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ORIGINAL ARTICLE

Incidence of brain metastases in early stage HER2 3+ breast cancer patients; Is there a role for brain CT in asymptomatic patients?

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Summary

Purpose: *Human epidermal growth factor receptor 2 overexpression (HER2 3+) is reported in retrospective studies as a factor that contributes to higher incidence of brain metastases (BM) in patients with metastatic breast carcinoma. Although there are some reports suggesting higher incidence of BM in adjuvant trastuzumab trials, the true incidence, as well as the time of occurrence of BM in early-stage high risk breast carcinoma patients, has not been widely prospectively explored.*

The main objective of this study was to prospectively explore the incidence of BM during and after adjuvant trastuzumab administration in HER2 3+ early-breast carcinoma patients.

Methods: *Two hundred and fifty-eight patients with early, HER2 3+ breast carcinoma have been included in this analysis. Brain computed tomography (CT) scan was scheduled once during adjuvant trastuzumab therapy and thereafter only if central nervous system (CNS) symptoms occurred.*

Results: *Eighty-five patients (33%) underwent brain CT in the absence of CNS symptoms. The median number of trastuzumab cycles at the time of brain CT was 9 (range 4-18). There were no BM detected by brain CT in these 85 asymptomatic patients.*

However, during a median follow up of 18 months 5/258 patients (1.93%) developed BM, but only 2 (0.77%) while still receiving adjuvant trastuzumab. The median time from breast cancer diagnosis to BM was 24 months (range 14-43).

Conclusion: *BM are a rare event during adjuvant trastuzumab treatment and brain CT screening is not justified in asymptomatic patients with early HER2 3+ breast carcinoma.*

Key words: adjuvant trastuzumab, brain metastases, early breast cancer, HER2 overexpression

Introduction

BM can develop as first metastatic site or later in the course of metastatic disease.

The incidence of symptomatic BM ranges from 10-46% in patients with metastatic breast cancer [1-6]. Also, one study has shown that 15% of metastatic breast carcinoma patients could harbor completely asymptomatic BM detected only with brain CT [7].

The true incidence of BM in metastatic breast carcinoma is probably even higher, because brain CT is not routinely used in asymptomatic patients, and many patients die of metastases in other organ sites before CNS symptoms develop [8]. In retrospective studies HER2 overexpression, negative steroid receptor status, presence of lung metastases and young patient age are reported as factors contributing to higher incidence of BM [2,5,8,9].

A tendency of HER2 overexpressing breast carcinoma to metastasize to the brain was observed in adjuvant trastuzumab trials, with slightly higher incidence of BM in the trastuzumab arm [10-12]. However, BM typically develop later in the course of metastatic breast carcinoma. Since there is no screening for BM in asymptomatic breast cancer patients the true incidence of BM is actually unknown.

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The main objective of this study was to prospectively explore the incidence of BM during and after adjuvant trastuzumab in HER2 3+ early-stage breast cancer patients.

Methods

Two hundred fifty-eight patients have been treated for early-stage HER2 3+ breast carcinoma with adjuvant chemotherapy, trastuzumab and ± hormonal therapy at the Institute for Oncology and Radiology of Serbia.

All patients had documented HER2 overexpression: 215 (83%) by IHC (HercepTest Dako) and 43 (17%) by CISH.

The patient median age was 49 years (range 25-77), 62% had hormone-independent breast carcinoma (Quick score 0-3), 39% had node-negative and 61% node-positive breast carcinoma; the median number of positive axillary nodes was 3.24 and 25% of the patients had metastases to ≥4 nodes.

Anthracycline-based ± taxanes adjuvant chemotherapy was administered to 92%, and CMF to 8% of the patients. All patients received adjuvant trastuzumab every 3 weeks for 1 year, initiated approximately 2 months after adjuvant chemotherapy termination.

During adjuvant trastuzumab, the patients had physical examination every 3 weeks and every 6 months after the termination of trastuzumab treatment.

Diagnostic tests were the same as in everyday clinical practice and, as an additional diagnostic test, brain CT was carried out once to all patients during adjuvant trastuzumab; subsequent brain CT was performed only if CNS symptoms were suspected. At each visit, the patients were asked about any symptoms, with special focus to potential CNS symptoms (headache, visual or balance disturbance etc).

None of the 258 patients had any CNS symptoms at the time brain CT was carried out.

Table 1. Patient and tumor characteristics

Characteristics	*Patients, N(%)*
Age, years	
Median (range)	49 (25-77)
Menstrual status	
Pre-menopausal	148 (57)
Post-menopausal	110 (43)
Operative treatment	258 (100)
Radical mastectomy	180 (70)
Breast conserving surgery	78 (30)
Postoperative irradiation	149 (58)
Anthracycline ± taxane based adjuvant chemotherapy	237 (92)
CMF	21 (8)
Adjuvant trastuzumab	258 (100)
Histology	
Ductal	191 (74)
Lobular	46 (17.83)
Other	21 (8.1)
Tumor grade	
1	6 (2.33)
2	192 (45.74)
3	40 (15.50)
Unknown	20 (7.75)
T stage	
T1	70 (27.13)
T2	118 (45.74)
T3	11 (4.26)
Unknown	27 (10.47)
N stage	
0	101 (39)
1-3	85 (33)
≥4	65 (25)
Unknown	7 (2.7)
Median	3.29
ER score	
0	116 (44.36)
1-3	46 (17.8)
4-8	90 (34.8)
NA	6 (2.33)
PGR score	
0	130 (50.39)
1-3	36 (14)
4-8	86 (33.3)
NA	6 (2.33)
HER2 3+ (IHC, HercepTest Dako)	215 (83)
HER2 3+ (CISH)	43 (17)

ER: estrogen receptor, PGR: progesterone receptor, NA: not available

Results

Patient and tumor characteristics are presented at Table 1.

Eighty-five patients (33%) consented to undergo brain CT in the absence of CNS symptoms. The median number of trastuzumab cycles at the time of brain CT was 9 (range 4-18). The remaining 173 patients did not consent to have brain CT and, therefore, were clinically monitored for CNS symptoms.

No occult BM metastases were detected by brain CT in these 85 asymptomatic patients.

During a median follow up of 18 months (range 12-41), 15 patients (5.8%) developed metastases in various organs, and among them, there were 5 patients (1.93%) with BM (Table 2).

The median age of patients with BM was 41 years (range 35-54); the median number of positive lymph nodes was 9.2 (range 2-15); the median estrogen receptor (ER) Quick score was 2.8 (range 0-5); the median progesterone receptor (PRG) Quick score was 1.2 (range 0-3); and the median time to BM was 24 months (range 14-41) (Table 3).

In all patients with BM, CNS symptoms preceded CT confirmation for at least 10 days (range 10-35).

Only 2 patients had a previous brain CT performed while they were asymptomatic at 19 and 22 months before BM development.

As incidental findings, in 2 patients who had un-

Table 2. Brain CT evaluation

CT evaluation	*Patients, N(%)*
Brain CT in asymptomatic patients	85 (33%)
Occult brain metastases detected by brain CT	0 (0%)
Brain metastases	5 (1.9%)
During adjuvant trastuzumab	2 (0.77%)
As a first relapse site	2 (0.77%)
Median time to brain metastases development (determined from breast cancer diagnosis to CT confirmation)	24 months (range 14-41)
Other than brain metastases abnormalities detected by brain CT	
Meningioma	1
Acoustic neurinoma	1
Median follow up	18 months (range 6-44)
Relapse to any organ site	15/258 (5.8%)

dergone brain CT in the absence of symptoms, 2 benign brain tumors (meningioma and acoustic neurinoma) were diagnosed and surgically removed.

At the time of this analysis, only 2 patients with BM are still alive, 7 and 4 months after BM diagnosis. The remaining 3 patients died of uncontrolled BM, approximately 2 months after diagnosis.

Because no BM were detected in asymptomatic patients during adjuvant trastuzumab, brain CT evaluation in asymptomatic patients was stopped.

Discussion

Whether some specific, still unrecognized biological characteristics enable breast carcinoma to metastasize preferentially to the brain, or this likelihood is related to a general metastatic potential, is still not known [13]. Some researchers are convinced that breast carcinoma that gives BM differs from those cancers that never metastasize to the brain [14].

In retrospective studies the most consistent characteristic predisposing breast cancer patients to BM is HER2 overexpression [2,5,11,12,14-18]. Despite a higher incidence of BM in patients with HER2 3+, routine clinical practice has not been changed; brain CT evaluation has not become a part of diagnostic procedures in the absence of CNS symptoms, in neither metastatic nor early breast carcinoma.

At least in part, this is a consequence of the dilemma regarding the significance of early BM detection. The dilemma is maintained by controversial reports about the impact of early treatment on survival of patients with asymptomatic BM.

In one study, survival of patients with BM diagnosed and treated in an asymptomatic stage was compared to the survival of patients with BM detected and treated upon symptoms development [19]. The authors concluded that early diagnosis did not improve survival, even if patients received treatment before symptoms development.

However, in that study [19] BM as the direct cause of death were significantly higher in patients who developed CNS symptoms, as compared to patients who were diagnosed with BM in asymptomatic stage (48 vs. 16%).

According to the results of that study, early detection and treatment might at least spare patients of devastating BM symptoms and that is certainly an important issue from the patient's perspective [19].

In our study, all patients had HER2 overexpressing early breast carcinoma and all have been treated with adjuvant trastuzumab.

Their median age was 49 years, the majority (~60%) had hormone independent disease, the median number of positive axillary nodes was 3.24, but 25% of the patients had metastases to ≥4 nodes (Table 1).

Table 3. Brain metastases: patient and tumor characteristics

Patients	*Age at BC diagnosis (years)*	*Histology/ grade*	*T status*	*N status (pos/totally excised)*	*ER score*	*PGR score*	*Brain CT before BM*	*BM interval (months)*	*DFI to other metastases (months)*
1	35	Medullary Grade 2	2	10/20	2	3	No	14	14
2	37	Ductal Grade 3	2	13/18	5	3	No	24	12
3	41	Ductal Grade 2	2	2/17	2	0	Yes, 19 months before BM	41	No other metastases
4	47	Ductal Grade 2	3	15/15	5	0	Yes, 22 months before BM	33	14
5	54	Mucinous Grade 3	3	6/15	0	0	No	18	No other metastases

BC: breast cancer, T: primary tumor size, N: axillary lymph nodes, ER: estrogen receptor, PGR: progesterone receptor, BM: brain metastases, DFI: disease free interval

Therefore, this study population represents a homogeneous group of high risk, early-stage patients. The median follow up time from breast carcinoma diagnosis was 18 months (range 8-43). Therefore, the patients were followed from the diagnosis through the time period when, according to literature data, the first sign of treatment failure usually occurs, and thereafter [20].

Because of the centralized type of oncological care in our country, all relapses (15/258; 5.8%) were registered at our institution, and there are no patients lost to follow up.

In total, 5 patients (1.93%) developed BM eventually, but only 2 (0.77%) during adjuvant trastuzumab. By peculiar chance, those 2 patients did not consent to have brain CT in the asymptomatic stage, and CT was performed only upon CNS symptoms development.

The remaining 3 patients (1.16%) developed BM upon adjuvant trastuzumab termination, 24, 33 and 41 months after breast carcinoma diagnosis.

Among those 3 patients, 2 underwent brain CT while receiving adjuvant trastuzumab, the findings of which were normal. BM actually developed 22 and 19 months after initial CT evaluation, i.e. 33 and 41 months after breast carcinoma diagnosis.

In our study, brain CT was performed upon the patient's choice during adjuvant trastuzumab treatment and of course, at any time of CNS symptoms occurrence. The median number of trastuzumab cycles at the time of brain CT was 9 (range 4-18).

Although this strategy could be criticized, it seems unlikely that any other brain CT strategy could be more appropriate in asymptomatic patients, because of expected low incidence of BM during adjuvant trastuzumab. According to the findings of our study, the actual incidence of BM during adjuvant trastuzumab was only 0.77%.

In all patients who eventually developed BM, CNS symptoms preceded CT confirmation by at least 10 days. Therefore, patients with BM could not be spared of CNS symptoms, because BM could not be detected by CT in asymptomatic stage. Hence no occult BM were detected, brain CT did not prove to be justified in the detection of asymptomatic BM in high-risk early breast cancer patients.

However, the main objective of the analysis to determine the incidence of BM in early-stage, high-risk breast cancer patients has been achieved. Although the majority of patients had tumor characteristics that predisposed them to BM, metastases to the brain seem to be quite rare as an early event.

Although the median follow up of 18 months is relatively short for definitive conclusion, 3 preliminary statements could be made based on the results of our study:

1. The incidence of BM during adjuvant trastuzumab treatment is low (2/258; 0.77%).

2. The total BM incidence within 18 months of median follow up increased to 1.93% (5/258).

3. Brain CT does not seem to be justified in asymptomatic, high-risk, early-stage patients during adjuvant trastuzumab in the routine clinical practice.

We are strongly convinced that these results could contribute to the increase of knowledge about the incidence of BM in breast cancer, risk factors and time of BM development.

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