J Breast Cancer. 2019 Mar;22(1):120-130
https://doi.org/10.4048/jbc.2019.22.e1
pISSN 1738-6756·eISSN 2092-9900

Journal of Breast Cancer JBC

Original Article

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Central Nervous System Failure in Korean Breast Cancer Patients with HER2-Enriched Subtype: Korean Radiation Oncology Group 16-15 Multicenter Retrospective Study

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OPEN ACCESS

Received: Sep 6, 2018
Accepted: Nov 30, 2018

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ABSTRACT

Purpose: The purpose of this study was to evaluate the risk of central nervous system (CNS) failure in Korean patients with human epidermal growth factor receptor 2 (HER2)-enriched breast cancer treated with surgery followed by postoperative radiotherapy (RT).
Methods: A total of 749 patients from eight institutions were enrolled in this study. All of them underwent surgery followed by postoperative RT from 2003 to 2011; 246 (32.8%) received neoadjuvant chemotherapy and 649 (81.7%) received adjuvant chemotherapy. Adjuvant trastuzumab was administered to 386 patients (48.6%).
Results: The median follow-up duration was 84 (range, 8–171) months. The 7-year disease-free and overall survival rates were 79.0% and 84.2%, respectively. On multivariate analysis, mastectomy, nodal involvement, and presence of lymphatic invasion were correlated with poor overall survival (p = 0.004, 0.022, and 0.011, respectively), whereas T stage and lymphatic invasion were associated with disease-free survival (p = 0.018 and 0.005, respectively). Regarding CNS failures, 30 brain metastases, 2 leptomeningeal metastases, and 8 brain and leptomeningeal metastases were noted. The 7-year CNS relapse-free survival rates in patients receiving and not receiving trastuzumab were 91.2% and 96.9%, respectively (p = 0.005). On multivariate analysis, the administration of adjuvant trastuzumab was the only prognostic factor in predicting a higher CNS failure rate (hazard ratio, 2.260; 95% confidence interval, 1.076–4.746; p = 0.031).
Conclusion: Adjuvant trastuzumab was associated with higher CNS failure rate in Korean patients with HER2-enriched breast cancer. Close monitoring and reasonable approaches such as CNS penetrating HER2 blockades combined with the current standard therapy could contribute to improving intracranial tumor control and quality of life in patients with CNS metastasis from HER2-enriched breast cancer.

Journal of Breast Cancer JBC

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Funding
This work was supported by the grant (#0820010) for Cancer Control Program from Korean Ministry of Health and Welfare and Seoul National University Bundang Hospital Research Fund (#18-2018-001) to In Ah Kim.

Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Conceptualization: Kim IA; Data curation: Shin KH, Kim JH, Choi DH, Park W, Kim YB, Kim HJ, Kim JH, Park H, Lee SY; Formal analysis: Kim K, Kim J; Funding acquisition: Kim IA; Investigation: Kim K, Kim IA; Methodology: Kim K, Kim J, Oh DH; Project administration: Kim IA; Resources: Shin KH, Kim JH, Choi DH, Park W, Kim YB, Kim HJ, Kim JH, Park H, Lee SY; Software: Oh DH; Supervision: Kim IA; Validation: Kim K; Visualization: Kim J; Writing - original draft: Kim K; Writing - review & editing: Kim K, Shin KH, Kim JH, Choi DH, Park W, Kim YB, Kim HJ, Kim JH, Park H, Lee SY, Kim J, Oh DH, Kim IA.

Keywords: Breast neoplasms; Central nervous system neoplasms; ERBB2 protein; Radiotherapy; Trastuzumab

INTRODUCTION

Human epidermal growth factor receptor-2 (HER2) is an adverse risk factor for relapsed breast cancer [1]. Trastuzumab, a monoclonal antibody targeting HER2, has dramatically improved the overall survival (OS) and disease-free survival (DFS) in patients with HER2 overexpression in both adjuvant and palliative settings [2-4]. The administration of trastuzumab has become the standard treatment in patients with HER2-positive breast cancers [5].

HER2 overexpression is reportedly associated with increased risk of brain metastasis both as the site of the first (4.3% vs. 0.4%) and eventual relapse [6]. Autopsy data show that the incidence hazard ratio (HR) of central nervous system (CNS) metastasis is higher (up to 50%) in HER2-positive than in HER2-negative breast cancer [7]. A retrospective study on 9,524 patients with early breast cancer identified HER2 positivity as a clear risk factor for the development of CNS relapse [8]. However, the exact biological mechanism for the tendency of HER2-positive cancer cells to metastasize to the CNS remains to be completely elucidated.

In addition, more CNS relapses have been observed in patients treated with trastuzumab for metastatic breast cancers [9,10]. In the adjuvant setting, a meta-analysis of randomized controlled trials comparing adjuvant trastuzumab and no trastuzumab administration in HER2-positive breast cancers noted that the CNS as the first site of failure was more common in patients receiving trastuzumab [11]. Moreover, a population-based study reported that adjuvant trastuzumab treatment was associated with higher CNS failure rate [12]. However, whether the increased CNS relapse is correlated with adjuvant trastuzumab remains controversial [13].

Among the patients with HER2-positive breast cancers, those with hormonal receptor-negative tumors are known to have more CNS failures than those with hormonal receptor-positive tumors [14]. However, most studies on HER2-positive tumors have included both types of tumors with their different molecular subtypes; thus, the interpretation is somewhat complicated.

This study evaluated the outcomes of surgery followed by postoperative radiotherapy (RT) in Korean patients with breast cancer having HER2-enriched subtype and compared the risk of CNS failures according to the administration of adjuvant trastuzumab.

METHODS

Study population

Medical records of 749 patients meeting the following inclusion criteria from eight institutions were reviewed and retrospectively analyzed: those who underwent systemic chemotherapy and local treatment including surgery followed by postoperative RT for stage I–III HER2-enriched breast cancer between January 2003 and December 2011. Pathologic information was retrieved from the reports of each institution. HER2-enriched breast cancer was defined as hormonal receptor-negative and HER2-positive tumor. HER2 positivity was

https://doi.org/10.4048/jbc.2019.22.e1

determined as a score of 3+ on immunohistochemical staining for c-erbB-2, or positive for *HER2* gene amplification on in situ hybridization if 2+. This study was approved by the Institutional Review Board (approval No. B-1609/364-103), and the requirement for obtaining informed consent was waived owing to its retrospective design.

Statistical analysis

The time between the initial treatment and corresponding recurrences or last follow-up was measured as locoregional relapse-free survival (LRRFS), distant metastasis-free survival (DMFS), and DFS. CNS relapse-free survival was defined from the date of the initial treatment to brain or leptomeningeal metastases irrespective of initial recurrences. OS was defined from the date of initial treatment to the last follow-up or death from any cause. The actual survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test. For multivariate analysis, Cox proportional hazards model was used. Factors with p-value of < 0.1 on univariate analysis were included in the multivariate analysis. A p-value of < 0.05 was considered statistically significant. Differences in categorical variables were compared using the standard χ^2 test or Fisher's exact test. All statistical analyses were performed using SPSS software (release 18.0.1.; SPSS Inc., Chicago, USA).

RESULTS

Characteristics and treatments

The median age of all patients was 51 (range, 26–81) years. Most patients (728 of 749, 97.2%) had invasive ductal carcinoma. With regard to T stage, 627 patients had T1–2 disease and 122 had T3–4 disease. A total of 229 patients were node negative, whereas 520 had nodal involvement. Patient and tumor characteristics are summarized in **Table 1**.

All patients received either neoadjuvant or adjuvant chemotherapy. Neoadjuvant chemotherapy was administered for clinically node-positive patients (n = 246): anthracycline-based chemotherapy in 27 patients, anthracycline followed by taxane in 60 patients, and taxane-based chemotherapy in 159 patients. A total of 443 and 306 patients underwent breast-conserving surgery and mastectomy, respectively. Regarding the axillary surgery, 601 and 144 patients underwent axillary lymph node dissection and sentinel lymph node biopsy. A total of 649 patients received adjuvant chemotherapy: anthracycline-based chemotherapy, 215; anthracycline followed by taxane, 260; taxane-based chemotherapy, 137; and others, 37 patients.

All patients underwent postoperative RT, either breast-conserving surgery or mastectomy. Post-mastectomy RT was indicated for patients with tumor size of > 5 cm or ≥ 4 involved axillary lymph nodes or both. The extent of regional nodal irradiation was determined as per the attending physicians' discretion. The median RT dose was 50.4 (range, 44.0–66.4) Gy.

A total of 386 patients received adjuvant trastuzumab (trastuzumab [+] group), whereas the remaining 363 did not (trastuzumab [−] group). Given that adjuvant trastuzumab has been covered by the Korean National Health Insurance since July 2009, pre-trastuzumab and trastuzumab eras were defined accordingly (n = 467 and 282, respectively). Trastuzumab was administered in 176 of 467 patients (37.7%) during the pre-trastuzumab era and in 210 of 282 patients (74.5%) during the trastuzumab era. The reason for missing trastuzumab administration in 72 patients during the trastuzumab era was not specified; however, the

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Table 1. Patient and tumor characteristics

Variables	No. of patients (%)
Age (yr)	
< 40	103 (13.8)
≥ 40	646 (86.2)
Type of breast surgery	
BCS	443 (59.1)
Mastectomy	306 (40.9)
Type of axillary surgery	
ALND	601 (80.2)
SLNBx	144 (19.2)
T stage	
1–2	627 (83.7)
3–4	122 (16.3)
N stage	
Negative	229 (30.6)
Positive	520 (69.4)
Histologic grade	
1	19 (2.5)
2	201 (26.8)
3	483 (64.5)
Missing	46 (6.1)
Lymphatic invasion	
Absent	388 (51.8)
Present	311 (41.5)
Missing	50 (6.7)
Trastuzumab	
Yes	386 (51.5)
No	363 (48.5)

BCS = breast-conserving surgery; ALND = axillary lymph node dissection; SLNBx = sentinel lymph node biopsy.

tumor characteristics were as follows: tumor size of ≤ 1 cm and node negative status in only 11 patients and tumor size of > 1 cm or node positive status or both in the remaining 61 patients.

Outcomes and prognostic factors

The median follow-up duration was 84 (range, 8–171) months for all patients, and 80 (range, 8–141) and 91 (range, 9–171) months in the trastuzumab (+) and trastuzumab (−) groups, respectively. A total of 24 local, 40 regional, and 23 locoregional recurrences were noted. Distant metastases occurred in 124 patients; 57 of them had locoregional recurrences. The 7-year DFS and OS rates were 79.0% and 84.2%, respectively (**Figure 1**).

In the univariate analysis, age, type of breast surgery, type of axillary surgery, T stage, N stage, and lymphatic invasion were significantly associated with DFS. DFS of patients receiving trastuzumab was higher than of those not receiving trastuzumab; however, the difference did not reach statistical significance (**Figure 2A**). In the multivariate analysis, advanced T stage (HR, 1.621; 95% confidence interval [CI], 1.086–2.420; $p = 0.018$] and the presence of lymphatic invasion (HR, 1.672; 95% CI, 1.173–2.384; $p = 0.005$) were significant prognosticators of lower DFS (**Table 2**).

Regarding OS, age, type of breast surgery, type of axillary surgery, T stage, N stage, and lymphatic invasion were significant prognosticators in the univariate analysis, but the administration of trastuzumab was not (**Figure 2B**). Among these, mastectomy (HR, 1.980; 95% CI, 1.245–3.150; $p = 0.004$), node positivity (HR, 2.620; 95% CI, 1.150–5.969; $p = 0.022$), and presence of lymphatic invasion (HR, 1.696; 95% CI, 1.126–2.555; $p = 0.011$) were the independent significant prognosticators of poor OS (**Table 2**).

https://doi.org/10.4048/jbc.2019.22.e1

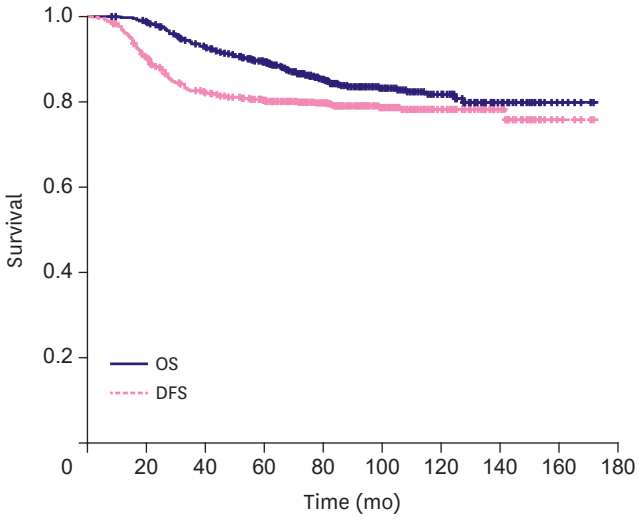

Figure 1. DFS and OS curves for all patients.
DFS = disease-free survival; OS = overall survival.

CNS relapse according to the administration of adjuvant trastuzumab

Patient and tumor characteristics according to the administration of adjuvant trastuzumab are compared in **Table 3**. In brief, the number of patients with nodal involvement, high-grade tumor, and lymphatic invasion was higher in the trastuzumab (+) group than that in the trastuzumab (−) group. Regarding CNS relapse, 40 CNS failures (5.3%), including 30 brain metastases, two leptomeningeal metastases, and eight brain and leptomeningeal metastases, were found. The 7-year CNS relapse-free survival rates of the trastuzumab (−) and trastuzumab (+) groups were 96.9% and 91.2%, respectively ($p = 0.005$, **Figure 3**). The type of breast surgery, T stage, N stage, and lymphatic invasion were also associated with 7-year CNS relapse-free survival. In the multivariate analysis, administration of trastuzumab was the only significant factor affecting CNS relapse (HR, 2.260; 95% CI, 1.076–4.746; $p = 0.031$) (**Table 4**).

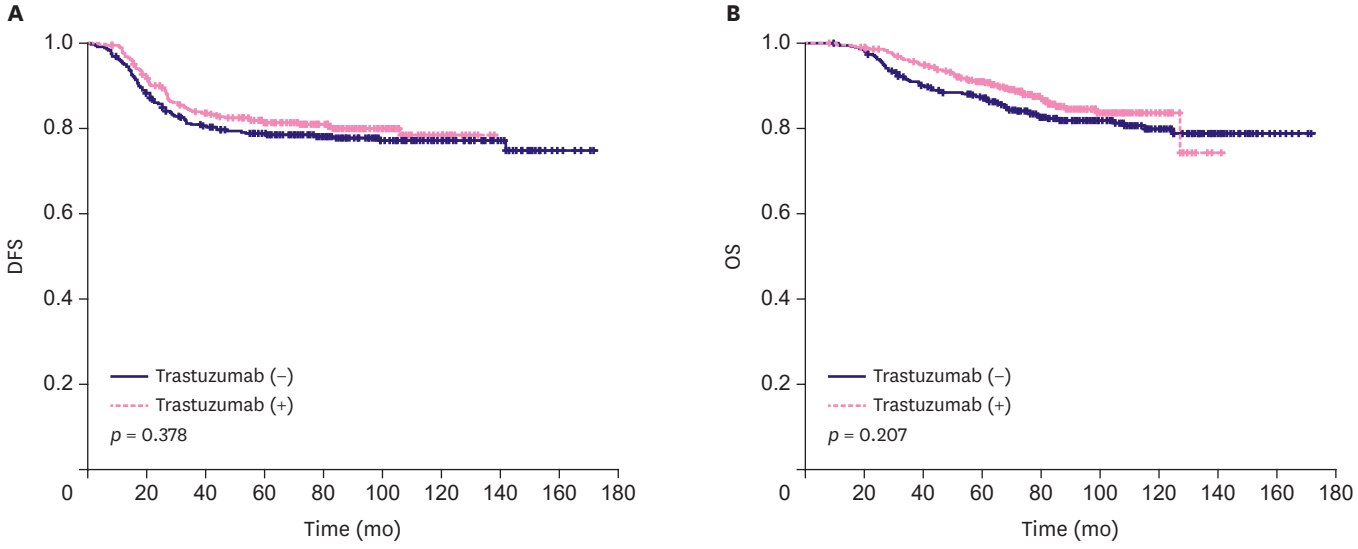

Figure 2. (A) DFS and (B) OS curves according to trastuzumab receipt.
DFS = disease-free survival; OS = overall survival.

https://doi.org/10.4048/jbc.2019.22.e1

Table 2. Univariate and multivariate analyses for DFS and OS

Variables	No. of patents	DFS			OS		
		7-yr rate (%)	*p*-value*	*p*-value†	7-yr rate (%)	*p*-value*	*p*-value†
Age (yr)			0.004	0.075		0.033	0.104
< 40	103	68.1			79.8		
≥ 40	646	80.7			84.9		
Type of breast surgery			< 0.001	0.114		< 0.001	0.004
BCS	443	84.2			91.5		
Mastectomy	306	71.4			73.7		
Type of axillary surgery			0.047	0.296		< 0.001	0.973
ALND	601	77.7			81.9		
SLNBx	144	84.7			94.2		
T stage			< 0.001	0.018		< 0.001	0.235
1–2	627	81.8			96.7		
3–4	122	66.0			71.0		
N stage			< 0.001	0.106		< 0.001	0.022
Negative	229	87.7			95.6		
Positive	520	75.0			79.2		
Histologic grade			0.635			0.256	
1	19	76.3			89.2		
2	201	77.1			81.7		
3	483	79.4			84.8		
Lymphatic invasion			< 0.001	0.005		< 0.001	0.011
Absent	388	84.8			89.7		
Present	311	70.3			76.7		
Trastuzumab			0.378			0.207	
No	363	77.8			82.4		
Yes	386	80.0			85.8		

DFS = disease-free survival; OS = overall survival; BCS = breast-conserving surgery; ALND = axillary lymph node dissection; SLNBx = sentinel lymph node biopsy.
*Univariate analysis; †multivariate analysis.

Table 3. Patient and treatment characteristics according to the receipt of trastuzumab

Variables	Trastuzumab (−) (n = 363)	Trastuzumab (+) (n = 386)	*p*-value
Age (yr)			1.000
< 40	50 (13.8)	53 (13.7)	
≥ 40	313 (86.2)	333 (86.3)	
Type of breast surgery			0.905
BCS	216 (59.5)	227 (58.8)	
Mastectomy	147 (40.5)	159 (41.2)	
Type of axillary surgery			0.672
ALND	294 (81.4)	307 (79.9)	
SLNBx	67 (18.6)	77 (20.1)	
T stage			0.189
1–2	311 (85.7)	316 (81.9)	
3–4	52 (14.3)	70 (18.1)	
N stage			< 0.001
Negative	141 (38.8)	88 (22.8)	
Positive	222 (61.2)	298 (77.2)	
Histologic grade			0.032
1	13 (3.8)	6 (1.7)	
2	108 (31.7)	93 (25.7)	
3	220 (64.5)	263 (72.7)	
Lymphatic invasion			< 0.001
Absent	222 (64.5)	166 (46.8)	
Present	122 (35.5)	189 (53.2)	

Values are presented as number of patients (%).
BCS = breast-conserving surgery; ALND = axillary lymph node dissection; SLNBx = sentinel lymph node biopsy.

https://doi.org/10.4048/jbc.2019.22.e1

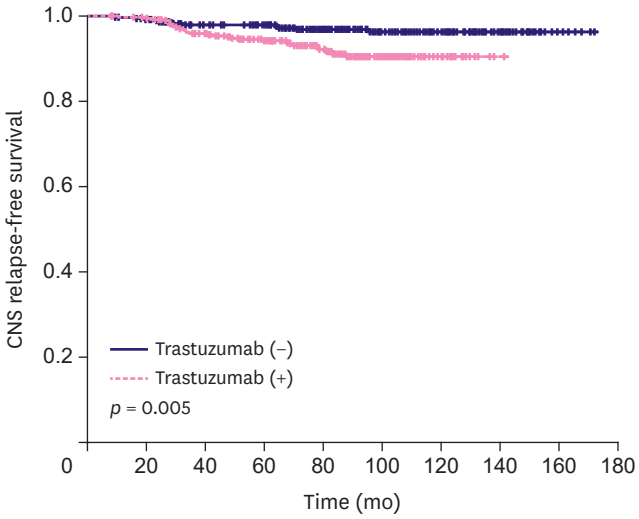

Figure 3. CNS-relapse free survival curves according to trastuzumab receipt.
CNS = central nervous system.

Table 4. Univariate and multivariate analyses for CNS relapse-free survival

Variables	7-yr CNS relapse-free survival (%)	*p*-value*	*p*-value†
Age (yr)		0.829	
< 40	94.2		
≥ 40	94.0		
Type of breast surgery		< 0.001	0.142
BCS	97.1		
Mastectomy	89.2		
Type of axillary surgery		0.108	
ALND	93.1		
SLNBx	97.7		
T stage		0.002	0.293
1–2	95.4		
3–4	86.2		
N stage		< 0.001	0.050
Negative	99.5		
Positive	91.4		
Histologic grade		0.503	
1	94.7		
2	92.8		
3	94.9		
Lymphatic invasion		0.010	0.415
Absent	96.8		
Present	90.6		
Trastuzumab		0.005	0.031
Yes	91.2		
No	96.9		

CNS = central nervous system; BCS = breast-conserving surgery; ALND = axillary lymph node dissection; SLNBx = sentinel lymph node biopsy.
*Univariate analysis; †multivariate analysis.

DISCUSSION

In this study, we observed that CNS relapse-free survival was associated with adjuvant trastuzumab in patients with HER2-enriched subtype of breast cancer. The administration of adjuvant trastuzumab was mainly determined according to the treatment period; however,

https://doi.org/10.4048/jbc.2019.22.e1

the number of patients with nodal involvement and lymphatic invasion in the trastuzumab (+) group was higher than that in the trastuzumab (−) group. After adjusting these covariates using the multivariate analysis, the adjuvant trastuzumab remained the only risk factor associated with higher CNS relapse rate.

HER2-positive breast cancer is a disease with distinct clinicopathological features and accounts for 15–20% of all invasive breast cancers, and it is characterized by a particularly aggressive course [15]. HER2-positive tumors have a higher risk of CNS relapse compared with HER2-negative tumors [6]. In addition, among the HER2-positive tumors, the HER2-enriched subtype presents with a higher risk of CNS relapse compared with HER2-/hormonal receptor-positive tumors. This was confirmed by Lim et al. who reported that the CNS relapse rate was higher in the HER2-enriched subtype than in HER2-/hormonal receptor-positive tumors (10-year rate, 3.5% vs. 0.0%, $p = 0.001$) [14]. In a population-based study of HER2-positive patients with breast cancer, hormonal receptor negativity was the independent predictive factor for CNS relapse with HR of 5.4 [12]. Given these observations, 749 patients from eight institutions in Korea were included, and the surgical outcomes followed by postoperative RT in HER2-enriched subtype evaluated. Consequently, we observed that the administration of adjuvant trastuzumab was associated with an increased risk of CNS relapse.

Regarding the correlation between trastuzumab and CNS relapse, 523 patients with metastatic breast cancer were enrolled in two clinical trials of the first-line trastuzumab therapy, which revealed a 10% incidence of isolated CNS progression [16]. Nearly one-third of patients with HER2-positive metastatic breast cancer are now developing CNS disease despite receiving trastuzumab-based therapy [9,17]. In contrast, the incidence of CNS metastasis in a historical series was only 10–16% [18,19]. These increased incidences of CNS events not only reflect the inherent behavior of HER2-positive tumors but also improved survival by trastuzumab treatment in these patients, allowing more CNS events to become clinically evident before death [10].

However, whether “adjuvant” trastuzumab is associated with increased risk of CNS failure remains controversial. Musolino et al. [12] evaluated the risk of CNS failure in a population-based cancer registry and noted that CNS failure, either as the first or a subsequent recurrence, was significantly more common in trastuzumab-treated patients with HER2-positive breast cancer based on the multivariate analysis. They postulated that the improved systemic control and OS because of trastuzumab may reveal the silent CNS failure. In a combined analysis of the NASBP B-31 and NCCTG N9831 trials, Romond et al. [3] reported that the incidence of isolated brain metastases as the first event was higher in the trastuzumab group. In addition, a meta-analysis of randomized controlled trials revealed that the adjuvant trastuzumab group had a higher CNS failure rate compared with the observation group [11].

Conversely, in the NASBP B-31 trial, the incidence of brain metastases as the first or subsequent event was similar between the trastuzumab and control groups [3]. Therefore, they explained that increased brain metastases as the first event in the trastuzumab group were due to early non-CNS failures in the control group. In addition, a retrospective analysis of the HERceptin Adjuvant (HERA) trial revealed that CNS relapse was not increased in trastuzumab-treated patients [13]. Pestalozzi et al. [13] observed that the frequency of CNS relapse at the first DFS event was comparable in patients receiving and not receiving trastuzumab.

Regarding these conflicting observations, most investigators agree that the improved survival because of trastuzumab treatment contributes to the paradoxical increase of CNS relapses

as the first sites of failure. Although prolonging OS, the penetration of trastuzumab into the intact blood–brain barrier is very limited due to its large molecular weight and limited efficacy in controlling micrometastasis in the CNS [20]. However, if OS is "relatively" limited in the control group, a significant proportion of CNS relapses may eventually be masked, resulting in increased CNS relapses as subsequent failures in the trastuzumab group. Conversely, if OS is maintained "relatively" enough to reveal the silent CNS failures in the control group, the incidence of CNS failures as subsequent events seems to be proportional between the 2 groups.

Most of these studies included both HER2-/hormonal receptor-positive and HER2-/hormonal receptor-negative tumors. In the present study, only HER2-enriched tumors were analyzed, and cumulative CNS relapses were counted. Consequently, in the multivariate analysis, administration of adjuvant trastuzumab was the only significant prognosticator of a higher CNS relapse rate. As previously mentioned, the number of patients with nodal involvement, high-grade tumor, and lymphatic invasion in the trastuzumab (+) group was higher, thus allowing for a higher risk of CNS failure. However, the similar survival rates between the trastuzumab (+) and trastuzumab (−) groups suggest the survival benefit of adjuvant trastuzumab in high-risk patients, although the difference was not statistically significant. This finding is consistent with the hypothesis that trastuzumab improves the survival but not the CNS control, resulting in increased CNS relapses. Although nodal involvement and lymphatic invasion were associated with CNS relapses on univariate analysis, statistical significance was not observed in the multivariate analysis. Lymphovascular invasion was also a strong prognosticator of both DFS and OS. Recently, Hamy et al. [21] noted that the magnitude of its effect was dependent on the molecular subtype with the greatest HR reported for the HER2-positive breast cancer. A recent study using the Surveillance, Epidemiology, and End Results database reported that HER2-enriched subtype showed the highest incidence of brain metastasis among 206,913 patients with breast cancer. The HER2-enriched and triple-negative subtypes with multiple extracranial metastases (bone, liver, and lung) showed high incidences of brain metastasis (28.0, and 30.8%, respectively). The authors concluded that patients with HER2-enriched and triple-negative subtypes having visceral metastasis should be closely monitored in order to contribute to early detection of brain metastasis [22]. Further research is warranted to elucidate the possible contribution of other risk factors to the occurrence of CNS relapse and to identify potential candidates for close surveillance, including brain imaging. Several ongoing prospective clinical trials are testing various HER2-targeting agents combined with whole-brain RT or stereotactic radiosurgery in patients with CNS failure (**Table 5**), and their findings are expected to recommend a reasonable combination strategy to improve the clinical outcomes in the near future.

Table 5. Representative ongoing prospective clinical trials on brain metastases from HER2-positive breast cancer

Agent	Phase	NCT No.	Study design
Lapatinib	2	01622868	WBRT or SRS +/− lapatinib
Tucatinib	2	02614794	Tucatinib + capecitabine/trastuzumab vs. capecitabine/trastuzumab
Pertuzumab/ trastuzumab	2	02536339	Intravenous pertuzumab + trastuzumab following WBRT or SRS
	1	02598427	Intrathecal pertuzumab + trastuzumab
Trastuzumab	1	02571530	Super-selective intra-arterial trastuzumab
Tesevatinib	1/2	02154529	Tesevatinib + trastuzumab
T-DM1	1/2	03190967	T-DM1 vs. T-DM1 + temozolomide following SRS
	2	03203616	T-DM1

HER2 = human epidermal growth factor receptor 2; WBRT = whole brain radiotherapy; SRS = stereotactic radiosurgery; T-DM1 = trastuzumab-emtansine.

https://doi.org/10.4048/jbc.2019.22.e1

One of the limitations of this study is its retrospective study design. Although the administration of trastuzumab was determined mainly according to the treatment period, potential biases may be present. As previously mentioned, the number of patients in the trastuzumab (+) group with nodal involvement and lymphovascular invasion, the significant prognosticators of CNS relapse-free survival in the univariate analysis, was higher. After adjusting for covariates including these two variables, adjuvant trastuzumab administration remained the only prognosticator with statistical significance; however, the imbalances of tumor characteristics may not be fully controlled in the multivariate analysis. In addition, although all patients underwent systemic chemotherapy and local treatment such as surgery followed by RT, differences in chemotherapeutic regimens and RT details may contribute to the heterogeneity.

In conclusion, adjuvant trastuzumab was associated with higher CNS failure rate in Korean patients with breast cancer with HER2-enriched subtype. These increased incidences of CNS events could reflect the limited penetration of trastuzumab into the blood–brain barrier and improved survival, which allowed more CNS events to become clinically evident before death. Close monitoring and reasonable approaches, such as CNS-penetrating HER2 blockades combined with current standard therapy, could contribute to improving the intracranial tumor control and the quality of life in patients with CNS metastasis from HER2-enriched breast cancer.

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