Original Article

Breast Cancer Subtypes and Response to Systemic Treatment After Whole-Brain Radiotherapy in Patients With Brain Metastases

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BACKGROUND: The aim of this study was to assess the role of systemic treatment after whole-brain radiotherapy (WBRT) in immunohistochemically defined biological subsets of breast cancer patients with brain metastases. **METHODS:** The group of 420 consecutive breast cancer patients with brain metastases treated at the same institution between the years of 2003 to 2009 was analyzed. Patients were divided into 4 immunohistochemically biological subsets, based on the levels of estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) receptors, and labeled as luminal A, luminal B, HER2, and triple-negative. Survival from brain metastases with and without systemic treatment after WBRT was calculated in 4 subsets. **RESULTS:** In the entire group, the median survival from brain metastases in patients without and with systemic treatment after WBRT was 3 and 10 months, respectively ($P < .0001$). In the triple-negative subset, the median survival from brain metastases with and without systemic treatment was 4 and 3 months ($P = .16$), and in the luminal A subset, it was 12 and 3 months, respectively ($P = .003$). In the luminal B subset, the median survival without further treatment, after chemotherapy and/or hormonal therapy, and after chemotherapy and/or hormonal therapy with targeted therapy was 2 months, 9 months, and 15 months, respectively ($P < .0001$). In the HER2 subset, the median survival was 4 months, 6 months, and 13 months, respectively ($P < .0001$). No significant response to systemic treatment was noted in the triple-negative breast cancer population. **CONCLUSIONS:** Systemic therapy, ordered after WBRT, appears to improve survival in patients with the luminal A, luminal B, and HER2 breast cancer subtypes. Targeted therapy was found to have an additional positive impact on survival. In patients with triple-negative breast cancer, the role of systemic treatment after WBRT appears to be less clear, and therefore this issue requires further investigation. ***Cancer* 2010;116:4238–47.** © *2010 American Cancer Society.*

KEYWORDS: brain metastases, human epidermal growth factor receptor 2 (HER2)-positive breast cancer, triple-negative breast cancer, systemic treatment, whole-brain radiotherapy.

Recently, it has been reported that the incidence of brain metastases from breast cancer has increased due to prolonged survival of patients and the development of imaging techniques. Generally, the prognosis of patients with brain metastases is poor. The median survival of untreated patients is approximately 1 month. Symptomatic treatment with steroids prolongs survival to approximately 2.5 months. Whole-brain radiotherapy (WBRT) increases the median survival to approximately 4 to 6 months. In 10% of patients, surgical excision of brain metastasis followed by whole-brain irradiation prolongs median survival up to 1 to 2 years.[1] Recently, the role of systemic therapy after WBRT has been investigated for 2 reasons. First, breast cancer is a rather chemosensitive disease. Second, it has been reported that not all breast cancer patients with central nervous system metastases die due to intracranial progression. The analysis of causes of death revealed that, in approximately 50% of cases, patients die from the cancer's progression within the brain and that the other 50% of patients die from the cancer's progression in the viscera.[2-5] The above results suggest that, to control at least extracranial disease, continuation of systemic treatment after WBRT appears to be a reasonable approach.

To the best of our knowledge, little is known regarding the survival differences among patients with breast cancer and various subtypes of brain metastases. In our previous study concerning 222 patients, the median survival from brain

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metastases in patients with luminal A, luminal B, human epidermal growth factor receptor 2 (HER2), and in triple-negative subtypes was 15 months, 9 months, 9 months, and 3.7 months, respectively.[6] In the study by Nam et al,[7] it was 4 months, 9 months, 5 months, and 3.4 months, respectively. Moreover, in the study by Lin et al, the median survival from brain metastasis in patients with triple-negative breast cancer was 4.9 months.[5]

The aim of this study was to assess the impact of systemic treatment sequenced after WBRT and the effect it had on survival from brain metastases in immunohistochemically defined biological subsets of breast cancer patients.

MATERIALS AND METHODS

Between January 1, 2003, and June 30, 2009, 420 patients with breast cancer and brain metastases were treated in Breast Cancer and Reconstructive Surgery Department at The Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland. The observation of patients started at the time of the detection of brain metastases, and all data were collected prospectively in a database. In each case, treatment options were approved by a team of medical oncologists, radiation oncologists, and neurosurgeons and were performed after patients provided written informed consent.

Of 420 patients, 399 patients were divided into 4 biological subtypes based on the expression of estrogen (ER [dilution scale 1:100, Klon, 6F11; Novocastra]), progesterone (PgR [dilution scale 1:200, Klon 16, Novocastra]), and human epidermal growth factor receptor 2 (HER2 [Polyclonal Hercep Test; Dako]) receptors. Twenty-one patients were unassigned because of insufficient tumor material for assay. Immunohistochemistry (IHC) was performed to evaluate levels of ER, PgR, and HER2 expression. IHC staining was performed on tissue sections that were cut from formalin-fixed, paraffin-embedded primary breast tumors. Staining was performed using primary antibodies against ER (Klon, 6F11; Novocastra; Lab Vision Polska) (dilution scale 1:100), PgR (Klon 16, Novocastra) (dilution scale 1:200), and HER2 (Polyclonal Hercep Test; Dako; Dako Polska). For the evaluation of ER and PgR expression, the Allred score was used. All cases classified as proportion score 3, 4, and 5 were considered as positive regardless of the outcome of the intensity score; all cases with $\geq$10% stained cancer nuclei were classified as positive. Fluorescence in situ hybridization (FISH) was used for all HER2 2+ tumors using the PathVysion HER2 DNA Probe Kit (Vysis PathVysion Kit; Abbott Laboratories, Abbott Park, IL). HER2-positive staining was defined as IHC 3+ or, in the case of IHC 2+, FISH positivity. HER2 negativity was defined as IHC 0, 1+, or 2+, along with negative FISH results. All ICH and FISH assays were performed in 1 institution by a team of pathologists involved in breast cancer research.

Patients were divided into 4 biological subtypes as 1) triple-negative (ER negative, PgR negative, and HER2 negative), 2) HER2 (HER2 positive, ER negative, and PgR negative), 3) luminal B (HER2 positive, ER positive, and/or PgR positive), and 4) luminal A (ER positive and/or PgR positive, HER2 negative). Triple-negative and luminal A subsets were HER2 negative. HER2 and luminal B subsets were HER2 positive.

Survival calculated from brain metastases was analyzed in all patients, in 4 biological subgroups, and in 3 recursive partitioning analysis of Radiation Therapy Oncology Group (RPA RTOG) prognostic classes. Class I included patients aged <65 years, with a Karnofsky performance status (KPS) score of $\geq$70, with controlled disease at the primary site, and without metastases outside the brain. Prognostic class III was comprised of patients with a KPS <70, regardless of other factors, whereas prognostic class II included all the remaining patients.[8] The analysis of survival from brain metastases depending on systemic treatment after WBRT was a special goal of the study. Patients with triple-negative and luminal A subtypes were divided into 2 subgroups: those treated and not treated with chemotherapy and/or hormonal therapy after WBRT. Patients with HER2 and luminal B subtypes were divided into 3 groups: those not treated after WBRT, those treated with chemotherapy and/or hormonal therapy, and treated with chemotherapy and/or hormonal therapy with targeted therapy.

Statistical Analysis

Descriptive statistics were used to determine patient demographics and clinical characteristics. All tests of hypotheses were conducted at the $\alpha = .05$ level with a 95% confidence interval (95% CI). To compare categorical tumor features in the 4 biological subgroups of patients, the chi-square test was used. For those categorical variables in which the chi-square test was inappropriate because of small numbers, the Fisher exact test was used. Survival rates from the detection of brain metastases were estimated using the Kaplan-Meier method and compared using the log-rank test.

To determine factors influencing survival from brain metastases, univariate and multivariate Cox analyses were performed. The following factors were included in the univariate analysis: KPS ($\geq$70 vs $<$70), age ($\geq$40 years vs $<$40 years, and $\geq$65 years vs $<$65 years), number of brain metastases (1 vs 2 and 1 vs multiple), localization of brain metastases in the brain (infratentorial vs supratentorial), biological subtype of breast cancer (triple-negative vs luminal A and triple-negative vs HER2 with luminal B), locoregional disease recurrence (yes vs no), lung metastases (yes vs no), liver metastases (yes vs no), bone metastases (yes vs no), controlled extracranial disease (yes vs no), and systemic treatment after WBRT (yes vs no). Factors that were found to be significant in univariate analysis were examined in the multivariate model. To obtain the final multivariate model, a forward stepwise procedure was used with a P value for removal $>$.1. The proportional hazard assumption in the final model was tested using Schoenfeld residuals.

RESULTS

Patient Demographics and Treatment

Brain metastases were detected on magnetic resonance imaging (408 of 420 patients; 97%) or computed tomography (12 of 420 patients; 3%). WBRT was performed in 411 patients (411 of 420 patients; 98%) using a 4 to 6-megavolt photon beam by 2 lateral opposed standard fields covering all intracranial contents. The most common regimen of WBRT was 30 grays (Gy) in 10 fractions. Nine patients (9 of 420 patients; 2%) were not irradiated due to poor KPS at the time of the diagnosis of brain metastases. All irradiated patients were treated with corticosteroids in the course of WBRT. Sixty-nine patients (69 of 420 patients; 16%) with 1 or 2 brain metastases underwent surgery before WBRT. Systemic treatment after WBRT was ordered in 297 (297 of 420 patients; 71%) patients. The majority of these patients (249 of 297 patients; 84%) received chemotherapy. Schedules with vinorelbine and capecitabine were the most frequent types of chemotherapy used. Hormonal therapy was used in 23% of patients (69 of 297 patients). Aromatase inhibitors were the most frequently ordered. Targeted therapy (trastuzumab or lapatinib) was ordered in 47% (105 of 223 patients) of all HER2-positive patients in the study. Clinical characteristics and type of systemic treatment after WBRT are presented in Table 1.

Pattern of Metastatic Spread Depending on Biological Subtype

In the group of 399 patients with brain metastases, the luminal A, luminal B, HER2, and triple-negative subtypes accounted for 81 (20%), 92 (23%), 120 (30%), and 106 (27%) of cases, respectively. Breast cancers from particular biological subtypes varied depending on the pattern of metastatic spread. In patients with HER2-positive breast cancer (HER2 and luminal B subtypes), metastases in many organs (lung, liver, bone, and soft tissue) were detected and brain metastases appeared after the dissemination to other organs. In patients with the luminal A subtype, the bones and lungs were the most frequent sites of metastasis. In approximately one-third of patients with triple-negative breast cancer, brain metastases developed as a first or the only distant event. They could also appear after lung metastases. The frequency of clinicopathologic variables within the 4 biological subsets is presented in Table 2.

Survival

Median time of prospective observation measured from the detection of brain metastases was 2.9 years (95% CI, 1.68-4.18 years).

The median survival calculated from brain metastases in the entire group was 8 months (luminal A, 10 months; luminal B, 9 months; HER2, 9 months; and triple-negative, 4 months; $P = .0005$).

The median survival calculated from brain metastases in RPA RTOG prognostic classes I, II, and III was 15 months, 11 months, and 3 months, respectively ($P < .0001$).

In the entire group, the median survival from brain metastases in patients without and with systemic treatment after WBRT was 3 months and 10 months, respectively ($P < .0001$). Survival from brain metastases depending on systemic treatment is presented in Figure 1.

In the group of patients with luminal A breast cancer, the median survival without and with systemic therapy was 3 months and 12 months, respectively ($P = .003$). In the group of patients with the luminal B subtype, the median survival without further treatment, after chemotherapy and/or hormonal therapy, and after chemotherapy and/or hormonal therapy with targeted therapy was 2 months, 9 months, and 15 months, respectively ($P < .0001$). In patients with the HER2 breast cancer subtype, the median survival without further treatment, after chemotherapy and/or hormonal therapy, and after chemotherapy and/or hormonal therapy with targeted therapy

Table 1. Characteristics of 420 Patients With Brain Metastases

Characteristic	No. of Patients	%
Age at initial diagnosis, y		
Median	50	
Range	21-76	
Initial TNM stage		
I	43	10
II	172	41
III	143	34
IV	62	15
Histologic type		
Ductal carcinoma	333	79
Lobular carcinoma	28	7
Medullar, apocrinal, papillar, mucinous, planoepithelial, neuroendocrine carcinomas	21	5
Cancer cells or invasive cancer after chemotherapy	38	9
ER/PgR status		
Positive	185	44
Negative	226	54
Missing	9	2
HER2 status		
Positive	223	53
Negative	187	45
Missing	10	2
Systemic adjuvant therapy		
Yes	269	64
No	151	36
Localization of metastases		
Brain as the first or only site	88	21
Liver	141	34
Lung	217	52
Bone	189	45
Locoregional recurrence		
Yes	131	31
RPA RTOG Prognostic class		
I	43	10
II	240	57
III	137	33
Neurosurgery		
Yes	69	16
Schedule of radiotherapy		
40 Gy/20 fractions	34	8
30 Gy/ 10 fractions or 20 Gy/5 fractions	377	90
No radiotherapy	9	2
Systemic therapy after brain metastases		
Yes	297	71
No	123	29
Type of systemic therapy[a]		
Hormonal therapy	69/297	23
Chemotherapy	249/297	84
Targeted therapy	105/297	35
Type of chemotherapy; schedules with[a]		
Vinorelbine	89/249	36
Capecitabine	55/249	22

(Continued)

Table 1. (Continued)

Characteristic	No. of Patients	%
Anthracycline	38/249	15
Platinum	35/249	14
Taxane	27/249	11
5-Fluorouracil	20/249	8
Cyclophosphamide	18/249	7
Etoposide	15/249	6
Other	4/249	2
Type of endocrine therapy[a]		
Aromatase inhibitors	34/69	49
Tamoxifen	19/69	28
Goserelin	8/69	11.5
Megestrol acetate	8/69	11.5
Fulvestrant	7/69	10
Type of targeted therapy[a]		
Trastuzumab	98/105	93
Lapatinib	9/105	9

TNM indicates tumor node metastases classification; ER indicates estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; RPA RTOG, recursive partitioning analysis of Radiation Therapy Oncology Group; Gy, grays.

[a] In some patients, many types of systemic treatment were ordered.

was 4 months, 6 months, and 13 months, respectively ($P < .0001$). In patients with triple-negative breast cancer, the median survival without and with chemotherapy was 3 months and 4 months, respectively ($P = .16$). The results are presented in Table 3 and in Figure 2.

Factors Influencing Survival After WBRT

The Cox multivariate analysis confirmed the following factors as influencing survival: KPS, number of brain metastases, biological subtype of breast cancer, locoregional disease recurrence, liver metastases, control of extracranial disease, and systemic treatment after WBRT. Patients with good KPS, with 1 brain metastasis, without locoregional failure and distant metastases or with controlled extracranial disease, with a biological subtype other than triple-negative, and who were treated systemically after WBRT were found to survive longer. In contrast to this finding, poor KPS, multiple brain metastases, triple-negative breast cancer subtype, disseminated uncontrolled disease, and lack of systemic treatment after WBRT were factors found to worsen survival. Patients treated systemically after WBRT had a risk of death that was 3 times lower than patients without further treatment. The results of multivariate analysis are presented in Table 4.

DISCUSSION

The goal of the current study was to build on our previous work and explore the prognostic influence of systemic therapy after WBRT for patients with brain metastases from breast cancer in a subtype-specific manner. A group of breast cancer patients with brain metastases who were treated at 1 institution during a relatively short period of time using similar, modern methods of treatment was analyzed. To our knowledge, it is the largest group of patients with breast cancer brain metastases in whom the role of systemic treatment after WBRT within biological subgroups has been assessed.

Gene expression profiling divides breast cancer into several distinct diseases with heterogeneous expression of ER, PgR, and HER2 receptors as well as different responses to treatment and outcomes.[9] Basal-like and HER2-positive tumors are more likely to metastasize to the brain, and they have the worst prognosis.[10] Without being able to perform gene expression profiling, we have defined subsets of patients based on the expression of ER, PgR, and HER2 receptors, which were proposed by Hugh et al.[11] Metastatic pattern and propensity of biological subtypes to the brain, observed in our study, were discussed elsewhere.[6] We have observed a good response to hormonal therapy in the luminal A patient subset and to chemotherapy with targeted therapy in the HER2-positive breast cancer patients (those with HER2 and luminal B subtypes). We have not achieved satisfactory results with the systemic treatment in patients with triple-negative breast cancers. This suggests that triple-negative breast cancer is a distinct and very aggressive biological subtype. Our observations are in agreement with the data that have already been published.[5,12,13]

Table 2. Characteristics of Patients in Biological Subgroups (399 Patients)

Characteristic	Luminal A (HER2-negative, ER/PgR-positive)	Luminal B (HER2-positive, ER/PgR-positive)	HER2/neu (HER2-positive, ER/PgR-negative)	Triple-negative (HER2-negative, ER-negative, PgR-negative)	*P*
	No. %	No. %	No. %	No. %	
No. of patients					
Age at initial diagnosis, y	81 (20)	92 (23)	120 (30)	106 (27)	—
Median	55	52	55	55	
Range	29-79	23-77	27-91	23-81	.205
Initial TNM stage					
I	10 (12)	8 (8)	9 (8)	16 (15)	
II	32 (39)	37 (40)	50 (42)	46 (43)	
III	23 (29)	29 (32)	45 (38)	37 (35)	
IV	16 (20)	18 (20)	16 (14)	7 (7)	.128
Histologic type					
Lobular carcinoma	16 (20)	6 (7)	4 (3)	2 (2)	
Ductal carcinoma Grade 3	20 (25)	28 (30)	49 (41)	57 (54)	
Ductal carcinoma Grade 2 and other	45 (55)	58 (63)	67 (56)	47 (37)	**<.001**
Brain metastases as the only site of dissemination	19 (23)	10 (11)	18 (15)	36 (34)	**<.001**
Localization of other metastases					
Liver	24 (29)	43 (47)	47 (39)	18 (17)	**<.001**
Lung	39 (48)	55 (60)	60 (50)	53 (50)	.590
Bone	46 (57)	53 (58)	57 (47)	25 (24)	**<.001**
Local recurrence	15 (19)	42 (46)	42 (35)	30 (29)	**.001**
KPS					
≥70	55 (68)	69 (75)	88 (73)	60 (57)	
<70	26 (32)	23 (25)	32 (27)	46 (43)	.025
RPA RTOG prognostic class					
I	13 (16)	6 (7)	9 (7)	14 (14)	
II	42 (52)	63 (68)	79 (66)	46 (43)	
III	26 (32)	23 (25)	32 (27)	46 (43)	**.004**
Systemic treatment of brain metastases					
Yes	59 (73)	77 (84)	91 (76)	59 (56)	
No	22 (27)	15 (16)	29 (24)	47 (44)	**<.001**

HER2 indicates human epidermal growth factor receptor 2; ER, estrogen receptor; PgR, progesterone receptor; TNM, tumor node metastases classification; KPS, Karnofsky performance status; RPA RTOG, recursive partitioning analysis of Radiation Therapy Oncology Group.

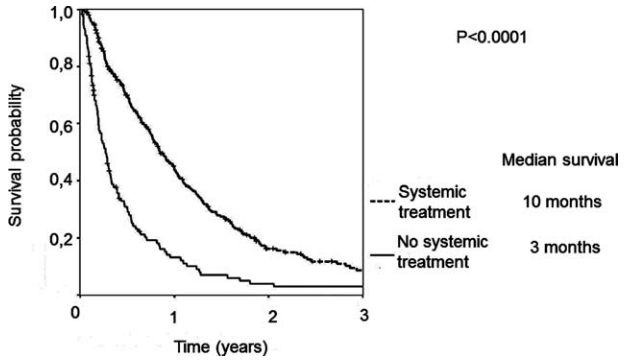

Figure 1. Survival from brain metastases depending on systemic treatment after whole-brain radiotherapy is shown.

The results of the current study confirmed that IHC enables us to divide breast cancer patients into biological subtypes with different prognosis and prediction outcomes. With regard to the lack of gene expression profiling, it should be a useful surrogate in everyday clinical practice.

It is difficult to determine whether systemic treatment ordered after WBRT prolongs survival due to control of extracranial disease only or whether it influences cerebral disease as well. In patients with breast cancer and brain metastases, disease progression at other organs is often observed.[5,6,14] Therefore, there is a need for the introduction or continuation of systemic therapy after WBRT

Table 3. Median Survival and 1-Year Survival From Brain Metastases in 4 Biological Subgroups Depending on Systemic Treatment After WBRT

Biological Subtype	No Systemic Treatment	Chth/Ht	Chth/Ht With Targeted Therapy	*P*
Luminal A (HER2-negative ER/PgR-positive):				
Median survival, mo	3	12	—	
95% CI	0.01-7.68	8.40-16.44	—	.003
1-y survival rate	10%	51%	—	
Luminal B (HER2-positive ER/PgR-positive):				
Median survival, mo	2	9	15	
95% CI	2.04-2.76]	6.60-11.52	10.08-19.80	
1-y survival rate	0	33%	58%	<.0001
HER2 (HER2-positive ER/PgR-negative):				
Median survival, mo	4	6	13	
95% CI	(3.36-4.32	4.56-7.92	9.96-16.44]	
1-y survival rate	5%	33%	55%	<.0001
Triple-negative:				
Median survival, mo	3	4	—	
95% CI	1.44-4.08	1.32-7.32	—	
1-y survival rate	14%	23%	—	.16

WBRT indicates whole-brain radiotherapy; Chth, chemotherapy; Ht, hormonal therapy; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PgR, progesterone receptor; 95% CI; 95% confidence interval.

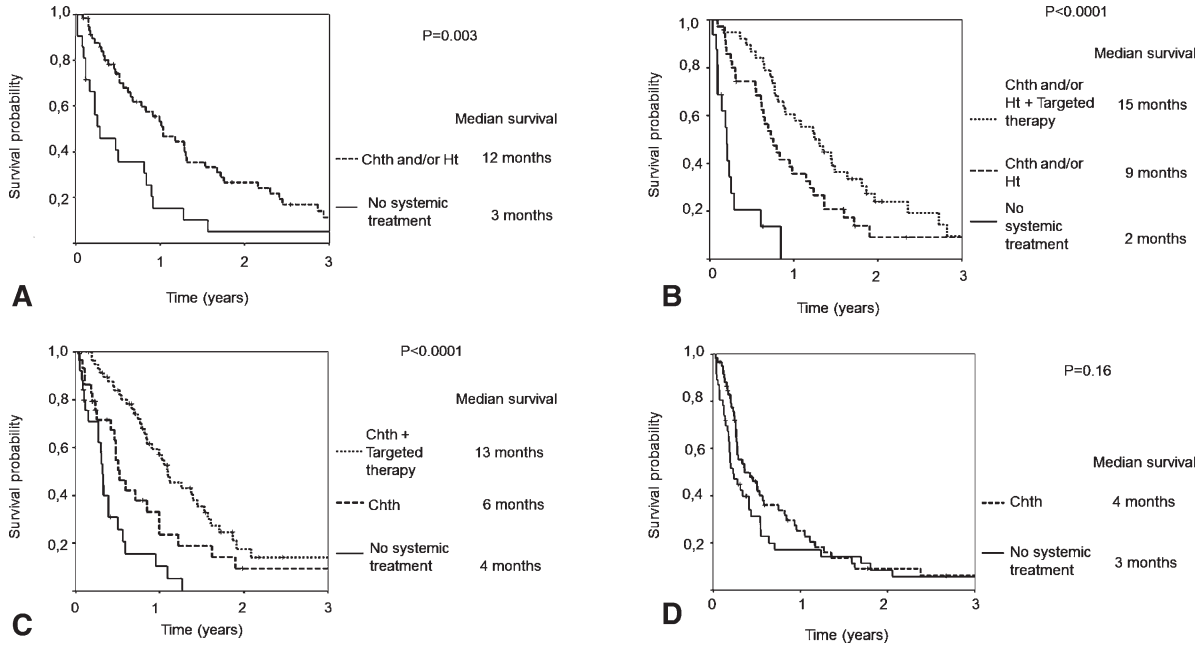

Figure 2. Survival from brain metastases is shown depending on systemic treatment in separate biological subtypes of breast cancer: (A) luminal A, (B) luminal B, (C) human epidermal growth factor receptor 2 (HER2), and (D) triple-negative. Chth indicates chemotherapy; Ht, hormonal therapy.

in this patient population. In the current study, in approximately 80% of patients with brain metastases, extracranial disease was accompanied by brain recurrent. Our previous studies, concerning patients with breast cancer and brain metastases and patients with leptomeningeal metastases, revealed that improvement in survival after systemic therapy could be attributed mainly to the control of extracranial disease[14] and that systemic treatment was effective in patients with good as well as poor performance status.[6,15]

Table 4. Factors Influencing Survival From Brain Metastases: Multivariate Analysis

Factor	HR	*P*	95% CI (HR)
KPS (≥70 vs <70)	0.34	<.001	0.26-0.44
Biologic subtype (HER2 and luminal B vs triple-negative)	0.6	.002	0.45-0.83
Biological subtype (luminal A vs triple-negative)	0.6	.004	0.42-0.84
Locoregional failure (yes vs no)	1.3	.025	1.03-1.69
Liver metastases (yes vs no)	1.3	.022	1.04-1.72
Systemic disease (controlled vs uncontrolled)	0.53	<.001	0.38-0.73
Systemic treatment after WBRT (yes vs no)	0.35	<.001	0.26-0.48
No. of brain metastases (multiple vs 1)	2.2	<.001	1.56-3.09
No. of brain metastases (1 vs 2)	1.64	.60	0.97-2.76
Localization of brain metastases (infratentorial vs supratentorial)	1.57	.065	0.97-2.53

HR indicates hazard ratio; 95% CI, 95% confidence interval; KPS, Karnofsky performance status; HER2, human epidermal growth factor receptor 2; WBRT, whole-brain radiotherapy.

The activity of systemic drugs in relation to brain lesions remains unclear, and this clinical issue is still unresolved. It appears that some chemotherapeutics and hormonal agents can reach the brain tumor, because in patients with brain metastases, the blood-brain barrier (BBB) is in part disrupted. WBRT additionally increases its permeability. To the best of our knowledge, the role of systemic treatment in the management of brain metastases has been explored in a very limited number of controlled comparative trials. These studies have been conducted mostly in patients with non-small cell lung cancer. Among 10 clinical trials assessing the role of chemotherapy in the management of patients with newly diagnosed brain metastases,[16] only 1 applies to patients with breast cancer.[17] In this study, the role of temozolomide was assessed. In patients in whom temozolomide was ordered after WBRT, the benefit observed in the response rate within the brain was achieved, but without the influence on survival noted. Temozolomide does not appear to play an active role in the treatment of brain metastases from breast cancer.

Some retrospective studies have evaluatee the response to various chemotherapeutic drugs in brain metastases from breast cancer. These regimens were considered either before or after WBRT in patients with newly diagnosed metastatic breast cancer to the brain, particularly in the presence of active systemic disease. An objective response rate after cyclophosphamide, 5-fluorouracil, methotrexate, epirubicin, cisplatin, and etoposide was achieved in 38% to 55% of patients, and the median survival time was 7 to 13 months.[3,18]

In the current study, the majority of patients were heavily pretreated before the detection of brain metastases. Vinorelbine and capecitabine were used most frequently. Both are effective in patients with dissemination to the viscera, but to the best of our knowledge, little is known concerning its efficacy to the brain. Capecitabine as a single agent has been shown to have activity in small series of breast cancer patients with recurrent brain metastases.[19-21] Three of 7 patients demonstrated a complete response and 3 achieved stable disease, with a median overall and progression-free survival after treatment of 13 months and 8 months, respectively.[22] The combination of capecitabine and temozolomide demonstrated a clinical response in patients who recurred after WBRT.[23] To our knowledge, data regarding the efficacy of vinorelbine in the treatment of breast cancer brain metastases are also scarce. In the study of Omuro et al, no response was achieved after a combination of temozolomide with vinorelbine for brain metastases, however, only 6 of the 21 cases were breast cancer patients.[24]

In recent years, targeted therapies with the use of trastuzumab and lapatinib have been increasingly investigated in patients with breast cancer metastases to the brain. A retrospective analysis of patients' data has been performed to evaluate the effect of trastuzumab on survival in patients with brain metastases. In some studies, overall survival from the time of diagnosis of brain metastases was compared between patients with HER2-positive disease who received trastuzumab and patients with either HER2-positive or HER2-negative disease who did not. The studies confirmed that, in HER2-positive breast cancer patients with brain metastases, trastuzumab treatment that continued after WBRT prolonged survival due to control of extracranial disease. The median survival from the time of the diagnosis of brain metastases in patients treated with trastuzumab ranged from 12 to 24.9 months.[25-29] In the current study, approximately half of HER2-positive breast cancer patients continued to receive trastuzumab after WBRT. The median survival after

chemotherapy and/or hormonal therapy with targeted therapy was 13 months for breast cancer patients with the HER2 subtype and 15 months for those with the luminal B subtype. This result was even better than that observed in patients with the luminal A subtype of breast cancer (12 months), which is known as a subset with the best prognosis. We believe that, in patients with HER2-positive breast cancer, targeted therapy added to chemotherapy and/or hormonal therapy has an additional impact on survival and should be continued after the detection of brain metastases.

Lapatinib is the second targeted drug investigated in patients with brain metastases from breast cancer, but to the best of our knowledge, only modest activity of this drug was assessed.[30] In the current study, only 9 patients were treated with lapatinib after progression to trastuzumab, so it was difficult to assess the efficacy of this drug in the current group of patients.

Conclusions

Systemic treatment ordered after WBRT appears to improve survival in patients with the luminal A, luminal B, and HER2 subtypes of breast cancer. Targeted therapy was found to have an additional positive impact on survival. The role of systemic treatment after WBRT in triple-negative breast cancer cannot be clearly defined, and therefore there is a need for more prospective data targeting this patient population. We are of the opinion that, in breast cancer patients with brain and extracranial metastases, systemic therapy should be continued after local treatment (WBRT, surgery, and stereotactic radiosurgery). Even if systemic therapy after WBRT affects only extracranial disease, the results of trastuzumab therapy, not crossing the BBB, indicate that visceral regression can prolong survival. However, prospective randomized trials that include a homogenous group of breast cancer patients with brain metastases are needed to assess the response rate of systemic treatment in the brain and in the viscera and to evaluate the causes of death. Improvements in systemic therapy for triple-negative breast cancer are urgently needed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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