

Prophylactic Cranial Irradiation in HER-2 Positive Metastatic Breast Cancer Patients

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Abstract: Purpose: Brain metastasis in patients with breast cancer is associated with decreased overall survival (OS) and impaired quality of life (QoL). In this prospective study, we assessed the effect of prophylactic cranial irradiation (PCI) in HER-2 positive metastatic breast cancer (MBC) patients aiming at decreased incidence of CNS metastasis with tolerated toxicities. **Patients and Methods:** Forty patients with metastatic HER-2 positive breast cancer were randomly assigned to PCI or no PCI between December 2013 and November 2014. The whole brain received 2.4 Gy per fraction, to a total dose of 24 Gy. MRI brain was a part of the neurological assessment of all patients. Neuro-cognitive function (NCF) was evaluated using Mini-Mental state examination (MMSE). **Results:** Two patients in the PCI group (10%) developed brain metastases in comparison to five patients in no PCI group (25%) with insignificant difference between both groups, $P=0.4$. Changes in MMSE scores were documented in 10% in Group A versus 25% in Group B. **Conclusion:** PCI resulted in a numerical halving of the incidence of symptomatic brain metastases with tolerated toxicities, but this was not statistically significant.

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1. Introduction

Breast cancer is the most common malignancy of women worldwide. These tumors commonly metastasize to bone, lung and liver. The brain metastasis is rare and usually a late manifestation of advanced breast cancer. In contrast, metastatic breast cancer (*MBC*) patients have an elevated risk for cerebral metastases affecting 25-45% [1,2].

Brain metastasis in patients with breast cancer is associated with decreased survival and impaired quality of life. Even in young patients with the best performance status, and controlled extra-cranial disease, the median survival remains poor at approximately 3-9 months [3,4].

Several studies have focused on clinicopathological features as risk factors that could predict brain metastasis in breast cancer. These have identified younger age, hormone receptor-negative tumors, heavy burden of disease (i.e. large tumors, positive lymph node status, previous lung, liver, or bone metastasis, and increased number of metastatic sites) and over-expression of human epidermal growth factor receptor 2 (*HER-2*) [5,6,7].

HER-2 over-expression defines an aggressive subtype of breast cancer characterized by rapid cell proliferation, increased angiogenesis, deficient apoptosis and increased metastasis formation [8].

Controlling and eradicating undetectable micro-metastases with subsequent decrease in the incidence of brain metastasis with acceptable effects on neurocognitive function would be a significant improvement in the care of patients with MBC [9]. In

this prospective study, we assessed the effect of prophylactic cranial irradiation (PCI) in metastatic HER-2 positive breast cancer patients aiming at decreased incidence of CNS metastasis with tolerated toxicities.

2. Patients and Methods

This study included 40 patients with HER-2 positive MBC who were prospectively treated in Clinical Oncology Department, Zagazig University Hospitals between December 2013 and November 2014. Patients were randomized into 2 groups: **Group A** who received prophylactic cranial irradiation (*PCI*) and **Group B** who did not receive PCI.

Eligibility Criteria

Inclusion criteria were: female patient with HER2-positive metastatic breast cancer (3+ positivity on immunohistochemistry or fluorescence in situ hybridization [*FISH*] positive); age ≥ 18 years; ECOG PS ≤ 2 ; Hemoglobin ≥ 10 g/dL, platelets $\geq 100,000/\mu\text{L}$, WCC $\geq 2,000/\mu\text{L}$; able to complete Mini-Mental state examination (*MMSE*) [10,11]; life expectancy ≥ 6 months and Signed informed consent form.

Exclusion criteria were: history of malignant brain disease; prior radiotherapy of the brain; prior stroke or brain hemorrhage and history of neurological/ psychiatric disorders.

Patient Assessment

Pre-radiotherapy assessment includes: detailed history taking; full physical examination; hematological and biochemical laboratory evaluation

(complete blood count, liver function tests and kidney function tests); magnetic resonance imaging (*MRI*) of the brain with contrast no more than 6 weeks prior to PCI and magnetic resonance spectroscopy (*MRS*) of the brain, if indicated; CT chest, abdomen and pelvis; bone scan and MMSE.

Treatment Plan

Patients with HER-2 positive MBC patients enrolled in this trial were randomized 1:1 into 2 groups: **Group A** includes patients who received PCI. **Group B** includes patients who did not receive PCI. PCI was arranged to be given without interruption of the patient's systemic treatment. So in patients under chemotherapy, PCI was given before starting combination chemotherapy or sequentially during assessment period between chemotherapy cycles.

Radiotherapy schedule

Patients were simulated in supine position with arms aside. Fixation was done using thermoplastic mask and a headrest was applied for each patient to be comfortable and reducible. The radiation course was implemented using Cobalt-60 machine or linear accelerator with 6 MV photon energy. Whole brain irradiation was administered through parallel-opposed lateral portals with the total dose calculated at mid plane. The whole brain received 2.4 Gy per fraction, to a total dose of 24 Gy, given in 10 fractions over 2 weeks.

Premedication

Intravenous hydration (at least 0.5 L of saline with 125 mg of mannitol) and corticosteroids such as dexamethasone in dose of 16-32mg were given daily before WBRT.

Evaluation of Treatment and Follow Up

Clinical and radiological follow up for patients' systemic disease was done monthly and every three months, respectively.

MRI brain was a part of the neurological assessment of all patients included prior to PCI every 6 months in the first year, and then annually. CNS metastasis was defined as the presence of either leptomeningeal disease and/or metastases in the brain parenchyma. Acute toxicities were graded based on WHO scale. Neuro-cognitive function (*NCF*) was evaluated basically prior to and then 6 months and 1 year after PCI using full neurological examination and MMSE.

The MMSE is a tool that can be used to systematically and thoroughly assess mental status. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. The MMSE takes only 5-10 minutes to administer and therefore practical to use repeatedly and routinely [12].

3. Results

In the present study, patients' age ranged between 23 - 76 years in Group A and between 28 - 72 years in Group B with a mean age of 48.3 years. All patients in both groups presented with infiltrating duct carcinoma (*IDC*). Among all patients, 14 patients in Group A and 11 patients in Group B had moderately differentiated tumor (G II), while 6 patients in Group A and 9 patients in Group B showed poorly differentiation tumors (G III). 70% of patients in Group A and 55% in Group B were hormonal receptor positive.

Most of the patients in both Groups progressed during the first two years after initial presentation. Among all patients; 7 patients in Group A (35%) and 8 patients in Group B (40%) progressed within the first year after initial presentation, while 7 patients in Group A (35%) and 6 patients in Group B (30%) progressed during the second year after initial presentation with no significant difference between both groups.

As regards site of metastasis, patients with bone, lung and liver metastasis constituted 65%, 45% & 25% for Group A compared to 75%, 45% & 20% for Group B, respectively (Table 1). In the present study, overall failure rate in Group A was 10% versus 25% in Group B with insignificant difference between the two groups.

Fourteen patients in Group A (70%) and 13 patients in Group B (65%) had single metastatic site. Five patients in Group A (25%) versus six patients in Group B (30%) presented with two metastatic sites.

As shown in Table 1, both groups were comparable regarding age, grade, stage at presentation, hormonal receptor (*HR*) status, disease free survival (*DFS*), sites of metastasis and number of metastatic sites.

In response to PCI, two patients in Group A (10%) versus five patients in Group B (25%) developed brain metastasis with no significant difference between both groups. Brain metastasis occurred within six months after PCI in single patient in Group A versus three patients in Group B while single patient in Group A and two patients in Group B developed brain metastasis within one year.

Concerning treatment toxicity, acute toxicities were mild in both groups. Among all patients, 30% of patients in Group A versus 20% of patients in Group B had grade 2 nausea, 15% of patients in Group A versus 10% of patients in Group B had grade I vomiting, and 35% of patients in Group A versus 25% of patients in Group B had grade II fatigue. Neuro-cognitive function of all patients was evaluated using MMSE at 6 month and one year. Changes in MMSE score was documented in 10% in Group A versus 25% in Group B. Changes in MMSE score was attributed to

occurrence of brain metastasis. Two patients in Group A versus five patients in Group B developed reduction

of MMSE score below 23 with no significant difference between both groups.

Table 1. Patient characteristics

<i>Patient characteristics</i>		<i>Group A n = 20</i>		<i>Group B n = 20</i>		<i>P value</i>
		<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	
<i>Age(years)</i>	<i>< 40</i>	3	15	7	35	0.51
	<i>40-60</i>	13	65	11	55	
	<i>> 60</i>	4	20	2	10	
<i>Grade</i>	<i>II</i>	14	70	11	55	0.32
	<i>III</i>	6	30	9	45	
<i>Stage</i>	<i>II</i>	7	35	8	40	1.0
	<i>III</i>	13	65	12	60	
<i>HR status</i>	<i>Positive</i>	14	70	16	55	0.46
	<i>Negative</i>	6	30	4	45	
<i>DFS(years)</i>	<i>1</i>	7	35	8	40	1.0
	<i>2</i>	7	35	6	30	
	<i>3</i>	4	20	3	15	
	<i>4</i>	1	5	2	10	
	<i>5</i>	1	5	1	5	
<i>Site of Met.</i>	<i>Bone</i>	13	65	15	75	1.0
	<i>Lung</i>	9	45	9	45	
	<i>Liver</i>	5	25	4	20	
<i>No. of Met. sites</i>	<i>1</i>	14	70	13	65	1.0
	<i>2</i>	5	25	6	30	
	<i>3</i>	1	5	1	5	

Table 2. Response to treatment in relation to patient characteristics

<i>Response to treatment</i>		<i>Group A n = 20</i>		<i>Group B n = 20</i>		<i>P value</i>
		<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	
<i>Overall Failure Rate (months)</i>	<i>≤ 6</i>	1	5	3	15	0.4
	<i>> 6</i>	1	5	2	10	
<i>Age(years)</i>	<i>< 40</i>	0/3	0	2/7	29	0.86
	<i>40-60</i>	2/13	15	3/11	27	0.83
	<i>> 60</i>	0/4	0	0/2	0	1.0
<i>Grade</i>	<i>II</i>	2/14	14	4/11	36	0.41
	<i>III</i>	0/6	0	1/9	11	0.83
<i>Stage</i>	<i>II</i>	1/7	14	1/8	12.5	0.92
	<i>III</i>	1/13	8	4/12	33	0.4
<i>HR status</i>	<i>Positive</i>	2/14	14	3/16	19	0.86
	<i>Negative</i>	0/6	0	2/4	50	0.25
<i>DFS(years)</i>	<i>1</i>	1/7	14	2/8	25	0.94
	<i>2</i>	0/7	0	2/6	33	0.72
	<i>3</i>	0/4	0	0/3	0	1.0
	<i>4</i>	0/1	0	1/2	50	0.85
	<i>5</i>	1/1	100	0/1	0	0.91
<i>Site of Met.</i>	<i>Bone</i>	2/13	15	4/15	27	0.79
	<i>Lung</i>	1/9	11	4/9	44	0.29
	<i>Liver</i>	1/5	20	2/4	50	0.81
<i>No. of Met. sites</i>	<i>1</i>	1/14	7	1/13	8	0.49
	<i>2</i>	0/5	0	3/6	50	0.24
	<i>3</i>	1/1	100	1/1	100	1.0

4. Discussion

HER-2 over-expression defines an aggressive subtype of breast cancer characterized by rapid cell proliferation, increased angiogenesis, deficient apoptosis and increased metastasis formation. As breast cancer shares many features with small cell lung cancer (*SCLC*) (although in a lesser fashion) like chemo-sensitivity, radio-sensitivity, risk of isolated brain relapse particularly in high risk groups, systemic nature of disease, effective control of extra-cranial disease with systemic therapies etc., and hence, this could be a model supporting the use of PCI in breast cancer. With the use of current modern radiation modalities, PCI has become very safe and tolerable [13,14]. At presentation, 70% of patients had bone metastasis and 60% had visceral metastasis compared to 40% of patients with bone metastasis and 80% of patients with visceral metastasis included in the study carried out by Dawood *et al.* in 2008 at MD Anderson Cancer Center, Texas, USA [15].

Twenty seven patients presented with single metastatic site (67.5%) and thirteen patients presented with two or more metastatic sites (32.5%); while 46.1% of patients presented with single metastatic site and 53.9% presented with two or more metastatic sites were included in the study carried out by Brufsky *et al.* in 2011 [16].

In the present study, PCI resulted in an approximate numerical halving of the incidence of symptomatic CNS disease in Group A, at one year of follow-up, compared with the no PCI, Group B. However, this did not reach statistical significance. These results are consistent with that reported by Canney *et al.* in 2015 who underwent a prospective, randomized phase III trial that tested whether PCI could reduce the incidence of CNS metastases in patients with HER2-positive tumors receiving trastuzumab therapy for metastatic breast cancer. The cumulative incidence of CNS metastases at 2 years was 32.4% on the no PCI arm and 21.0% on the PCI arm. PCI resulted in approximately 50% reduction in the incidence of symptomatic CNS disease which did not reach statistical significance. This insignificance was attributed to small sample size. The median survival was not reached at the end of the study. There was no evidence of cognitive dysfunction in PCI patients [17].

Neurocognitive deficits attributable to cranial irradiation are thought to be rare, but the true incidence and latency of CNS injury after PCI remain unknown. Late effects are reported to be more severe and more frequent at the extremes of age, and with concurrent chemotherapy, large fraction sizes, and a high total dose [18,19].

Changes in neurocognitive function had been documented using MMSE in two patients (10%) in Group A versus five patients in Group B (25%) at 6 months and one year after PCI. Changes in neurocognitive function were attributed to occurrence of brain metastasis. The neurocognitive toxicity was lower than 30% observed in the study by Huang *et al.* in 2009 [18].

Conclusion

PCI resulted in a numerical halving of the incidence of symptomatic brain metastases, but this was not statistically significant. This insignificance could be attributed to small sample size. Moreover, there was no excess toxicity in the PCI arm compared with the no PCI arm in respect of acute toxicities and neurocognitive function.

Further research is needed with larger number of patients and may be different radiotherapy dosing and fractionation aiming to minimize the treatment related morbidity and maximize the therapeutic gain.

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