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Research Article

Approachment to the Brain Metastasis without Extracranial Metastasis of the HER2 Positive Metastatic Breast Cancer

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ABSTRACT

Introduction: Breast cancer is one of the most common malignancy that metastases to brain with the risk of 10-16%. Brain metastasis has been reported to be more common among younger women with tumors larger diameter and higher grade, hormone negative and HER2 positive ones. We reviewed inhere treatment of patients with brain metastasis without extracranial metastasis of HER-2 positive breast cancer.

Patients and Method: Totally 470 HER2 positive breast cancer patients were evacuated and treatment and clinicopathological factors of 20 patients with brain progression without extracranial metastasis were revised retrospectively. Overall survival (OS) and progression free survival (PFS)and related factors were analysed with univariate analysis.

Results: Median survival could not to be reached but, 3 years survival rate was 77% and median PFS was 16.1 months. Brain metastasis were treated with surgery followed with radiotherapy among 9 patients (45%) and only with radiotherapy other 11 (55%) patients. While nearly half of the patients received trastuzumab based therapy after local treatment, lapatinib-capecitabine were given to 7 (35%) and TDM-1 to 4 (20%) patients. There is no significant relation with anti-HER2 therapy in respect to OS or PFS.

Conclusion: Although anti-HER2 therapy has known to be improve prognosis of HER-2 positive breast cancer with brain metastasis, there is no consensus which therapy is better. Treatment option can be based adverse effect, patient performance or cost-effectiveness until in the future prospectively designed study related the anti-HER2 therapy after local brain therapy will be come up.

Introduction

Incidence of brain metastasis from the breast cancer is increasing because of the developing imaging methods and new therapies to improve survival. The mean age was 50 years to diagnose brain metastasis [1]. HER2 positive and triple negative tumors demonstrate that higher rate of brain metastasis compared to hormone positive tumors [1]. Only brain metastasis without extracranial metastasis from the breast cancer was reported as 16% [2]. The incidence of the brain metastasis was also reported as 30-50% for HER2 positive breast cancer [3]. Survival of breast cancer with brain metastasis has poor without treatment in the range of 1 to 5 months [2]. On the other hand, median overall survival (OS) for brain metastatic breast cancer has been reported as 11.5 month after treatment [2] Brain metastasis has been treated with locally as whole brain radiotherapy (WBRT), surgery or stereotactic radiosurgery or combination of them [1].

Surgical resection of the solitary brain metastasis followed by WBRT has been reported to increase survival [4]. Because of low potential of

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certain pharmaceutical drug to cross blood brain barrier, there is limited data regarding efficacy of therapies against brain metastasis after local therapies [5]. Systemic therapy can be more effective after WBRT because of increasing blood brain barrier permeability [6]. Treatment of distant metastasis with systemic therapy including anti-HER2 agents known to be important in management of survival. If cranial disease is controlled, systemic therapy can improve survival because of progression is generally seen systemically [7]. For HER2 positive breast cancer systemic chemotherapy combined with anti-HER2 therapy showed improved survival compared with patient receiving systemic chemotherapy without anti-HER 2 therapy [6].

Isolated central nervous system (CNS) progression without extracranial metastasis respond well to anti-HER2 treatments [8]. Trastuzumab is monoclonal antibody targeting HER-2 oncoprotein which belongs to epidermal growth factor receptor (EGFR) family [9]. Although trastuzumab has high molecular weight with low capability to penetrate blood brain barrier, after WBRT the structure loses its function and trastuzumab also has been effective [10]. Lapatinib, dual EGFR tyrosine kinase inhibitor combined with capecitabine was active in metastatic breast cancer with brain metastasis [11]. Lapatinib belongs to family of small molecules and can cross the BBB and has activity against to the brain metastasis [12]. Lapatinib capecitabine compared trastuzumab capecitabine and overall CNS events was similar between two group and response rate of CNS lesion was reported as 65.9%with lapatinib based regimen [13]. Also, in CEREBEL study, both trastuzumab and lapatinib combined with capecitabine had low number of CNS progression as first site of relapse as primary endpoint [14]. TDM-1 is an another anti-HER2 targeted antibody-drug conjugate, had improved outcome compared to the lapatinib-capecitabine combination in breast cancer with brain metastasis (OS 26.8 vs 12.9 months) [15].

Only brain metastasis after the diagnosis of the HER-2 positive breast cancer has not been evaluated alone, in the literature these group was analysed as subgroups and there is no consensus which anti-HER2 therapy is more effective than others and according to which parameters can affect the choice. So, we reviewed the systemic treatment of brain metastasis without extracranial metastasis which develop after the diagnosis of HER-2 positive breast cancer.

Material and Methods

This study consisted of 20 breast cancer patients among 470 HER2 positive breast cancer with cranial metastasis without any extracranial metastasis who were treated in Oncology Department in Istanbul from 2014 to 2018. All patients were undergoing surgery, breast conserving (20%) or radical mastectomy (80%) for breast cancer. The data's like age, menopausal status, type of surgery, local treatment to brain, were collected from the patient's files after informed consent were taken. The histological type of the tumor, the size of the invasive component, the grade of the tumor, and the rate of lymph node involvement were recorded. Brain metastasis was confirmed by magnetic resonance imaging (MRI) with at least one measurable brain lesion. Histopathological features were assessed on paraffin-embedded tissue and stained with haematoxylin and eosin. HR and HER2/neu status were determined immunohistochemically. Pathologist scored HER2 by IHC staining as 0, 1+, 2++ or 3+ based on intensity and proportion of membrane staining according to criteria based on ASCO/CAP [16]. HER2 status were evaluated with immunohistochemical analysis, if score 2 (5 patient), gene expression analysis with FISH was also performed. HER-2 negative and unknown patients were excluded.

All patients received adjuvant trastuzumab median 16.5 cycle and 15 of them started trastuzumab during neoadjuvant therapy. Patients were followed-up and recurrences were recorded.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. Descriptive analysis examined the distribution of study-level variables. Survival analysis and curves were established according to the Kaplan-Meier method and compared using the log-rank test. PFS was defined as the time from surgery to the first evidence of brain metastasis. In addition, OS was described as the time from diagnosis to the date of the patient's death or last known contact. Univariate analysis of prognostic factors related to survival were performed by the Cox proportional hazards model. The relationship between anti-HER2 therapy and the clinicopathological factors were analysed using the Chi-square test. All p values were two-sided in tests and p values less than or equal to 0.05 were considered significant.

Results

The median age of patients was 47 years ranging from 32 to 73 years and 65% were premenopausal, while the remaining 35 were postmenopausal. Tumors were localized the right breast in12 patients (60%), the left breast in 7 patients (35%) and were bilateral in 1 patient (5%). Over the 9% of the tumor had Kİ67 >20% and 8 out of 20 was estrogen recceptor (ER) positive (40%) and progesterone (PR) receptor was positive in 4 patients (20%). The most common chemotherapy regimens which were used as neoadjuvant in 15 patients was anthracycline (doxorubicin-cyclophosphamide) and taxane (paclitaxel or docetaxel). All of the patients received also trastuzumab combined with taxanes as NAC, other 5 patients were given same chemotherapies as adjuvant. Median adjuvant trastuzumab cycle was 16. Because of dual-HER2 was not approved during study period we couldn't use pertuzumab in addition to trastuzumab.

Median follow-up time was 25.8 months and the median time from the diagnosis of breast cancer to diagnosis of brain metastasis was 16.1 months (range 12.3-19.8). While single brain metastasis was detected in 6 patients, 2 metastases in 3 patients and ≥3 metastasis in other 11 patients were diagnosed. After diagnosis of brain metastasis, 9 patients (45%) underwent surgery followed by WBRT or stereotactic surgery on the other hand only WBRT were performed for other 11 (55%) patients. After local brain therapy, systemic therapy with anti-HER2 treatment were given to all of them. Mostly used regimens were trastuzumab based regimen.

In order of frequency, lapatinib- capecitabine (35%), trastuzumab-capecitabine (25%), trastuzumab-taxane (20%), and TDM-1 (20%) were used. Table 1 shown the frequency of clinicopathological features of the patients and therapy type. There was no grade ≥3 toxicity causing to interrupt the therapy. While diarrhea and rash were more common with

lapatinib, fatigue and thrombocytopenia with grade 2 toxicity was seen among TDM-1 group. Chosen Anti-HER2 therapy could not be related with other factors such as menopausal status, grade, LVI, PNI, number of metastasis or local brain therapies (p>0.5).

Table 1: The treatment and survival time of the patient group.

Patients	Adjuvant trastuzumab cycle	Brain metastasis time (month) after diagnosis	Treatment	Overall survival (month)
1	17	17.87	lapatinib-capecitabine	37.53
2	17	18.13	lapatinib- capecitabine	23.43
3	17	23.27	lapatinib- capecitabine	46.23
4	17	16.1	lapatinib- capecitabine	59.43
5	9	11.23	lapatinib- capecitabine	36.97
6	17	18.83	herceptin- capecitabine	29.53
7	13	15.67	herceptin- capecitabine	16.7
8	8	9.63	lapatinib- capecitabine	12.07
9	10	17.5	herceptin- capecitabine	30.27
10	17	20.2	lapatinib- capecitabine	25.2
11	17	22.4	herceptin- capecitabine	25.67
12	13	23.8	TDM-1	25.93
13	13	24.97	taksan-herceptin	34.33
14	5	9	taksan-herceptin	20.57
15	55	54.7	TDM-1	78.37
16	17	15.47	taksan-herceptin	20.43
17	17	15.8	taksan-herceptin	20.43
18	16	14.77	TDM-1	23.67
19	6	8.43	herceptin- capecitabine	10.23
20	12	9.57	TDM-1	32.57

Table 2: The results of the univariate analysis.

Characteristics	Frequency	%	% 3 years OS	P	% 2 years PFS	P
menopausal status	13	65	76		15	
premenopause	7	35	86	0.6	13	0.4
postmenopause						
ER	8	40	80		0	
Positive	12	60	77	0.5	16	0.09
negative						
PR	4	20	66		na	
Positive	16	80	81	0.04	12	0.1
negative						
LVI	8	44.5	na		0	
Present	10	55.6	62	na	20	0.03
absent						
PNI	17	38.9	75		0	
Present	11	61.1	77	na	18	0.05
absent						
local brain therapy	11	55	71		1	
radiotherapy	9	45	83	na	12	0.5
operation-radiotherapy						
treatment type	4	20	na		25	
trastuzumab-taxane	7	35	66		0	
lapatinib-capecitabine	5	25	66	0.5	0	0.6
trastuzumab-capecitabine	4	20	na		25	
TDM-1						

OS: Overall Survival, PFS: Progression Free Survival, ER: Estrogen Receptor, PR: Progesterone Receptor, LVI: Lymph Vascular Invasion, PNI: Perineural Invasion.

OS could not be reached at the time of analysis. Three-year OS and 2 years PFS rates were 77% and 10%, respectively. While lymph vascular invasion (LVI) (p=0.03), perineural invasion (PNI) (p=0.05) were shown to be important for PFS, only PR(p=0.04) was found to be prognostic indicator for OS by univariate analysis. Any local brain therapy or

antiHER-2 therapy could not be found to be related with survival (Table 2).

Discussion

The risk of brain metastasis has been reported as 10-16% for breast cancer patients [17]. Younger age, larger tumors with high grade, lymph node metastasis or tumor with hormone receptor negative and/or HER2 overexpressed ones had a higher risk [1]. SystHERs trial is the observational registry trial enrolled HER-2 positive breast cancer. Nearly one fifth of the patients (212 of 977) developed cranial metastasis after breast cancer diagnosis and fifty-two of the patients had only brain metastasis without extracranial metastasis [5]. The median time to diagnose brain metastasis from the diagnosis of breast cancer was reported as 34 months [1]. For our study the median time from the diagnosis to the brain metastasis was 16.8 month (range. 8.4-54.7) but included only HER2 positive tumors which had known to be poor prognosis. Worse than our study, brain metastasis was detected median 9 months later from the diagnosis of 80 HER2 positive breast cancer with 53 months of overall survival. And presence of visceral metastasis was the only risk factor for brain metastasis [18]. Because we only included cranial metastasis without extracranial disease our PFS might be longer.

In the literature, there are a lot of study included treatment of brain metastasis from the HER2 overexpressed breast cancer, but none of them were directly included only cranial metastasis without extracranial disease detected after diagnosis of breast cancer. Because of poor survival we want to use strong choice for the extracranial metastasis due to local therapy can only control brain disease, so we don't know which anti-HER2 systemic therapy is better from the others. If tumor was HER2 positive and treated with targeted therapy (trastuzumab) had longer survival [1]. Kim *et al.* reported 57 brain metastases without extracranial disease among 400 breast cancer patients. Only 32 of them received anti-HER2 therapy as trastuzumab or lapatinib [6]. CNS metastasis included both brain parenchyma and leptomeningeal metastasis which were detected after median 34.6 months later irrespective from molecular subtype with median 44.3 months of survival [6]. The survival was reported as longest in the patients who received chemotherapy combined with anti-HER2 therapy compared without systemic therapy (12.8-month vs 2.2 month). There was no difference between survival and type of anti-HER2 therapy. We know that brain metastasis was more common among HER2 positive tumors and we detected after median 16.8 months later from the diagnosis of 20 HER2 positive breast cancer. Median survival of our group was also shorted because of included only HER2 positive ones (25.8 month).

Among brain metastasis, if tumor is single in the brain and <5cm without extracranial disease had better overall survival [1]. We could not find any difference among survival in respect to number of metastasis. All of our patients were HER-2 positive and treated with different anti-HER2 therapy as trastuzumab based (20% trastuzumab-taxanes, 25% trastuzumab-capecitabine), 35% capecitabine lapatinib and 20% TDM-1. There was no difference related with anti-HER2 therapy in respect to survival. CNS only metastasis at diagnosis received lapatinib based therapy more than trastuzumab combinations in SystHER observational study [5]. PFS and OS were 9.9 months and 38.3 month in patients with CNS metastasis observed after diagnosis. Median time to diagnosis of CNS metastasis was 15.1 month similar our study [5]. Rostami *et al.* also reported that trastuzumab therapy improved survival for HER2 positive breast cancer with brain metastasis (17.5 vs 11 month) there was no information about HER2 positive breast cancer with only brain metastasis [1]. Among 60 HER-2 positive brain metastatic breast cancer was treated with anti-HER2 therapy after WBRT (24 patients) had better outcome compared to only WBRT [19]. Patients were given trastuzumab (50%), lapatinib alone (37.5%), lapatinib trastuzumab (12.5%) combination or trastuzumab based therapy (29.2%). Lapatinib capecitabine combination was shown effective treatment after WBRT in brain metastatic breast cancer [13].

Miller *et al.* also evaluate 547 brain metastases from the breast cancer patients, 92 of them had only brain metastasis without extracranial metastasis and 15 of the were HER2 positive (16%). Lapatinib increased survival for this group median 16 month [20]. Metro *et al.* also reported longer survival with lapatinib-capecitabine treated patients compared to treated with trastuzumab based therapies for breast cancer patients with brain metastasis [21]. In Phase II Landscape trial, lapatinib-capecitabine was shown to be active in 45 metastatic HER2 positive breast cancer with brain metastasis, 7 of them without extracranial metastasis [22]. In another retrospective study showed that lapatinib capecitabine more improved survival compared to the undergoing only trastuzumab therapy after diagnosis of cranial metastasis with HER2 positive breast cancer [7]. Only 17 of the 111 had only brain metastasis without extracranial ones [7]. TDM-1 was shown to be effective among trastuzumab resistant HER2 positive breast cancer metastasis in EMILIA trial [23]. In this study, TDM-1shown to improve survival compared to lapatinib capecitabine in metastatic breast cancer with brain metastasis [23].

In retrospective French study also evaluated 39 TDM-1 usage for HER-2 positive brain metastatic breast cancer, only 7 of them had only brain metastasis and brain metastasis were detected median 16.8 months from the diagnosis with median 6.1 month of median PFS. Only cranial metastasis was shown to be related with poor survival [24]. Only 3 of our trastuzumab resistant patients were given TDM-1 without survival differences. We used anti-HER2 therapy for all of our study after local brain therapy and we could not find any difference in respect to survival among which anti-HER2 therapy was chosen. Because of only limited number of patients were evaluated, we could not say was there any difference among trastuzumab, capecitabine-lapatinib or TDM-1 for HER-2 positive brain metastasis without extracranial disease. There was no relation between antiHER-2 therapy choice and metastasis number, adjuvant trastuzumab duration and number. We found only PR positivity (p=0.04) was related with better OS, on the other hand, absence of LVI (P=0.03), PNI (p=0.05) were associated with longer PFS. Five-year relapse rate was 15-20% for patients who were treated with adjuvant trastuzumab [12]. All of our patient received adjuvant trastuzumab therapy with median number of 16. Ten of the 20 patients could be completed 1 year of trastuzumab, but brain metastasis was detected during adjuvant trastuzumab among 10 of them.

Conclusion

There is no consensus to treat HER-2 positive brain metastasis from the breast cancer without extracranial disease after local therapy. Generally, we don't use stronger targeted therapy choice without measurable

disease after local brain therapy. It should be better choice according to patient's brain metastasis recurrence time after adjuvant trastuzumab therapy and adverse effect. For patients without extracranial metastasis lapatinib-capecitabine or trastuzumab-taxane could be used after local cranial radiotherapy, reserving TDM-1 for those with extracranial progression. In the future prospective studies are needed to true choice as antiHER-2 therapies for only cranial metastasis.

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There are no financial or commercial interests to declare regarding the authors of the study.

Conflicts of Interest

None.

Statement of Ethics

The data were picked up from the patients' after informed consent were taken retrospectively, local ethical confirmation application could not be performed.

Author Contributions

Dr. İlker Nihat Okten, Dr. Eda Tanrikulu and Dr. Altay Aliyev took part in the data collection from the patient's file. Dr. Basak Oven and Dr. Serkan Celik prepared the manuscript and tables. Dr. Mesut Seker revised the grammatical and spelling errors.

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