Evaluating The Clinicopathologic Characteristics and Survival Outcome of Breast Cancer Patients with Isolated Brain Metastases after Adjuvant Treatment or at Initial Diagnosis

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ABSTRACT

CNS metastases usually appears late in the progression of metastatic breast cancer. Classical approach is evaluating and treating them when symptoms become evident. We evaluated the survival and described clinicopathologic characteristics of patients in whom the brain metastases after adjuvant treatment or at initial diagnosis are the first and the only side. Authors retrospectively evaluated about 3600 patients with breast cancer treated in two university hospitals. In those 31 patients with first and only metastases to brain and no other metastases were evaluated. ER, PR, cerbB2 status T, N stage, grade, adjuvant taxane, trastuzumab, hormonal treatment, trastuzumab and platine use after brain metastases didn't effect the survival. Surgery and WBRT may be more effective in cerbB2 negative patients, WBRT in cerbB2 positive ones. (p=0.06). The survival outcome may be better in pre and perimenouposal women. The mOS of pre and perimenopausal, postmenopausal women were 17.7 months and 10.3 months respectively (p=0.06) and lapatinib may affect the mOS of patients with isolated brain metastases. Some prognostic factor may help us to foresee which group may benefit more from which treatment modality. The need for studies with larger groups of patients is obvious.

Keywords: *Breast cancer, isolated brain metastases, treatment, lapatinib*

Adjuvan Tedavi Sonrası veya Tanıda İzole Beyin Metastazı Olan Hastaların Klinikopatolojik Özellikleri ve Sağ Kalımlarının Değerlendirilmesi

ÖZET

SSS metastazı meme kanserinin geç dönemlerinde ortaya çıkar. Klasik yaklaşım, semptomatik olunca tedavi etmektir. Adjuvan tedavi sonrası veya başlangıçta tanıda, yalnızca beyin metastazı olan hastaların, klinikopatolojik karekteristiklerini inceledik ve sağkalımı değerlendiridik. Yazarlar, retrospektif olarak iki üniversite hastanesinden 3600 meme kanserli hastayı değerlendirip, içlerinden sadece ve tek olarak beyin metastazlı olan 31 hastayı çalışmaya aldılar. ER, PR, cerbB2 durumu, T , N evresi , grad, adjuvan taksan, trastuzumab, hormonal tedaviler, trastuzumab ve palatinin beyin metastazından sonra kullanımı sağ kalımı etkilemedi. Cerrahi ve tüm beyin ışınlaması cerbB2 negatif hastlarda, tüm beyin ışınlaması ise cerB2 pozitif hastlarda daha etkili olabilir. (p=0.06). Sağ kalım pre ve perimenapozallerde daha iyi olabilir. mOS pre ve perimenapozallerde 17.7 ay postmenapozallerde 10.3 ay bulundu. (p=0.06) Lapatinib izole beyin metastazlı hastlarda mOS'ı etkileyebilir. Bazı prognostic faktörler, hangi tadaviden, hangi hasta gurubunun faydalanacağını öngörmemizi sağlayabilir. Daha çok hasta içeren çalışmalara olan ihtiyaç açıktır.

Anahtar kelimeler: *Meme kanseri, izole beyin metastazı, tedavi, lapatinib*

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INTRODUCTION

CNS metastases usually appears late in the progression of metastatic breast cancer and 1 and 2-year survival rates of only 20% and <2%, respectively (1, 2), Despite the poor prognosis associated with symptomatic CNS metastasis, most patients finally die of systemic disease progression.

In the era of more efficacious chemotherapeutic and targeted agents for metastatic breast cancer, control of systemic disease has brought the problem that the incidence of CNS metastasis may increase (3,4). Until now, all data we have only indicates that over all survival is same between the metastatic breast cancer patients whose brain metastases were diagnosed early without symptoms or lately when they are symptomatic. One of the compelling questions is if early diagnosis of cranial metastases effects the survival of patients if the brain is the first and only metastatic side after adjuvant treatment or at the initial diagnosis. And second question is 'Is better survival possible ıf we treat a patient with early diagnosed brain metastases with current new treatment modalities like targeted therapies and radiosurgery, or surgery with whole brain radiotherapy.

In this study we tried to answer these questions in a very rare group of patients selected from breast cancer data's of two cancer centers.

MATERIAL and METHODS

We have examined about 3600 patients with breast cancer treated in two university hospitals (Meram faculty of medicine hospital and Hacettepe faculty of medicine hospital) between years 2000 and 2012 In those 31 patients with first metastases to brain and no other metastases after adjuvant treatment or at initial diagnosis of breast cancer were evaluated considering treatment modalities like chemotherapy, targeted therapy, hormonal therapy, either in adjuvant setting or after metastases, surgery with whole brain radiotherapy (WBRT) , radiosurgery or conventional whole brain radiotherapy and mPFS and mOS , ostrogen receptor (ER), progesterone receptor (PR) and c-erb2 status were compared in all groups.

Statistical analysis

Data's were analyzed with SPSS 16.0 for Windows Evaluation Version (IBM Corporation, Armonk, NY, USA) İn addition to descriptive analysis like standard deviation. Median OS were calculated with the Kaplan-Meier test and the differences between groups were evaluated with the Log Rank test.

RESULTS

31 patients with first metastases to brain and no other metastases after adjuvant treatment or at initial diagnosis of breast cancer were evaluated. 14 patients 45.2% were pre-perimenouposal and 17 of patients 54.8% were postmenopausal. İn patients 12 38.7% were cerbB2 3+ and 19 of them 61.3% were cerbB2 – and 14 patients %45.25 were ER+ and 17 patients 54.8% were ER -. 16 patients 51.6% were found to be PR+ and 15 48.4% were PR-. 22 patients had adjuvant taxane, 15 patients had adjuvant hormonal therapy and 6 of them had adjuvant trastuzumab while 3 of them had trastuzumab, 14 had platine and 5 had lapatinib after brain metastases. Ten of these 30 patients were treated with surgery and WBRT and cyber-knife or gamma knife on progression. (Group 1) The other 20 patients were treated with WBRT alone. (Group 2)

We could not show significant effect of adjuvant taxane, hormonal therapy and trastuzumab on survival of patients. Also we could not find a significant change on survival of patients, due to trastuzumab and platin administration after brain metastases. But lapatinib administration after metastases showed a significant survival advantage. Five patients were administered lapatinib (mOS 41.8 months) and 23 patients weren't (mOS 16 months) p= 0.02 (Table 1).

Median overall PFS was 8.9 months. Median PFS of group 1 and 2 were 9.1 and 8.6 months (95% confidence interval). There wasn't significant difference between two groups (p=0.3) (Table-1). mOS after the diagnosis of brain metastases were found as 17.7 and 13.6 months respectively but the difference weren't significant (p= 0.2) (Table 2). We couldn't find statistically significant mOS difference between ER and PR receptor positive and negative patients. mOS of ER positive and negative patients were 16 and 17,2 months (p= 0.7) and PR positive and negative patients were 10 and 17.7 moths respectively (p= 0.1). mPFS and mOS of cerbB2 positive and negative patients were 8.6 and 6.1 moths (p=0.7) and 17 .3 and 16 months respectively (p=0.9) (Table 3).

***Table 1**. The effect of chemo-targeted therapy on survival*

Chemo-targeted therapy	*Variable*	*n*	*No of events*	*Median survival mounth*	*95%CI,%*	*p value*
Adjuvant Taxane	*Yes*	*22*	*18*	*17*	*15-19.6*	*0.2*
	No	*6*	*3*	*10*	*1.9-18.6*	
Adjuvant hormonal therapy	*Yes*	*15*	*11*	*17.3*	*7.4-27.2*	*0.5*
	No	*12*	*9*	*17.2*	*10.6-23.8*	
Adjuvant Trastuzumab	*Yes*	*6*	*4*	*17.3*	*7.3-27.3*	*0.6*
	No	*22*	*17*	*16*	*6.5-25.5*	
Trastuzumab after metastases	*Yes*	*3*	*2*	*18.6*	*16.5-20.8*	*0.1*
	No	*25*	*19*	*13.6*	*5.4-21.7*	
Platine after metastases	*Yes*	*14*	*10*	*17.3*	*1.6-33*	*0.7*
	No	*14*	*11*	*16*	*7.6-24.4*	
Lapatinib after metastases	*Yes*	*5*	*2*	*41.8*	*0-88.2*	*0.02*
	No	*23*	*19*	*16*	*6.3-25.8*	

mPFS of group 1 in cerbB2 positive and negative patients were 8.9 and 14.8 months (p= 0.3) and in group 2 patients 8.6 and 4.4 months (p= 0.1). Although the surgery with WBRT or cyber-knife or gamma-knife, seems like more effective in cerbB2 negative group and WBRT alone in cerbB2 positive group, the difference were statistically insignificant. mOS of group1 in cerbB2 positive and negative patients were 10.8 and 26.7 months (p= 0.1) and in group 2 17.3 and 10.3 months (p= 0.06). Although results couldn't reach statistically significance, surgery with WBRT and radiosurgery may be more effective in cerbB2 negative group and WBRT alone in cerbB2 positive group which also tented to be statistically significant. mOS for pre and postmenopausal women were 17 and 10 months. The difference was tended to be significant (p= 0.06).

DISCUSSION

CNS metastases are not considered to be a common follow-up parameter in patients with breast carcinoma ıf the patient isn't symptomatic. Several prognostic factors associated with this type of disease recurrence have been identified. It was shown that CNS metastases tend to develop in younger patients who have higher T stage and with more aggressive tumor histology. Many clinical and autopsy data shows that the median age of patients who develop CNS metastases is 5 years younger than that of patients whose disease is metastatic to other sites (5). Pestalozzi et al. (6) were also able to define risk factors for CNS metastases, but they could not show any group at enough risk to justify routine screening for occult CNS metastases. Miller et al. (7) investigated whether cranial metastases in breast cancer patients occult or symptomatic, have an impact on impaired survival. According to the their data occult CNS metastases

***Table 2**. The effect of cerbB2 status on the outcome of treatment modalities*

	Variable	*n*	*No of events*	*Median survival mounths*	*95%CI,%*	*p value*
Surger+WBRT	*cerbB2+*	*3*	*3*	*10.8*	*5.7-18*	*0.1*
	cerbB2-	*7*	*4*	*26.7*	*8.4-45*	
WBRT	*cerbB2+*	*9*	*7*	*17.3*	*9.4-30.2*	*0.06*
	cerbB2-	*11*	*9*	*10.3*	*5.7-15.2*	

Table 3. *Overall survival comparisons from diagnosis of central nervous system metastases*

	Variable	n	No of events	Median survival mounths	95%CI,%	p value
Menopausal status	Pre-peri	13	11	17.7	14.9-20.5	0.06
	Post	15	12	10.3	3.5-17	
Grade	1	1	1	6	16.6-18.8	0.2
	2	10	9	17.7	0-20.8	
	3	13	11	7.1		
Estrogen receptor	Positive	11	9	16	2.8-29.2	0.7
	Negative	17	14	17.2	4.09-30.3	
Progesterone receptor	Positive	14	12	10.3	4-16.5	0.1
	Negative	14	11	17.7	16.4-19	
CerbB2	3+	12	10	17.3	0-34	0.9
	Negative	19	13	16	7.5-24.6	
Brain met treatment modality	Surgery+WBRT	10	7	17.7	0-37.6	0.2
	WBRT	18	16	13.6	2.5-24.6	
T stage	Tx	2	2	4.4		0.06
	T1	2	2	1.3		
	T2	12	11	16.06	5.4-26.7	
	T3	7	4	41.8	4.5-79.1	
	T4	5	4	17.3	5.8-28.8	
N stage	N0	7	4	19.9	3.8-16.7	0.8
	N1	6	5	18	17.1-17.5	
	N2	5	5	14.2	0.4-21.2	
	N3	10	9	14.1	0-25.1	

were found to be relatively common, but they showed that impact of treating occult CNS disease on survival in patients with progressive systemic metastases was uncertain. But still the compelling question is if there are no systemic metastases except for the brain metastases 'does the treatment modality of cranial metastases effect the survival of patients? ' There are only a few pathfinder studies on this issue. DiStefeno et al in 1979 (1) and patchell et al in 1990 (8) showed that surgery plus RT offers better outcome compared with RT alone in isolated brain metastases. Finding the answer of this question isn't so easy because in study by Pestalozzi et al, they showed in 9524 patients that overall, CNS was a component of first recurrence in 1.3% of patients (126 of 9524). In ten years the incidence were found to be 1% for her2 – and 2.7% for Her2+ disease (6). That is why the patient population of this study is so rare.

We couldn't find significant effect of adjuvant chemotherapy, hormonal therapy or trastuzumab on survival after brain metastases. Also trastuzumab and platins in metastatic setting didn't effect the survival, patients who were administered lapatinib after they were diagnosed with brain metastases, live longer than the patients who weren't. This date is consistent with data of Cetin et al (9). They showed that median progression free survival of patients who received lapatinib and and capecitabine was 7 months (95% confidence interval (CI) 5–9), with a median overall survival of 13 months (95% Cl 9–17). mOS in our date look longer than expected. It may be due to a patient who lived longer than normal and due to the limited number of patients evaluated in this subgroup.

In our study like the previous guiding studies surgery and WBRT has better survival out comes (mPFS 8.1 vs. 9.1 months and mOS 17.7 vs 13.6 months). But the results could not reach the statistical significance, probably due to the limited umber of patients. Altundag et al found that only age at diagnosis and ER status were associated significantly with overall survival in the multivariate analysis in patients with breast cancer brain metastases (10). Although, ER, PR positivity are known to be good prognostic factors, it seems like they don't have signifi-

cant effect on prognosis of patients with brain metastases in this study. CerbB2 status also weren't related with mPFS and mOS but we found that cerbB2 + patients have better mPFS and mOS with WBRT alone when cerbB - patients have better outcome with surgery and WBRT or radiosurgery approaches. If we draw analogy, cerbB2 positivity is known to be a bad prognostic factor and related with the aggresivity of tumors. Surgical approaches to metastatic tumors, which are more tended to metastases like small cell lung cancer or pancreatic cancer, are generally disappointing. Histopathological features and clinical behavior of cerB2+ tumors may resemble and remind us the characteristics of these tumors and more conservative approaches like WBRT which will also enable patients to have systemic treatment earlier may turn out better outcome. But for better decision on this subject we need an analyze on a larger group of patients. Although it isn't statistically significant mOS of premenopausal women were better than the postmenopausal ones. This may be due to age and comorbidities of older patients. This result is similar with the finding of Altundag et al. They found that patients <50 year old have better mOS (7.8 m) than patients >50 years old. (p= 0.04).

Brain metastases in breast cancer patients is an issue which have to be reevaluated in the era of modern treatment modalities, targeted therapies and prognostic factors. Unlike the classical approach to these patients, which suggests only evaluating and treating them when they become symptomatic, some subgroups may benefit from early and different treatment modalities and also targeted therapies after metastases may yield a better outcome. Some prognostic factor may help us to foresee which group may benefit more from which treatment modality. To clarify these issues, the need for studies with larger groups of patients is obvious.

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