Breast Cancer Research and Treatment (2019) 175:781–788
https://doi.org/10.1007/s10549-019-05170-7

BRIEF REPORT

Clinical outcomes of breast leptomeningeal disease treated with intrathecal trastuzumab, intrathecal chemotherapy, or whole brain radiation therapy

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Received: 10 February 2019 / Accepted: 15 February 2019 / Published online: 11 March 2019

Abstract

Purpose Leptomeningeal disease is a rare presentation of advanced metastatic breast cancer. The purpose of this study was to evaluate craniospinal progression between intrathecal (IT) trastuzumab, IT chemotherapy, and whole brain radiation therapy (WBRT) in leptomeningeal disease.

Methods A total of 56 patients were identified with breast cancer leptomeningeal disease at our institution treated with IT trastuzumab ($n=18$; 32%), single-agent IT chemotherapy (methotrexate $n=14$ or thiotepa $n=1$; 27%), or WBRT alone ($n=23$; 41%). Patients were treated beginning November 2012 and followed until November 2018.

Results Median time from breast cancer diagnosis to development of leptomeningeal disease was 4.3 years. There were no significant differences noted between IT trastuzumab, IT chemotherapy, or WBRT groups in age ($p=0.4$), Karnofsky Performance Status (KPS) ($p=0.07$), or receipt of systemic therapy at time of leptomeningeal disease treatment ($p=0.47$). Median follow-up of patients from leptomeningeal diagnosis was 5 months (range 0.2–81.1 months). Significant differences were noted in Kaplan–Meier (KM) craniospinal progression-free survival (CS-PFS) with 6-month rates of 44%, 18%, and 26% ($p=0.04$) between IT trastuzumab, IT chemotherapy, and WBRT, respectively. Craniospinal control > 10 months was achieved in four patients treated with IT trastuzumab. Twelve-month KM OS rates were 54%, 10%, and 19% ($p=0.01$) between IT trastuzumab, IT chemotherapy, and WBRT groups, respectively. IT therapy was adequately tolerated with three patients undergoing treatment-related hospitalizations.

Conclusions In our institutional series, significant differences were noted in CS-PFS and OS by treatment modality. IT trastuzumab should be considered in the management HER2+ breast leptomeningeal disease.

Keywords Intrathecal trastuzumab · Intrathecal herceptin · HER2+ breast cancer · Leptomeningeal disease

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Introduction

Approximately 5–15% of breast cancer patients will develop central nervous system (CNS) metastases within the course of their illness [1, 9, 17]. Although relatively rare, leptomeningeal disease (LMD) is a devastating complication with a median survival of 3–4 months reported in historical series [15]. Management of LMD presents a challenge to practitioners with limited treatment options and requires a multidisciplinary approach that can include radiation therapy and/or intrathecal (IT) therapy.

The advent of trastuzumab revolutionized the management of HER2 overexpressing breast tumors with objective

responses achieved in approximately 26% of patients in the first line metastatic setting [18]. Given the impressive systemic response rates in HER2+ tumors, there has been increased interest in determining the role of trastuzumab in the prevention and treatment of CNS metastases [2, 19]. In an early pharmacologic study, concentrations of trastuzumab were found to be 300 times lower in the cerebrospinal fluid (CSF) than in the serum after IV administration [14]. This led to the hypothesis that the drug could not cross an intact blood brain barrier (BBB) due to its large molecular size. Upon further analyses of serum vs. CSF drug concentrations, it was confirmed that trastuzumab only passed from the serum to CSF in minute quantities; yet, interestingly was able to pass from the CSF to serum much more readily [4, 5]. In order to bypass the limitations of the CSF sanctuary, two approaches have been used: (1) improve delivery of the drug by disrupting the BBB via radiotherapy and (2) administer the drug directly into the CSF via an intrathecal route or Ommaya reservoir.

IT therapy is a treatment option for patients with leptomeningeal metastases [8]. To date, outcomes of IT trastuzumab in the treatment of breast leptomeningeal disease (LMD) have been published in case reports, small-pooled analysis, and a recent phase I feasibility analysis [3, 4, 10–12, 16, 20]. We previously reported results of 13 patients with HER2+ LMD treated with IT trastuzumab at our institution [6]. This report demonstrated an acceptable safety profile with improved survival compared to historical controls [6, 8]. The goal of this current study was to compare craniospinal progression rates in patients with breast LMD at our institution treated with IT trastuzumab, IT chemotherapy, or whole brain radiation therapy (WBRT) alone.

Patients and methods

Patients and follow-up

Data were analyzed retrospectively from prospective registries of patients receiving IT therapy and radiation therapy at our institution. Patients initiated treatment beginning November 2012 and were followed until November 2018. The study was approved by the University of South Florida Institutional Review Board. All patients had radiographic evidence of LMD in the brain and/or spinal cord with some patients having positive CSF studies. Patients in this study were followed by the treating neuro-oncologist and/or radiation oncologist with MRI imaging and clinical examination at 2-month intervals. Intracranial and/or spinal progression was defined by the evidence of new and/or progression of enhancing lesions on MRI imaging.

IT therapy and whole brain radiation therapy administration

Patients underwent administration of IT therapy through an Ommaya reservoir. Patients were administered IT trastuzumab at initial doses between 20 and 50 mg. Patients were administered IT trastuzumab twice a week for 4 weeks, weekly for 4 weeks, followed by every 2 weeks for 4 weeks. After the initial treatment phase, patients were typically maintained on doses of 80 mg every 2 weeks or every month. Methotrexate was administered at doses of 12 mg weekly. One patient received IT thiotepa 10 mg twice weekly.

The majority of patients ($n=20$; 87%) receiving WBRT were treated to doses of 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. Two patients were treated to doses of 20 Gy in 5 fractions and one patient received 12 Gy in 2 fractions.

Statistical analyses

Statistical analyses were carried out using JMP 13 (SAS Institute, Inc., Cary, NC). Descriptive statistics were used to summarize the cohort including median and range for continuous variables or counts and percentages for categorical variables. The craniospinal progression-free survival (CS-PFS), overall survival (OS), and systemic PFS were calculated from the date of first LMD treatment to the date of progression or death using the Kaplan–Meier (KM) method. To test differences between cohorts, the Kruskal–Wallis, Pearson's Chi-square and Fisher's exact tests were used when appropriate. Cox proportional hazard model analyses were performed using univariate analysis (UVA) and multivariate analysis (MVA). Variables that showed significant effects on UVA ($p<0.1$) were included in the MVA.

Results

Patient characteristics

A total of 56 metastatic breast cancer patients with LMD were identified for analysis. Eighteen (32%) patients received IT trastuzumab, 15 (27%) received single-agent IT chemotherapy (methotrexate $n=14$, thiotepa $n=1$), and 23 (41%) received WBRT alone. The median age at time of LMD treatment was 52 years (range 27–78) with a median duration of 4.3 years (range 0.7–27.8) from initial diagnosis of breast cancer to LMD diagnosis. The full description of patient characteristics is summarized in Table 1.

Table 1 Patient and treatment characteristics

Variable	*n*	%
No. of patients	56	
Follow-up from LMD diagnosis (months)		
Median	5	
Range	0.2–81.1	
Breast cancer diagnosis to LMD diagnosis (years)		
Median	4.3	
Range	0.7–27.8	
Age at LMD diagnosis (years)		
Median	52.4	
Range	27.1–77.7	
Treatment type		
IT trastuzumab	18	32
IT chemotherapy	15	27
Whole brain radiation	23	41
KPS% at diagnosis		
100	3	5
90	10	18
80	16	29
70	15	27
60	5	9
50	7	13
Receptors		
HR+/HER2+	13	23
HR-/HER2+	7	13
HR + HER2−	26	46
HR-/HER2−	10	18
Sites of disease		
CNS only	10	18
Systemic and CNS	46	82
Systemic therapy at time of LMD treatment		
Yes	39	70
No	17	30
Brain metastases at time of LMD diagnosis		
Yes	35	63
No	21	37

IT intrathecal, *LMD* leptomeningeal disease, *KPS* Karnofsky performance status, *HR* hormone receptor, *CNS* central nervous system

IT trastuzumab cohort

Details for all 18 patients treated with IT trastuzumab are listed in Table 2. The majority of patients had systemic metastases at the time of LMD diagnosis ($n = 11$; 61%) and were hormone receptor positive (HR)+/HER2+ ($n = 12$; 67%). The majority of patients ($n = 12$; 67%) received WBRT prior to receiving IT trastuzumab with an additional three patients receiving WBRT at the time of progression. A total of 14 patients (78%) were on systemic treatment at the time of IT trastuzumab treatment. Median CS-PFS following treatment initiation for IT trastuzumab-treated patients was 5.4 months (95% CI 2.7–11.9 months). Craniospinal control > 10 months was achieved in four patients treated with IT trastuzumab. Median systemic PFS and OS was 7.2 months (95% CI 2.7–25.7 months) and 13.2 months (95% CI 4.4 months–not reached), respectively.

In the 18 patients who received IT trastuzumab, eleven had documented evidence of craniospinal progression. Median survival in these patients following progression was 1.7 months (95% CI 1.0 months–not reached). Of these, six patients continued IT treatment with the addition of another IT agent as detailed in Table 2.

Patient and treatment characteristics among groups

Comparisons between IT trastuzumab, IT chemotherapy, and WBRT alone groups are listed in Table 3. There were no significant differences in patient age ($p = 0.4$), Karnofsky Performance Status (KPS) ($p = 0.07$), presence of parenchymal brain metastases ($p = 0.1$), or use of systemic therapy at time of LMD treatment ($p = 0.47$) between the three groups. As expected, differences were noted in receptor statuses between groups and the receipt of prior WBRT (both $p < 0.001$). The IT chemotherapy and WBRT cohorts were more likely to have systemic disease at the time of LMD diagnosis compared to the IT trastuzumab cohort 93%, 91% vs., 61% $p = 0.02$, respectively.

CSF cytologic response

CSF cytologic analysis was performed in all patients who received IT therapy. In the 18 patients who received IT trastuzumab, 6 patients had evidence of malignant CSF prior to the initiation of treatment all of which responded on subsequent cytology analyses following treatment. Of the 15 IT chemotherapy patients, nine had a positive cytology at initiation of treatment, of which 4 responded. Most WBRT patients ($n = 18$; 78%) underwent no CSF evaluation. Of the four WBRT patients with a positive CSF, one had a documented cytologic response following treatment.

Craniospinal PFS

Median follow-up of patients from LMD diagnosis was 5 months (range 0.2–81.1 months). KM analyses demonstrated significant differences in CS-PFS between groups. The 6-month KM CS-PFS rates were 44%, 18%, and 26% and 12-month rates were 23%, 0%, 6% ($p = 0.04$) between the IT trastuzumab, IT chemotherapy, and WBRT groups, respectively (Fig. 1). On UVA, treatment type was found to affect CS-PFS as detailed in Table 4.

Table 2 Summary of IT trastuzumab-treated patients

Patient no	Age at LMD diagnosis	Systemic disease at time of LMD diagnosis	CSF+	Prior WBRT	Craniospinal progression after IT start	Time to craniospinal progression from IT start (months)	Additional IT treatment at progression	Status	OS from IT start (months)
1	29	Yes	Yes	No	Yes	11.9		Dead	13.2
2	50	Yes	No	Yes[a]	Yes	2.7	Thiotepa followed by xeloda	Alive	21.1
3	41	Yes	No	Yes	Yes	6.2	Thiotepa	Alive	17.2
4	70	Yes	No	No	Yes	2		Dead	3
5	61	Yes	Yes	Yes	Yes	5.7	Methotrexate	Dead	7.2
6	47	No	Yes	Yes	No			Alive	73
7	53	Yes	No	Yes	Yes	5.2	Methotrexate, then thiotepa, then cytarabine followed by 2 years trastuzumab alone	Alive	61.2
8	45	Yes	No	Yes	Yes	1.2	Cytarabine	Dead	2.1
9	43	Yes	No	Yes[a]	Yes	11.2	Thiotepa	Alive	59.4
10	54	Yes	Yes	Yes	No			Dead	1.7
11	47	Yes	No	Yes	No			Dead	2.7
12	37	Yes	Yes	Yes	No			Alive	5.2
13	57	No	Yes	Yes	Yes	2.8		Dead	4.5
14	44	No	No	Yes	No			Alive	15.1
15	63	No	No	Yes[a]	Yes	0.7		Dead	10.5
16	44	No	No	Yes	Yes	3		Dead	4.4
17	74	No	No	Yes	No			Dead	25.7
18	70	No	No	No	No			Alive	7.5

IT Intrathecal, *WBRT* whole brain radiotherapy, *OS* overall survival, *LMD* leptomeningeal disease

[a]WBRT at progression

Systemic PFS and overall survival

Significant differences were noted in systemic PFS between groups with 6- and 12-month rates of 44%, 18%, 26%, and 23%, 0%, 6% between IT trastuzumab, IT chemotherapy, and WBRT groups, respectively.

Similar differences were noted in OS rates. The 6- and 12-month rates of OS were 67%, 39%, and 31% and 54%, 10%, and 19% ($p=0.01$) between IT trastuzumab, IT chemotherapy, and WBRT alone groups, respectively (Fig. 2). On UVA, KPS, and treatment of LMD were predictive of OS. LMD treatment remained significant on MVA for OS, Table 5.

Toxicity

The use of IT agents was overall well tolerated. There were three documented episodes of treatment-related ventriculitis requiring hospital admission. Two patients treated with IT trastuzumab had source infections from the Ommaya reservoir which required shunt removal, administration of intravenous antibiotics, and shunt replacement with continuation of IT therapy following infection clearance. One patient was noted to have possible chemically induced meningitis secondary to IT methotrexate and was treated with steroids.

Discussion

In the first reported analysis comparing IT trastuzumab to IT chemotherapy or WBRT in patients with breast LMD, we note several findings. First, significant differences were noted in CS-PFS among intracranial treatments for LMD. Similar differences were noted in systemic PFS which likely both contributed to improved OS in IT trastuzumab-treated patients. All patients with positive CSF cytology treated with IT trastuzumab had responses following treatment initiation with selected patients having durable craniospinal

Table 3 Comparison between groups

	IT trastuzumab	IT chemotherapy	WBRT	*p* value
Number of patients	18	15	23	
Age (years)				
Median	49.1	52	57.5	0.4
Range	29.5–75	27.1–72	40.4–77.7	
KPS at Treatment Start				
50	0	5 (33%)	2 (9%)	0.07
60	1 (6%)	2 (13%)	2 (9%)	
70	3 (16%)	4 (27%)	8 (35%)	
80	6 (33%)	3 (20%)	7 (30%)	
90	6 (33%)	0	4 (17%)	
100	2 (11%)	1 (7%)	0	
Receptors				
HR+/HER2+	12 (66%)		1 (4%)	< 0.001
HR−/HER2+	6 (33%)		1 (4%)	
HR+/HER2−		14 (93%)	12 (52%)	
HR−/HER2−		1 (7%)	9 (39%)	
Systemic therapy at time of LMD treatment				
Yes	14 (78%)	11 (73%)	14 (61%)	0.47
No	4 (22%)	4 (27%)	9 (39%)	
Prior WBRT				
Yes	12 (67%)	8 (53%)	0	< 0.001
No	6 (33%)	7 (47%)	23 (100%)	
Sites of disease				
CNS only	7 (39%)	1 (7%)	2 (9%)	0.02
Systemic and CNS	11 (61%)	14 (93%)	21 (91%)	
Brain metastases at time of LMD diagnosis				
Yes	12 (67%)	6 (40%)	17 (74%)	0.1
No	6 (33%)	9 (60%)	6 (27%)	

IT intrathecal, *LMD* leptomeningeal disease, *KPS* Karnofsky performance status, *HR* hormone receptor, *CNS* central nervous system

control > 10 months. Finally, IT therapy was adequately tolerated in our institutional experience.

To achieve an adequate CSF concentration in the management of HER2+ LMD, administering trastuzumab intrathecally has become increasingly accepted [4]. This technique has been described in several case reports [4, 10, 11, 13, 16, 20] demonstrating improved disease control with minimal toxicity. A systematic review and pooled analysis of 13 articles evaluating 17 patients treated with IT trastuzumab demonstrated clinical improvement in 69%, CSF response in 67%, and radiographic improvement in 56% of cases [20]. There were no reports of adverse events in 88% of patients with one patient developing grade 3 anemia/neutropenia and one patient developing an ischemic lesion in the left frontal lobe. We previously reported our single-institution results of 13 patients treated with IT trastuzumab which demonstrated an acceptable safety profile with an improved survival compared to historical controls [6].

Bonneau et al. recently published results from an initial prospective phase I dose-escalation trial with IT trastuzumab. The study achieved its target CSF concentration at the maximum dose level (150 mg) without any patients experiencing a dose-limiting toxicity. Their group therefore recommends 150 mg of IT trastuzumab to be administered weekly for HER2+ LMD [3]. A median OS after enrollment of 7.3 months was reported. We currently await the results from the phase II portion of their study, along with the final results of a multicenter prospective phase I/II dose-escalation trial (Clinical Trial ID: NCT01325207). Early abstract results were recently reported from 34 patients, 26 of which were phase II enrolled, that received 80 mg every 2 weeks [7]. A median PFS of 2.4 months (95% CI 1.0–5.5 months) and median OS of 12.1 months (95% CI 4.3–19.6 months) was reported. Despite not achieving their primary endpoint, 69% of patients demonstrated a clinical benefit with the use of IT trastuzumab. NCT02598427 attempted to evaluate the role of concurrent IT trastuzumab and pertuzumab

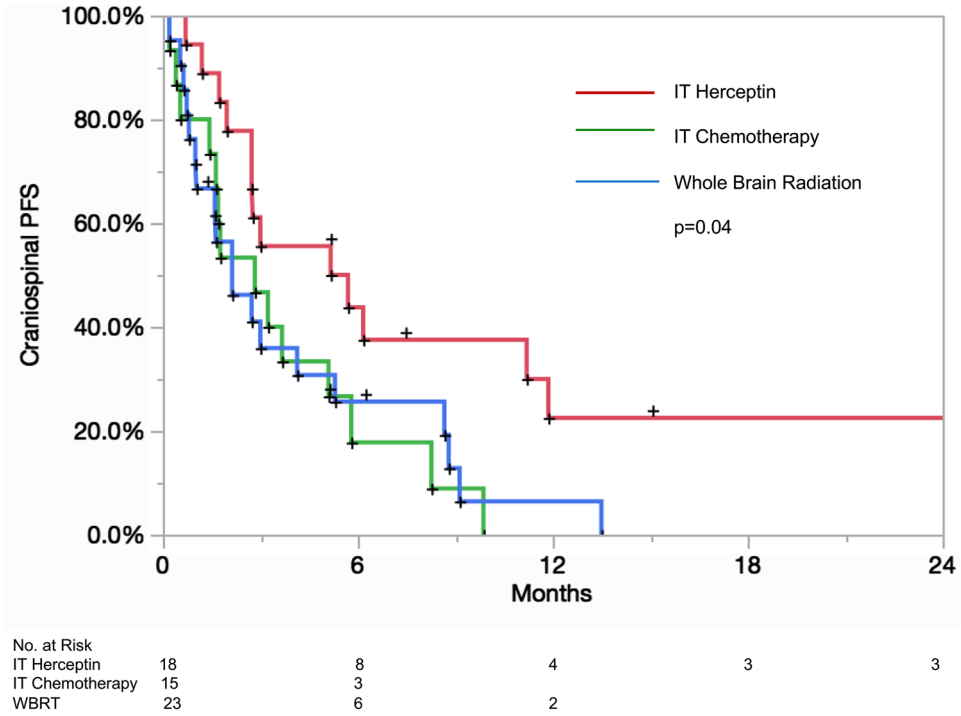

Fig. 1 Kaplan–Meier craniospinal progression-free survival following treatment initiation between groups

Table 4 Analysis of CS-PFS from treatment start

	HR	95% CI	*p* value
CS-PFS univariate analysis			
Age			
≥ 52/< 52	1.3	0.7–2.3	0.41
KPS			
≤ 70/> 70	1.6	0.9–2.9	0.11
Systemic therapy			
No/yes	1.6	0.86-3.0	0.13
Treatment			
IT chemotherapy/IT herceptin	2.4	1.1–5.2	0.03
WBRT/IT herceptin	2.2	1.1–4.6	0.03
WBRT/IT chemotherapy	0.9	0.46–1.9	0.83
Brain metastases at LMD diagnosis			
Yes/no	0.94	0.53–1.7	0.84

IT intrathecal, *LMD* leptomeningeal disease, *KPS* Karnofsky performance status, *WBRT* whole brain radiation therapy

for HER2+ asymptomatic or minimally symptomatic brain metastases; however, the trial closed due to poor patient accrual.

In our current analysis, we retrospectively reviewed our institutional experience comparing outcomes of 56 metastatic breast cancer patients diagnosed with LMD treated with either IT trastuzumab ($n=18$, 32%), IT single-agent chemotherapy ($n=15$, 27%) or WBRT alone ($n=23$, 41%). The patients were relatively balanced across the groups with respect to age, KPS, and use of concurrent systemic therapy. In a patient cohort with historically poor prognosis, the patients treated with IT trastuzumab had superior CS-PFS at 6 and 12 months compared to IT chemotherapy and WBRT alone. Four patients who received IT trastuzumab continue to have craniospinal disease control > 10 months indicating the potential for a durable response in select patients. The maximum dose of IT trastuzumab administered was 80 mg (similar to NCT01325207) and was commonly administered weekly and gradually extended to monthly, significantly less than the weekly 150 mg dose recommended by Bonneau et al.

The OS in the IT trastuzumab cohort exceeds historical controls and appears to be similar to initially reported data from NCT01325207. The improved OS noted in the IT trastuzumab cohort may be due not only to improved CS-PFS but also improved systemic control in HER2+ patients as noted by the improved systemic PFS in this cohort. It is apparent that IT trastuzumab is a treatment option in selected patients with HER2+ LMD. IT therapy appears to be well tolerated. In our study, there were three documented episodes of ventriculitis: two infectious and one chemically induced with IT methotrexate. There was no reported evidence of trastuzumab-induced toxicity in our report. This has been supported in previous small retrospective analyses and the prospective study from Bonneau et al. [3, 20].

Our study results are subject to the limitations inherent to those of retrospective analyses. In addition, significant differences in biological subtypes across treatments were noted with all IT trastuzumab-treated patients being HER2+. However, no study has yet shown craniospinal progression to

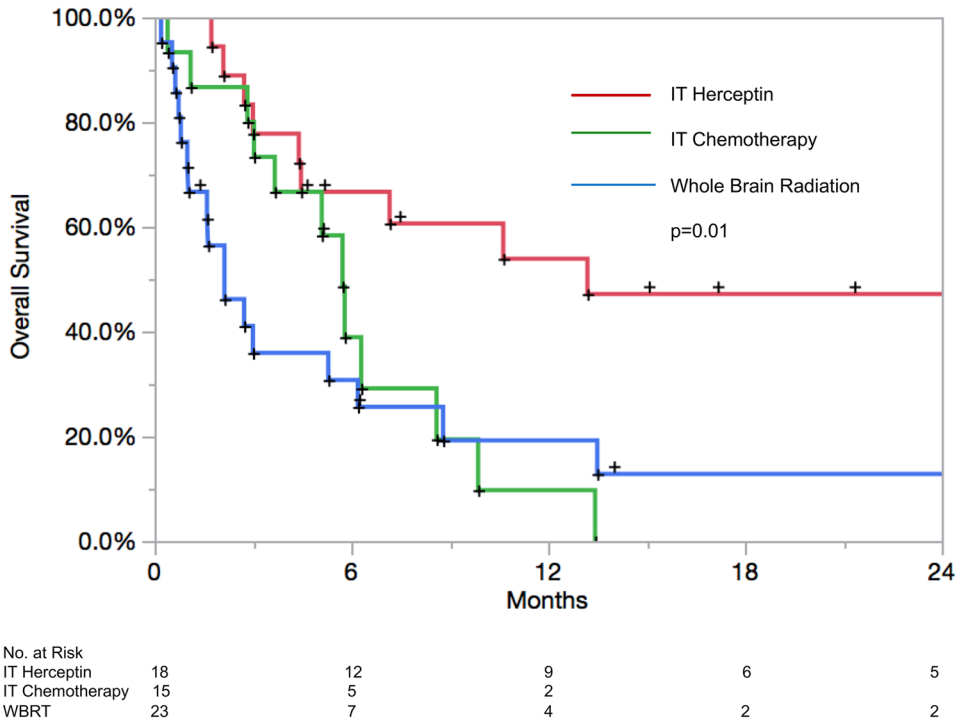

Fig. 2 Kaplan–Meier overall survival following treatment initiation between groups

Table 5 Analysis of OS from treatment start

	HR	95% CI	*p* value
Overall survival univariate analysis			
Age			
≥ 52/< 52	1.3	0.7–2.6	0.35
KPS			
≤ 70/> 70	2	1.03–3.7	0.03
Systemic therapy			
No/yes	1.6	0.8–3	0.18
Treatment			
IT chemotherapy/IT herceptin	2.4	1.03–6.1	0.04
WBRT/IT herceptin	3.2	1.5–7.7	0.003
WBRT/IT chemotherapy	1.3	0.63–2.8	0.47
Multivariate analysis			
KPS			
≤ 70/> 70	1.7	0.86–3.3	0.13
Treatment			
IT chemotherapy/IT herceptin	2	0.78–5.1	0.15
WBRT/IT herceptin	3	1.3–7.2	0.008
WBRT/IT chemotherapy	1.5	0.7–3.4	0.27

IT Intrathecal, *LMD* leptomeningeal disease, *KPS* Karnofsky performance status, *WBRT* whole brain radiation therapy

differ based on the type of therapy delivered and this study indicates the potential role of targeted agents in the advanced LMD state.

In our single-institution retrospective review evaluating breast cancer patients with LMD, we note improved CS-PFS for patients treated with IT trastuzumab with minimal associated toxicities. In addition, there was evidence of durable responses in selected patients treated with IT trastuzumab with responses to CSF cytology in all patients who tested positive prior to treatment initiation. Our findings support the use of IT trastuzumab in the management of HER2+ breast cancer LMD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE (2004) Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 22:2865–2872. https://doi.org/10.1200/JCO.2004.12.149
2. Bendell JC, Domchek SM, Burstein HJ, Harris L, Younger J, Kuter I, Bunnell C, Rue M, Gelman R, Winer E (2003) Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 97:2972–2977. https://doi.org/10.1002/cncr.11436 doi
3. Bonneau C, Paintaud G, Tredan O, Dubot C, Desvignes C, Dieras V, Taillibert S, Tresca P, Turbiez I, Li J, Passot C, Mefti

F, Mouret-Fourme E, Le Rhun E, Gutierrez M (2018) Phase I feasibility study for intrathecal administration of trastuzumab in patients with HER2 positive breast carcinomatous meningitis. Eur J Cancer 95:75–84. https://doi.org/10.1016/j.ejca.2018.02.032

4. Bousquet G, Darrouzain F, de Bazelaire C, Ternant D, Barranger E, Winterman S, Madelaine-Chambin I, Thiebaut JB, Polivka M, Paintaud G, Culine S, Janin A (2016) Intrathecal trastuzumab halts progression of CNS metastases in breast cancer. J Clin Oncol 34:e151–e155. https://doi.org/10.1200/JCO.2012.44.8894
5. Brosnan EM, Anders CK (2018) Understanding patterns of brain metastasis in breast cancer and designing rational therapeutic strategies. Ann Transl Med 6:163. https://doi.org/10.21037/atm.2018.04.35
6. Figura NB, Long W, Yu M, Robinson TJ, Mokhtari S, Etame AB, Tran ND, Diaz R, Soliman H, Han HS, Sahebjam S, Forsyth PA, Ahmed KA (2018) Intrathecal trastuzumab in the management of HER2 + breast leptomeningeal disease: a single institution experience. Breast Cancer Res Treat 169:391–396. https://doi.org/10.1007/s10549-018-4684-3
7. Kumthekar P, Gradishar W, Lin N, Pentsova E, Groves M, Jeyapalan S, Melisko M, Grimm S, Lassman AB, Raizer J (2018) Intrathecal (IT) trastuzumab (T) for the treatment of leptomeningeal metastases (LM) in patients (Pts) with human epidermal growth factor receptor 2-positive (HER2+) cancer: a multicenter phase 1/2 study. Neuro-oncology 20:Vi58
8. Le Rhun E, Taillibert S, Zairi F, Kotecki N, Devos P, Mailliez A, Servent V, Vanlemmens L, Vennin P, Boulanger T, Baranzelli MC, Andre C, Marliot G, Cazin JL, Dubois F, Assaker R, Bonneterre J, Chamberlain MC (2013) A retrospective case series of 103 consecutive patients with leptomeningeal metastasis and breast cancer. J Neuro-oncol 113:83–92. https://doi.org/10.1007/s11060-013-1092-8
9. Lin NU, Bellon JR, Winer EP (2004) CNS metastases in breast cancer. J Clin Oncol 22:3608–3617. https://doi.org/10.1200/JCO.2004.01.175
10. Lu NT, Raizer J, Gabor EP, Liu NM, Vu JQ, Slamon DJ, Barstis JL (2015) Intrathecal trastuzumab: immunotherapy improves the prognosis of leptomeningeal metastases in HER-2 + breast cancer patient. J Immunother Cancer 3:41. https://doi.org/10.1186/s40425-015-0084-y
11. Mir O, Ropert S, Alexandre J, Lemare F, Goldwasser F (2008) High-dose intrathecal trastuzumab for leptomeningeal metastases secondary to HER-2 overexpressing breast cancer. Ann Oncol 19:1978–1980. https://doi.org/10.1093/annonc/mdn654
12. Nayar G, Ejikeme T, Chongsathidkiet P, Elsamadicy AA, Blackwell KL, Clarke JM, Lad SP, Fecci PE (2017) Leptomeningeal disease: current diagnostic and therapeutic strategies. Oncotarget 8:73312–73328. https://doi.org/10.18632/oncotarget.20272
13. Park WY, Kim HJ, Kim K, Bae SB, Lee N, Lee KT, Won JH, Park HS, Lee SC (2016) Intrathecal Trastuzumab Treatment in Patients with Breast Cancer and Leptomeningeal Carcinomatosis. Cancer Res Treat 48:843–847. https://doi.org/10.4143/crt.2014.234
14. Pestalozzi BC, Brignoli S (2000) Trastuzumab in CSF. J Clin Oncol 18:2349–2351. https://doi.org/10.1200/JCO.2000.18.11.2349
15. Scott BJ, Oberheim-Bush NA, Kesari S (2016) Leptomeningeal metastasis in breast cancer—a systematic review. Oncotarget 7:3740–3747. https://doi.org/10.18632/oncotarget.5911
16. Stemmler HJ, Schmitt M, Harbeck N, Willems A, Bernhard H, Lassig D, Schoenberg S, Heinemann V (2006) Application of intrathecal trastuzumab (Herceptintrade mark) for treatment of meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer. Oncol Rep 15:1373–1377
17. Tsukada Y, Fouad A, Pickren JW, Lane WW (1983) Central nervous system metastasis from breast carcinoma. Autopsy study. Cancer 52:2349–2354
18. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, Slamon DJ, Murphy M, Novotny WF, Burchmore M, Shak S, Stewart SJ, Press M (2002) Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 20:719–726. https://doi.org/10.1200/JCO.2002.20.3.719
19. Witzel I, Oliveira-Ferrer L, Pantel K, Muller V, Wikman H (2016) Breast cancer brain metastases: biology and new clinical perspectives. Breast Cancer Res 18:8. https://doi.org/10.1186/s13058-015-0665-1
20. Zagouri F, Sergentanis TN, Bartsch R, Berghoff AS, Chrysikos D, de Azambuja E, Dimopoulos MA, Preusser M (2013) Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2-positive metastatic breast cancer: a systematic review and pooled analysis. Breast Cancer Res Treat 139:13–22. https://doi.org/10.1007/s10549-013-2525-y