disease. Similarly, metastatic triple negative breast cancer (TNBC) also harbors an increased risk of CNS involvement (approximately 46%) [9]. While remarkable advances in drug development improved control of some subtypes of MBC, improvement in the treatment of patients with CNS metastasis has been stagnant. For instance trastuzumab (a monoclonal antibody targeted against the HER2 oncoprotein) has been approved for the treatment of patients with HER2+ MBC since the 1998; at least one clinical trial is ongoing and

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http://dx.doi.org/10.1016/j.ctrv.2017.02.006
0305-7372/

studies its efficacy for the treatment of intracranial metastasis (NCT02536339). Remarkably, patients with a preserved performance status and CNS metastasis remain excluded from participation in early phase clinical trials based assumed lack of efficacy in the treatment of intracranial lesions with therapies primarily directed towards extracranial metastatic disease [10]. The goal of this systematic review is to better define the limitations and patterns with which patients with MBC and concomitant CNS metastasis are enrolled into early phase clinical trials for patients with MBC.

Methods

Search strategy

Phase 1, 2 and phase 1/2 clinical trials were identified by a PubMed search using the following keyword "breast cancer". A filter for phase 1 and phase 2 clinical trials was used. No language limit was used. The database was searched for articles published up to June 2nd 2016.

Selection of trials and data extraction

Clinical trials were required to meet the following inclusion criterion: (i) phase 1, phase 2 or phase 1/2 trials for patients with MBC. Early phase multiple-histology trials were excluded.

For clinical trials meeting the inclusion criterion, the first author's name, year publication, and study phase (1, 2, 1/2) were documented. Clinical trials were classified according to breast cancer type included in the following manner: (i) HER2+ regardless of hormonal receptor (HR) status, (ii) HR+HER2-, (iii) ER/PR/HER2-negative or TNBC, (iv) any immuhistochemically defined subtype of breast cancer and, (v) HER2-regardless of HR status. Type of breast cancer therapy was classified as follows: (i) chemotherapy, (ii) targeted therapies including anti-angiogenic therapy, (iii) anti-estrogen therapy, (iv) immunotherapy, and (v) other (i.e.; systemic supportive therapies, drugs with undefined mechanisms of action, etc.). Eligibility for enrollment of patients with concurrent CNS MBC was performed as follows: (i) allowed if previously treated for CNS disease, (ii) allowed even without previous CNS-directed treatment, (iii) not documented, (iv) not allowed with CNS radiologic imaging required prior to study entry, (v) not allowed with CNS radiologic imaging not required prior to study entry, (vi) not allowed if leptomenigeal disease (LMD) present. For manuscripts meeting inclusion criteria both the methods (inclusion criteria) and results sections (patient population accrued) were reviewed for appropriate classification study classification. Trials aiming to study drugs targeting CNS metastatic disease and required CNS involvement at study entry were also reviewed but not included in statistical analyzes. All PubMed titles from our search were reviewed by two independent. Discrepancies between the two investigators were resolved by combined review of manuscript.

Statistical methods

One outcome variable [CNS involvement, three categories ((i) allowed, (ii) not allowed, and (iii) not documented)]and four covariates (cancer type, therapy type, phase of study and year) were analyzed. Descriptive analyses of the three outcome categories and each of the covariates was done using cross tabulations and chi-square tests. Linear trend over time was estimated using an odds ratio (change in odds of CNS involvement per one year increment) in a univariate logistic regression. Correlations between the outcome and covariates were analyzed by dichotomizing the outcome to be CNS disease allowed or not. For each covariate (except year), a dichotomous variable was created for each category to be that category versus all the other categories. The correlation between the two dichotomous variables was analyzed using univariate and multivariate (adjusting linearly for year) logistic regression. Odds ratios, 95% confidence intervals and p-values were calculated using the odds of CNS disease allowed in the covariate category of interest divided by the odds of CNS disease allowed in all other categories of that covariate. Trials published in 2016 were excluded from year-adjusted analysis as total number of publications was not yet available for 2016.

Results

Study inclusion and characteristics

Our search yielded 3145 publications. Articles in Japanese ($n = 34$), Chinese ($n = 1$), and German ($n = 1$) were excluded as translators were not available for these languages. 3109 articles were reviewed including articles in Spanish ($n = 1$), Russian ($n = 3$), and French ($n = 2$). All other articles were published in English. 1474 studies published between 1992 and 2016 met inclusion criterion and data were extracted (Fig. 1). Most of the early phase clinical trial (64%) treated patients with chemotherapy followed by targeted therapies (23%). Immunotherapy trials encompassed only 39 out of 1474 (2.6%) trials reviewed (Table 1). Trials, which enrolled patients with HER2+ MBC, represented 11% of the trials published and the majority of patients (74%) enrolled had any type of breast carcinoma; trials for patients with HR+, HER2− MBC represented only 7% of the. Phase 2 and phase 1 trials represented 82% and 11% of the studies reviewed, respectively. Of note 39 studies required patients with solid tumors including MBC to have CNS involvement prior to study enrollment, as these trials were primarily designed to assess the anti-tumor efficacy of new drugs in treating CNS metastasis. Out of the 39 trials, 16 enrolled only patients with a diagnosis of MBC and concomitant CNS metastasis.

The inclusion of patients with CNS disease in trials for patients with MBC

Among the 1474 early phase clinical trials for patients with MBC 281 (19%) allowed for the inclusion of patients with CNS metastasis, and 423 (29%) did not (Table 1). Among the studies that did not allow for CNS metastasis, only 6 required CNS imaging prior to study entry to rule out metastatic disease to the brain. In the majority of the trials (52%) there was no clear documentation allowing inclusion of patients with CNS disease. Among the trials that allowed for CNS disease (281) 9 excluded patients with LMD and 78 (5.3%) trials only allowed enrollment if patients had previously been treated with CNS-directed therapies (i.e.; radiation therapy and or surgical resection). A total of 194 (13%) trials allowed for enrollment even if patients had not been previously treated with CNS-directed therapies (Fig. 3). For the trials that allowed enrollment of patients with MBC with CNS involvement, patients could not have clinical evidence of CNS disease progression at the time of enrollment.

Trend over time of inclusion of patients with MBC CNS metastasis into early phase clinical trials

There were significant differences in the number of trials allowing for CNS involvement over time (Chi-Square $p < 0.0001$). Between 1992 (year of earliest study published) until 2015 there was a trend for higher odds of accrual of patients with CNS involvement into early phase clinical trials (odds ratio = 1.10, 95% CI