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BRIEF REPORT

Intrathecal trastuzumab in the management of HER2+ breast leptomeningeal disease: a single institution experience

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Abstract

Purpose Leptomeningeal disease is a rare and devastating presentation of advanced stage metastatic breast cancer with historically poor overall survival. We assessed the safety and feasibility of intrathecal (IT) trastuzumab in HER2+ leptomeningeal disease.

Methods A total of 13 patients were treated at our institution with IT trastuzumab beginning November 2012 and followed until November 2017. Outcomes including craniospinal progression as well as overall survival (OS) following initiation of IT trastuzumab were assessed from review of the clinical chart and radiologic examinations.

Results The median age of patients was 48 (range 29–75). Median time from breast cancer diagnosis to development of brain metastases was 87.7 months with a median of 4.6 months from brain metastases diagnosis to the development of leptomeningeal disease. Previous whole brain radiotherapy was received by the majority of patients (92%) and prior surgery for brain metastases was performed in 23%. Median duration of IT trastuzumab treatment was 6.4 months. Median time from IT trastuzumab start to craniospinal progression was 5.7 months with 6- and 12-month Kaplan–Meier rates of 41 and 21%, respectively. Sustained responses > 6 months were achieved in 4 patients. Median survival from the start of IT trastuzumab was 10.6 months with 6- and 12-month OS rates of 68 and 47%, respectively. IT trastuzumab was well tolerated with one patient developing ventriculitis, which resolved with IV antibiotics.

Conclusions IT trastuzumab was well tolerated with prolongation of OS over historical controls. IT trastuzumab should be considered for management of HER2+ leptomeningeal disease patients.

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

Introduction

Trastuzumab has revolutionized the management of HER2 overexpressing breast tumors with objective responses achieved in approximately 26% of patients in the first line metastatic setting [1]. However, given these improved systemic response rates in HER2+ tumors, the incidence of brain metastases in these patients has become an increasing problem [2, 3].

Leptomeningeal disease is a rare but devastating complication that usually has a median survival of only 15 weeks [4]. The absolute incidence is unknown but it can occur in approximately 1–5% of breast cancer patients [5, 6]. Development of leptomeningeal disease typically arises at later stages of disease and takes years to develop. The management of leptomeningeal disease requires a multidisciplinary

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approach with radiation therapy as well as possible intrathecal (IT) therapy. Given the efficacy of trastuzumab in all stages of breast cancer there has been interest in administering it intrathecally in the management of HER2+ leptomeningeal disease [7].

Several case reports have reported outcomes utilizing IT trastuzumab in the management of breast leptomeningeal disease [7–12]. These reports have revealed the potential for improved survival over historical controls. Several prospective studies are ongoing to assess the efficacy of IT trastuzumab in the management of leptomeningeal disease including phase I–II studies open by the Institut Curie (NCT01373710) and the Northwestern University (NCT01325207). Given the promising results of case reports, we treated our first patient in November 2012 with IT trastuzumab, and report our experience in the management of this historically poor prognosis cohort.

Patients and methods

Patients and follow-up

Data were analyzed retrospectively from a prospective registry of patients receiving IT therapy at our institution. Patients initiated treatment between November 2012 and May 2017 and were followed until November 2017. The study was approved by the University of South Florida Institutional Review Board. All patients had radiographic evidence of leptomeningeal disease 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 with MRI imaging and clinical examination at 2-month intervals. A focused clinical exam also took place at each IT treatment. Intracranial and/or spinal progression was defined by the evidence of new and/or progression of enhancing lesions on MRI imaging.

IT trastuzumab administration

All patients underwent administration of IT trastuzumab 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.

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 control rates as well as overall survival (OS) were calculated from the date of first IT trastuzumab administration to the date of progression or death using the Kaplan–Meier (KM) method.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. A total of 13 patients received treatment with IT trastuzumab at our institution. Median follow-up from the start of IT trastuzumab was 6.4 months. The median age of patients was 48. Median time from breast cancer diagnosis to the development of brain metastases was 87.7 months with a median of 4.6 months from the time of brain metastases diagnosis to the development of leptomeningeal disease. Previous whole brain radiation was received by the majority of patients (92%) and surgery for brain metastases was conducted in 23%. Median duration of treatment was 6.4 months. A total of 7 patients were on additional treatment for management of systemic metastases including 7 patients on IV trastuzumab, 1 patient lapatinib, 2 patients trastuzumab and emtansine, 1 patient gemcitabine, and 1 patient vinorelbine.

Treatment results

Median time from IT trastuzumab start to craniospinal progression was 5.7 months with 6- and 12-month KM craniospinal progression rates of 41 and 21%, Fig. 1. Sustained responses > 6 months were achieved in four patients with one patient with a continued response at last follow-up approximately 5 years from the start of IT trastuzumab. Four patients had positive CSF studies for malignancy at the start of IT trastuzumab. These patients had negative CSF studies following IT therapy measured at 1, 6, and 8 months post treatment initiation with one patient having a negative study following the first dose. Median survival from IT trastuzumab start was 10.6 months with 6- and 12-month OS rates of 68 and 47%, Fig. 2. Median survival from brain metastases diagnosis and leptomeningeal disease diagnosis were 18.8 months and 12.7 months, respectively.

A total of eight patients were noted to have craniospinal progression from the start of IT trastuzumab, all eight patients continued IT trastuzumab treatment following progression with six of these patients receiving additional concurrent IT therapies. Median survival in these eight patients was 4.3 months from the date of progression. Additional IT treatments after progression are detailed in Table 2.

Table 1 Patient and treatment characteristics

Variable	*n*	%
No. of patients	13	
FU from IT start		
Median	6.4	
Range	1.3–60.4	
Age (years)		
Median	48	
Range	29–75	
KPS %		
100	2	15.0
90	3	23.0
80	5	38.0
70	2	15.0
60	1	8.0
Median time from breast cancer diagnosis to brain metastases (months) diagnosis		
Median	87.7	
Range	6.5–328.2	
Median time from brain metastases diagnosis to LMD (months)		
Median	15.4	
Range	0–52.1	
Brain metastases presentation with LMD		
Yes	5	38.0
No	8	62.0
Length of IT treatment		
Median	6.4	
Range	0.7–60.4	
Previous WBRT		
Yes	12	92.0
No	1	8.0
Previous surgery for brain metastases	13	
Yes	3	23.0
No	10	77.0
Receptor status ER/PR		
Neg/Neg	5	38.0
Pos/Pos	7	54.0
Pos/Neg	1	8.0
Previous stereotactic radiation		
Yes	5	38.0
No	8	62.0
CSF+ at time of IT treatment		
Yes	4	31.0
No	9	69.0

IT intrathecal, *LMD* leptomeningeal disease, *WBRT* whole brain radiotherapy

Toxicity

Overall, IT trastuzumab was tolerated well. One patient was noted to have ventriculitis approximately 2 years following the start of IT treatment and was started on IV vancomycin with the source attributed to an infected Ommaya reservoir. The patient had their reservoir removed with clearance of the infection from the CSF prior to reservoir replacement and resuming IT trastuzumab.

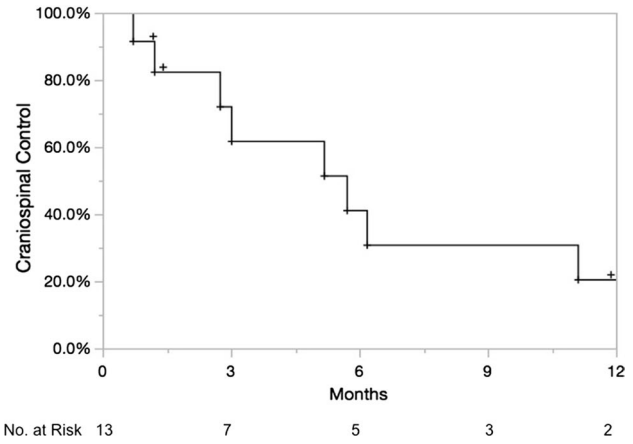

Fig. 1 Kaplan-Meier craniospinal control following the start of IT trastuzumab

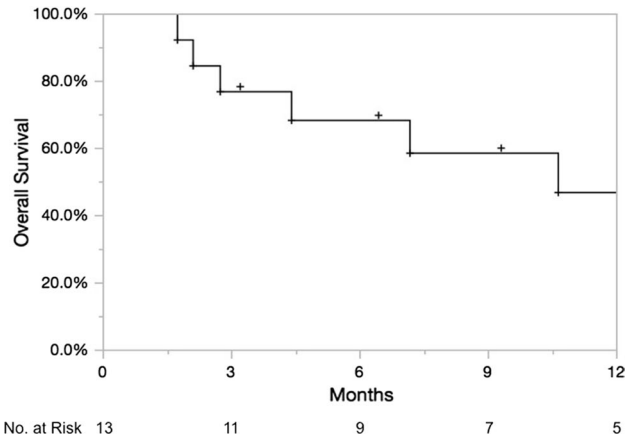

Fig. 2 Kaplan-Meier overall survival following the start of IT trastuzumab

Discussion

In this manuscript, we report our institution's experience managing HER2+ leptomeningeal disease with IT trastuzumab. The main findings of our series are that IT trastuzumab is a safe and feasible approach to this rare advanced presentation of the disease with survival rates that appear improved over historical controls. We also show that despite intracranial progression, IT trastuzumab can be continued in a select cohort of HER2+ patients with potential for concurrent IT therapies.

Given the effectiveness of trastuzumab in numerous stages of HER2 overexpressing breast cancer, there has been interest in utilizing the agent intrathecally for leptomeningeal disease. Options for this cohort of patients are limited with many patients and practitioners choosing palliative approaches [13]. Traditional IV administration of trastuzumab has poor penetration into the CSF. Stemmler et al. detailed that in patients receiving IV trastuzumab with an adequate blood brain barrier (BBB) median concentrations in the serum compared to the CSF are 420:1 [14]. Radiotherapy has been shown to improve drug delivery by disrupting the BBB [15]. As expected, CSF concentrations of trastuzumab increased to 76:1 following radiotherapy with an intact BBB. CSF concentrations further increased with leptomeningeal disease to 49:1 following radiotherapy. However, these levels are still far below therapeutic serum doses and thus case reports have discussed IT administration of trastuzumab [7–12].

Park et al. reported on two patients that received IT trastuzumab [10]. Survival durations of 20 and 29 months were reported. Another case reported from Lu et al. described the course of a 51-year-old patient who progressed with leptomeningeal metastases while receiving systemic trastuzumab. An IT approach led to an OS of 46 months following the start of therapy [8]. Bousquet et al. reported a case of a 34-year-old patient administered IT trastuzumab with a target intraventricular concentration of more than 10 mg/L, which was achieved after 4 months of close monitoring [7]. The patient continued to be alive 2.5 years after initial treatment without progression of disease in the brain and spinal cord. However, more modest results were reported by Mego et al. with OS times of 6 and 13.5 months and 1.5 months reported by Stemmler et al. [16, 17]. Given concomitant advanced systemic disease and/or poor performance status with leptomeningeal carcinomatosis, it is not surprising to note modest clinical outcomes.

Current ongoing trials assessing the safety and efficacy of IT trastuzumab in HER2+ leptomeningeal disease include a phase I–II study open by the Institut Curie (NCT01373710). The purpose of the phase I portion of the study is to determine the maximum tolerated dose (MTD) with weekly administration in order to reach an intra CSF target concentration of 30 µg/mL. The phase II portion of the study will assess neurological progression free survival at 2 months. Northwestern University also has a phase I/II study open (NCT01325207). The primary outcome is to determine the safety at the MTD of IT trastuzumab with secondary outcomes including the response to IT trastuzumab: radiological, cytological, clinical and to determine the CSF pharmacokinetics of IT administration of the drug. Both of these prospective studies have target accruals of 34 patients. Our group as well as others await the results of these trials. However, given the outcomes of our study as well as others, IT trastuzumab in the management of HER2+ leptomeningeal disease should be considered a treatment option in adequate performance status patients when other options are scarce.

The primary limitations of this study are its retrospective nature without prospective collection of safety and response

Table 2 Summary of 13 treated patients

Patient No	Age at start of IT treatment	Previous WBRT	Craniospinal progression after IT start	Time to craniospinal progression or F/U from IT start (months)	Additional IT treatment at progression	Status	OS from IT start (months)
1	55	Yes	No	No imaging		Dead	1.7
2	75	Yes	No	1.4		Alive	3.2
3	41	Yes	Yes	6.2	Thiotepa	Alive	6.4
4	44	Yes	Yes	3		Dead	4.4
5	47	Yes	No	1.2		Dead	2.7
6	61	Yes	Yes	5.7	Methotrexate	Dead	7.2
7	46	Yes	Yes	1.2	Cytarabine	Dead	2.1
8	50	Yes	Yes	2.7	Thiotepa	Alive	9.3
9	63	Yes	Yes	0.7		Dead	10.6
10	29	No	No	1.9		Dead	13.2
11	53	Yes	Yes	5.2	Methotrexate, then thiotepa, then cytarabine followed by 2 years trastuzumab alone	Alive	49.9
12	43	Yes	Yes	11.1	Thiotepa	Alive	50.9
13	48	Yes	No	59.5		Alive	60.4

IT intrathecal, *WBRT* whole brain radiotherapy, *OS* overall survival

data such as the RANO criteria [18]. However, we report the largest experience of IT trastuzumab from a single institution while awaiting results of prospective studies. We note the safety and efficacy of utilizing IT trastuzumab in the management of leptomeningeal disease in a poor prognosis cohort with limited treatment options. Survival appears improved over historical controls with acceptable safety profiles.

Compliance with ethical standards

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

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