



Original Research

Phase I feasibility study for intrathecal administration of trastuzumab in patients with HER2 positive breast carcinomatous meningitis



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Abstract Purpose: Leptomeningeal carcinomatosis (MC) is commonly associated with HER2-positive breast cancer (HER2-BC), with a poor prognosis and no standardised treatment. We conducted a phase I dose-escalation study of intrathecal (IT) administration of trastuzumab in HER2-BC patients with MC to determine the maximum tolerated dose (MTD), which was based on both the achievement of a trastuzumab intra-cerebrospinal fluid

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concentration close to a conventional therapeutic plasma concentration (30 mg/L) and/or dose-limiting toxicity (DLT).

Methods: The protocol planned IT administration of trastuzumab (30 mg, 60 mg, 100 mg or 150 mg dose levels) once a week, over the course of at least 4 weeks. Sixteen patients with MC from HER2-BC received IT trastuzumab. Intra-cerebrospinal fluid samples were obtained before each injection for pharmacokinetics.

Results: We did not observe DLT of IT trastuzumab. Eleven patients had no toxicity attributed to IT trastuzumab. For 60 mg or higher dose levels, minor toxicities attributed to IT trastuzumab included headache (2 patients), nausea (2 patients), vomiting (1 patient), cervical pain (1 patient) and peripheral neuropathy (1 patient). Two patients experienced immediate toxicity including headache or vomiting. The mean residual intra-cerebrospinal fluid concentration of trastuzumab was 27.9 mg/L for the 150 mg dose level. Three patients achieved a clinical response, seven patients had stable disease and four patients had progressive disease.

Conclusions: The MTD and recommended phase II weekly dose of IT trastuzumab in patients with HER2-BC and MC is 150 mg. A phase II trial using this dose regimen in MC from HER2-BC is ongoing.

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1. Introduction

Leptomeningeal carcinomatosis (MC) is a critical turning point in breast cancer evolution due to reduced quality of life, dismal prognosis (median survival of 16 weeks) and poorly standardised treatment (radiotherapy, systemic chemotherapy or intrathecal (IT) chemotherapy such as methotrexate, cytarabine or thiotepa) [1]. Since the widespread use of trastuzumab for HER2-positive breast cancer (HER2-BC), the incidence of MC is increasing not only in patients with advanced metastatic breast cancer but also in patients with controlled systemic metastatic disease [2,3]. The effectiveness of intravenous (i.v.) trastuzumab administration appears limited for central nervous system (CNS) metastasis and MC because trastuzumab is not able to cross the blood-meningeal barrier to enter this ‘sanctuary’ territory. Indeed, cerebrospinal fluid (CSF) levels of trastuzumab in patients given i.v. infusions were 49–420 times lower than matched serum levels [4]. Trastuzumab IT administration in rat models of CNS metastatic HER2-BC was safe without toxicity events and was superior to systemic delivery or to isotype-matched control antibody in terms of survival [5–7]. In a recent review of the literature pooling 17 case reports of IT administration of trastuzumab for MC in HER2-BC, Zagouri *et al.* reported no serious adverse events in 88.2% of cases and found significant clinical improvement in 68.8% of cases [8]. This is consistent with the absence of HER2 expression in normal human CNS tissues [9]. IT or intraventricular trastuzumab administration is therefore a promising approach for HER2-BC patients with MC in addition to systemic treatment to maintain control over the extra-CNS disease.

The objective of this phase I dose-escalation study was to determine the maximum tolerated dose (MTD) of trastuzumab administered weekly by IT or intraventricular injection, based on both (1) the achievement of a trastuzumab intra-CSF concentration close to the conventional therapeutic serum concentration (30 mg/L) and (2) the dose-limiting toxicity (DLT).

2. Material and methods

2.1. Study design

We performed a multicentre phase I open-label sequential dose-escalation study. The primary endpoint was determination of the MTD of trastuzumab administered weekly by IT or intraventricular injection with a composite criterion assessed after 4 weeks of treatment consisting of (1) the DLT according to the Common Terminology Criteria for Adverse Events and (2) an intra-CSF trastuzumab concentration close to a conventional therapeutic serum concentration (30 mg/L). Secondary criteria included determination of the recommendation dose (RD), toxicity, survival analysis and IT and i.v. trastuzumab concentrations.

All patients provided written informed consent, and local ethics committee approval was obtained (CPP approval No. 10 04 38 and ANSM approval No. 100377-77). The study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki.

2.2. Eligibility criteria

Men or women \geq 18 years of age with HER2-BC (3+ overexpression of HER2 by immunohistochemistry or

HER2 gene amplification by *in situ* hybridisation) [10] and MC diagnosed by CSF cytology and/or clinical symptoms of MC and MC evident on magnetic resonance imaging (MRI) were eligible. Other eligibility criteria included life expectancy ≥ 2 months, adequate bone marrow, liver and kidney function and good baseline left ventricular ejection fraction. Prior treatment with trastuzumab was permitted. The presence of brain metastases was permitted without prior treatment if they were asymptomatic and without threat of cerebral herniation. Patients with symptomatic brain metastases could be included if (1) surgery and/or radiotherapy was performed; (2) the cerebral localisation did not contraindicate IT or intraventricular administration and (3) a period of at least 3 weeks had passed since the last session of radiotherapy or surgery. With the exception of lapatinib, all systemic treatments (chemotherapy, hormone therapy and/or trastuzumab i.v.) could be initiated, maintained or modified during the study.

Principal non-inclusion criteria were defined by suspicion of disorder of CSF circulation, recent administration of lapatinib (wash-out period > 2 weeks required), allergy to trastuzumab, pre-existing cardiac dysfunction, severe pre-existing cerebrovascular dysfunction, pregnancy and inability to give informed consent. Concurrent radiotherapy was contraindicated during IT trastuzumab therapy.

2.3. Treatment schemes

Three patients in the first dose-escalation cohort were given a starting dose of 30 mg of trastuzumab IT and were monitored for toxicity. If no neurological DLT was observed during the first 4 weeks and if the target intra-CSF trastuzumab concentration (30 mg/L) was not reached, then three additional patients were entered at the next dose level with Fibonacci dose escalation (trastuzumab 60 mg then 100 mg then 150 mg maximum) continuing until neurological DLT was observed or intra-CSF trastuzumab concentration was reached in the absence of DLT. If one of three patients experienced a DLT at a particular dose level, three additional patients were entered at that level. If two or more patients experienced a neurological DLT at a given dose level (X), the X-1 dose level would be the RD. The RD was defined as the dose of trastuzumab at which no more than one in six patients experienced neurological DLT and/or the dose achieving the target intra-CSF trastuzumab concentration. Furthermore, at least three patients should be completely assessable (week 1 to week 4) for DLT criteria and intra-CSF trastuzumab concentration before moving to the next level.

Trastuzumab stock solution (150 mg of lyophilised powder per bottle) was reconstituted with 7.2 mL of sterile water for injection to a concentration of 21 mg/mL and then diluted in 0.9% saline to a total volume of

either 5 mL or 8 mL according to the trastuzumab dose level (30–100 mg and 150 mg, respectively).

Trastuzumab was administered once a week for 8 weeks through iterative lumbar puncture, Ommaya reservoir or indwelling IT drug delivery device (IDDD). All patients received systematic corticosteroid therapy (at least 20 mg/day of prednisolone or equivalent) established at least 3 days before each IT injection. Just before the trastuzumab IT injection, a volume equivalent to the volume of trastuzumab injection was removed (including 50 drops for CSF analyses), and 25 mg of hydrocortisone hemisuccinate was administered IT. After the injection, patients maintained a recumbent posture for 60 min to improve the distribution of trastuzumab through the cranial–spinal axis from the lumbar region into the brain ventricles. From the 4th week and if the MC was worsening, methotrexate could be added IT at a dose of 15 mg once per week just before each trastuzumab injection. Trastuzumab IT could be continued in the same way beyond the 8-week period if clinical benefit was suggested.

2.4. Evaluation during therapy, response and toxicity criteria

DLTs were evaluated during the first 4 weeks of IT trastuzumab according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale, version 4.0 (<http://ctep.cancer.gov/>), with a focus on neurotoxicity and systematic search for exacerbation of leptomeningeal and/or neurological signs. Any grade 3 or 4 toxicity attributable to IT trastuzumab persisting despite appropriate symptomatic treatment and requiring a postponement of IT trastuzumab treatment for more than 2 weeks was considered a DLT. Additionally, the following events indicated poor tolerance (DLT) when they occurred within 24 h after IT administration: generalised seizure despite prophylactic antiepileptic treatment, grade 3 or 4 meningeal syndrome persisting for at least 3 days or grade 4 headache.

The MTD referred to the highest dose at which one or more DLT was observed during the first 4 weeks of treatment. The MTD was reached if one in three patients or two in six patients experienced a DLT at the same dose level according to the dose escalation rules.

At least once a week, patients had a clinical examination with a standardised neurological and DLT assessment, biologic assessment, CSF and serum concentration of trastuzumab before IT injection (Supplementary Table S1) [11,12]. Brain and spine MRI was performed at week 5. A global evaluation and systemic staging was performed at week 9 and then every 3 months for 2 years as detailed in the Supplementary Table S1.

Clinically and radiologically responsive disease, stable disease and progressive disease were assessed at week 5, before the 5th injection, with neurological clinical

Table 1
Patients and tumour characteristics.

Patient No.	Patient age (years)	ER/ PgR status	Baseline ECOG PS	Extent of disease at inclusion	Delay between diagnosis and first metastasis (years)	Delay between diagnosis and neoplastic meningitis (years)	Type of prior therapy regimens				Last therapy regimen at inclusion ^a
							Anti-HER2 therapy	Cytotoxic chemotherapy (Number of lines of Ct for metastatic disease)	Hormonotherapy	IT therapy against neoplastic meningitis	
1	47	1/0	0	MC, brain	2.3 (brain)	3.4	Yes	Yes (0)	Yes	No	Ht
2	52	1/1	0	MC, brain	2.4 (brain)	2.9	Yes	Yes (0)	Yes	No	Ht
3	64	0/0	Na	MC, local relapse, lung, brain	24.5 (brain)	27.1	Yes	Yes (2)	Yes	No	0
4	57	1/1	2	MC, liver, bone, brain	3.9 (bone and liver)	4.7	Yes	Yes (2)	Yes	No	Ct i.v. Tr
5	66	1/1	2	MC, liver, bone, nodes, brain	3.4 (bone and liver)	8.0	Yes	Yes (3)	Yes	No	Ct i.v. Tr
6	63	0/0	1	MC, brain	1.2 (brain)	3.0	Yes	Yes (3)	No	No	Ct i.v. Tr
7	41	0/0	2	MC, liver, lung, brain	2.2 (liver)	5.0	Yes	Yes (4)	No	Yes	Ct IT Ct
8	33	0/0	Na	MC, liver, nodes, brain	3.9 (liver, nodes)	4.6	Yes	Yes (1)	No	No	i.v. Tr
9	24	0/0	1	MC, brain	1.4 (brain)	2.4	Yes	Yes (3)	No	Yes	Ct IT Ct i.v. Tr
10	65	0/0	2	MC, liver, brain	1.0 (liver)	2.5	Yes	Yes (2)	No	No	i.v. Tr
11	49	0/0	0	MC, liver, bone, lung, brain	4.6 (liver, bone and lung)	8.4	Yes	Yes (4)	No	No	Ct i.v. Tr
12	57	1/1	0	MC	6.3	6.3	Yes	Yes (0)	Yes	No	Ht
13	60	0/0	1	MC, local relapse, nodes	5.3 (nodes)	10.7	Yes	Yes (4)	No	No	i.v. Tr
14	59	1/0	2	MC, local relapse, liver, bone, skin, pleura, peritoneum, nodes, brain	12.3 (nodes)	20.8	Yes	Yes (6)	Yes	No	Ct IT Ct i.v. Tr
15	40	0/0	3	MC, liver, bone, lung, brain	3.4 (bone, lung)	6.5	Yes	Yes (4)	Yes	Yes	Ct i.v. Tr
16	57	0/0	0	MC, pancreas, brain	1.2 (brain)	2.7	Yes	Yes (1)	No	No	Ct i.v. Tr

ECOG PS, Eastern Cooperative Oncology Group performance status; ER, oestrogen receptor; PgR, progesterone receptor; IT, intrathecal; i.v., intravenous; MC, leptomeningeal carcinomatosis; Ct, chemotherapy; Tr, trastuzumab injection.

^a Last therapy regimen during the 2 months before inclusion.

examination (Supplementary Table S2) and MRI (using Response Evaluation Criteria in Solid Tumours [RECIST] criteria) compared with the first evaluation [13]. Exploratory analyses on CSF cytology were performed using an adaptation of the Response Assessment in Neuro-Oncology (RANO) proposal for response criteria [14]. A responsive disease was considered when CSF converts from positive at week 1 to negative at week 3 and 4. A stable disease was considered when CSF was negative at week 1, 3 and 4. Otherwise, it was considered as progressive disease. However, CSF cytology was not taken into account to define the therapeutic response and subsequent adaptation of the therapeutic strategy according to recent guidelines [15].

2.5. Trastuzumab concentrations

Serum and CSF concentrations of trastuzumab were determined by enzyme-linked immunosorbent assay. The biological end-point of the study was a trastuzumab residual concentration equal to or greater than 30 mg/L, the concentration associated with optimal inhibition in previous preclinical models [16–19].

2.6. Biostatistics

Patients were assessed for toxicity and were included in the final analysis on receipt of at least one dose of IT trastuzumab. A maximum of 24 patients were planned

Table 2
Intrathecal trastuzumab: attributed toxicity.

Patient No.	Dose level administered (mg)	Major toxicity attributed to intrathecal trastuzumab ^a or toxicity that forced postponement of the treatment for more than 2 weeks	Minor toxicity attributed to intrathecal trastuzumab (total duration of symptoms in weeks)	Immediate toxicity
1–3 and 7 ^b	30	None	None	None
4–6 and 8	60	None	<i>Patient No.6:</i> Nausea grade 1 (4 weeks), cervical pain grade 1 (1 week) <i>Patient No.8:</i> Headache grade 2 (4 weeks) followed by headache grade 1 (4 weeks)	<i>Patient No.8:</i> Headache grade 2
9–12	100	None	<i>Patient No.9:</i> Peripheral neuropathy grade 1 (4 weeks) <i>Patient No.12:</i> Nausea grade 2 (3 weeks), vomiting grade 2 (3 weeks)	<i>Patient No.12:</i> Vomiting grade 1
13–16	150	None	<i>Patient No.16:</i> Headache grade 2 (2 weeks) followed by headache grade 1 (1 week)	

^a Major toxicities attributed to intrathecal trastuzumab were grade 3 or 4 toxicities attributed to intrathecal trastuzumab.

^b Patient No. 7 was assigned a 60 mg dose of trastuzumab but accidentally received a 30 mg dose of trastuzumab at each injection.

for this phase I trial. Overall survivals (OSs, the interval between the date of enrolment in the study and the date of death or last news) were estimated by the Kaplan–Meier method and compared with the Log–Rank test using Prism (GraphPad Software Inc., USA). Correlation between clinical and radiological responses was evaluated with McNemar’s test.

3. Results

3.1. Patients

A total of 19 patients were enrolled in this phase I trial. However, three patients were excluded from the final analyses because they died before receiving the first IT injection. Patient characteristics and assigned treatment for the 16 assessable patients are listed in Tables 1–3 and Supplementary Table S3.

The median age at baseline was 57 years (range 24–66 years). The median time between diagnosis of breast cancer and the occurrence of MC metastases was 4.85 years (range 2.4–27.1 years) (Table 1). There were concomitant brain metastases in 14 patients (87.5%). All patients had received prior adjuvant cytotoxic chemotherapy and anti-HER2 therapy (trastuzumab, trastuzumab emtansine and/or lapatinib) before inclusion (Table 1 and Supplementary Table S3). Six patients had HER2-BC (37.5%) with a significant expression of hormonal receptors; all of them had previously received hormonal therapy. Three patients had previously received another IT drug (methotrexate for patient No. 7, thiotepa for patient No. 9 and liposomal cytarabine for patient No. 14, Table 1).

One patient per dose level was not completely assessable (week 1 to week 4) for DLT criteria and intrathecal trastuzumab concentration. Hence, four patients were treated at the 30 mg dose level, four at the 60 mg dose level, four at the 100 mg dose level and four at the

150 mg dose level. During the first 8 weeks of the study, a total of 101 doses were administered (median, 8 doses; range 1–8 doses per patient) (Table 3). Six patients continued to receive the injection beyond the 8th week, and at least 32 IT injections were the maximum observed in a single patient.

Ten patients (62.5%) received the full eight-dose course of IT trastuzumab scheduled in the trial (Table 3). Thirteen patients were assessable for neurological DLT during the first 4 weeks. After one dose of IT trastuzumab, patient No. 4 experienced extra-meningeal disease progression that prevented her from staying in the trial. Patients No. 6, 7 and 10 did not complete the full treatment due to disease progression. Patient No. 14 died of an unknown cause before receiving the second dose of IT trastuzumab.

3.2. Toxicity

Toxicities attributed to IT trastuzumab that were observed in the 13 assessable patients at week 5 are listed in Table 2. We did not observe DLT of IT trastuzumab in this trial. Considering the whole cohort, 11 patients had no toxicities attributed to IT trastuzumab (minor or major, immediate or delayed). No toxicity was reported for the 30 mg dose level. For other dose levels, minor toxicities (grade ≤ 2) potentially related to IT trastuzumab included headache (2 patients), nausea (2 patients), vomiting (1 patient), cervical pain (1 patient) and peripheral neuropathy (1 patient) (Table 2). Two patients experienced immediate toxicity (within 24 h after IT administration) potentially related to IT trastuzumab including headache (1 patient) and vomiting (1 patient).

3.3. Antitumour activity

The median OS after enrolment was 7.3 months (range 12 days–27.9 months) (Fig. 1). Fourteen patients were

Table 3
Relationship of prior treatment and response to IT trastuzumab.

Patient No.	Dose level assigned (mg)	Dose level administered (mg)	Mode of administration	No. of doses administered	Modification of systemic therapy regimen	Response to IT Trastuzumab at week 5			Adjunction of IT MTX	Survival in days (vital status at last follow-up)
						Clinical	CSF	Radiological		
1	30	30	IDDD then LP	≥32	No change	SD	Na	SD	No	853 (D)
2	30	30	Ommaya	8	Stop systemic therapy regimen	SD	PD	SD	No	826 (A)
3	30	30	IDDD	8	No change	PD	SD	SD	No	96 (D)
4	60	60	Ommaya	1	No change	Na	Na	Na	No	21 (D)
5	60	60	LP then IDDD	8	New line of Ct, keep i.v. Tr	SD	RD	PD	No	168 (D)
6	60	60	LP	5	No change	PD	RD	PD	No	96 (D)
7	60	30 ^a	Ommaya	4	No change	PD	SD	PD	No	108 (D)
8	60	60	LP then IDDD	19	New line of Ct, keep i.v. Tr	SD	PD	SD	No	629 (D)
9	100	100	IDDD then LP	17	No change	SD	SD	SD	No	381 (D)
10	100	100	Ommaya	3	No change	PD	Na	PD	Yes ^b	198 (D)
11	100	100	Ommaya	8	No change	RD	SD	SD	No	436 (D)
12	100	100	LP then IDDD	≥17	Stop Ht, new line of Ct and i.v. Tr	RD	PD	SD	No	771 (D)
13	150	150	IDDD	17	No change	SD	PD	SD	No	247 (D)
14	150	150	IDDD	1	Na	Na	Na	Na	No	12 (D)
15	150	150	Ommaya	7	Stop anti-HER2 therapies, new line of Ct	RD	SD	SD	No	183 (D)
16	150	150	IDDD	≥8	Stop i.v. Tr, same Ct	SD	SD	PD	No	600 (A)

A, alive; CSF, cerebrospinal fluid; D, dead; IDDD, intrathecal delivery drug device; IT, intrathecal; LP, lumbar puncture; PD, progressive disease; RD, responsive disease; SD, stable disease.

^a Patient No. 7 was assigned a 60 mg dose of trastuzumab but accidentally received a 30 mg dose of trastuzumab at each injection.

^b Patient No. 10 received two injections of IT methotrexate in association with IT trastuzumab during the first 2 weeks of the study.

assessable for clinical antitumour activity at week 5. From the clinical perspective and considering neurological symptoms, three patients experienced responsive disease, seven patients had stable disease and four patients had progressive disease (Table 3). Among the patients with responsive or stable disease, six were receiving an identical or reduced systemic regimen compared to the last regimen before inclusion. Four patients had a new line of chemotherapy initiated concurrently with their inclusion (Table 3 and Supplementary Table S3). No patients with a new concurrent line of chemotherapy had progressive disease at week 5. Radiologically, according to RECIST criteria on MRI, nine patients had stable disease and five patients had progressive disease (Table 3). Clinical and radiological responses were not correlated ($p = 0.23$). Considering the CSF cytology, two patients had a responsive disease, six patients had a stable disease and four patients had a progressive disease. CSF cytology was not correlated to clinical or radiological responses ($p = 1$ and 0.09 , respectively) (Table 3). There was no significant differences in the survival of patients with stable or responsive disease compared to patients with a progressive disease defined by CSF cytology ($p = 0.26$).

3.4. Trastuzumab concentrations

Complete data were obtained from 13 patients until week 4 (Fig. 2). Before the first IT trastuzumab injection, mean trastuzumab CSF concentrations were 0.30 mg/L (range 0 – 1.41 mg/L) in patients with concurrent i.v. trastuzumab and 0.0002 mg/L in patients without concurrent i.v. trastuzumab. At this time, the

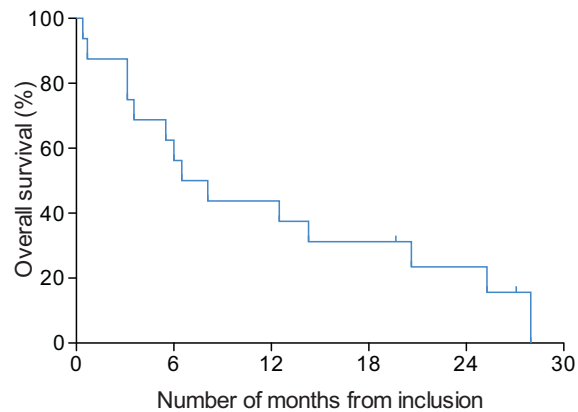


Fig. 1. Overall survival of patients with HER2+ breast cancer and leptomeningeal carcinomatosis treated with intrathecal trastuzumab.

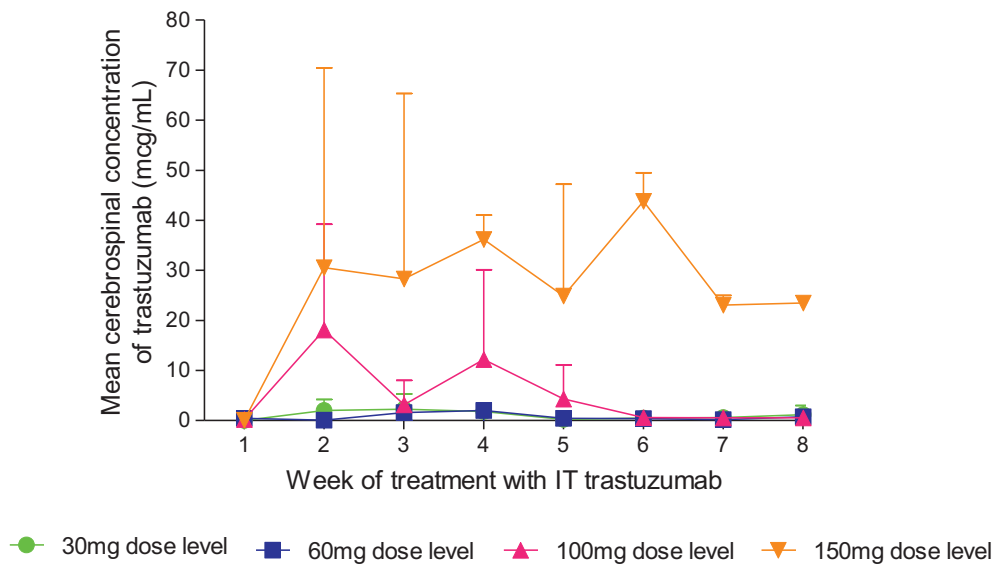


Fig. 2. Mean (standard deviation) cerebrospinal concentration of trastuzumab by dose level. Cerebrospinal (CSF) concentration of trastuzumab was assessed once a week, just before the IT injection of trastuzumab. CSF concentrations of trastuzumab were determined by enzyme-linked immunosorbent assay (ELISA). The biological endpoint of the study was a trastuzumab residual concentration equal to or greater than 30 mg/L, the concentration associated with optimal inhibition in previous preclinical models [16–19].

mean trastuzumab serum concentration was 53.34 mg/L (range 10.42–113.61 mg/L) in patients with concurrent i.v. trastuzumab, almost 177 times the concurrent CSF trastuzumab concentration. Between week 2 and week 8, mean residual trastuzumab CSF concentrations were 1.23 mg/L, 0.79 mg/L, 7.08 mg/L and 27.88 mg/L for the 30, 60, 100 and 150 mg dose levels, respectively. These results do not include the data of patient No. 13, who was an outlier with concentrations ranging from 0 to 3636.58 mg/L, the maximum value observed, probably due to sampling through an IDDD. Individual CSF concentrations according to dose level are depicted in the Supplementary Figure S1.

4. Discussion

In this study, we demonstrated the feasibility of administering IT trastuzumab to HER2-BC patients with MC. The RD for subsequent study in a similar cohort of patients is 150 mg. We did not observe DLT, and this dose led to a mean trastuzumab CSF residual concentration close to our target concentration. Until the results of a phase II study are available, we strongly recommend IT trastuzumab once weekly at 150 mg per injection for HER2-BC MC until progression of MC.

According to previous observations, IT trastuzumab had a tolerable safety profile [8]. At 60 mg and higher dose levels, we observed minor toxicities including headaches, nausea or vomiting, cervical pain and peripheral neuropathy. Immediate toxicities (headache or vomiting) were rare. The use of IT corticosteroids could also have impacted the adverse events seen. Up to now, there is no well-defined effect of IT corticosteroids,

positive or negative, for non-haematologic cancers [14]. The majority of our patients were heavily pretreated before inclusion and during IT trastuzumab treatment. However, we did not observe an increased rate of toxicities in our patients, and IT trastuzumab seemed to be compatible with other systemic or IT therapies. Our findings are consistent with those reported for IT injections of other monoclonal antibodies such as rituximab and bevacizumab [20,21]. According to our preliminary data, quality of life was not impaired by this treatment, and some patients were able to maintain this therapy for many weeks. Because these results are preliminary, we continue to evaluate potential toxicity carefully in an ongoing phase II study.

To our knowledge, this represents the first phase I study of trastuzumab administered into the CSF of humans. We planned the protocol with one IT injection of trastuzumab per week as its half-life is around 28 days, and the therapeutic scheme for systemic injections is once a week too [22]. We confirmed in this study that CSF concentrations of trastuzumab after i.v. injection are on average 177 times lower than serum concentrations which are probably insufficient to induce an anti-tumour effect in the CNS. The dose of 150 mg resulted in residual trastuzumab CSF concentrations closest to our predefined target concentration. Technically, it would have been complicated to administer a higher dose because of the volume of injection required. Furthermore, we observed an unexpected high variability of CSF concentrations at the 150 mg dose level. To manage the quality of life of our patients, we decided to avoid the compulsory use of an Ommaya reservoir for all patients, and we limited the pharmacokinetic dosages

to one assessment concomitantly to the injection. The residual concentration profiles may have been distorted by the sample taken directly from the IDDD. There is a risk of retention of part of the injection into the IDDD because of incomplete wash-out, especially for high doses that limit the potential wash-out volume. This could have caused falsely elevated concentrations (patient No. 13, for example). However, no side-effect was observed for the highest CSF concentrations of trastuzumab.

Intraventricular trastuzumab monotherapy is associated with encouraging anti-MC HER2-BC activity and clinical benefit in a heavily pretreated population of patients. Three patients had a clinical response, and 10 patients had a clinical stabilisation of their symptoms. This is hopeful considering that most of neurological deficits due to MC are considered fixed and irreversible and that the best response to treatment will be stabilisation of the disease. To follow the RANO proposal for response criteria, progressive disease was defined by either conversion of negative to positive CSF cytology or failure to convert positive to negative following induction of the treatment [14]. We did not observe correlation between the clinical or radiological responses and response defined by CSF cytology with RANO criteria. This definition was not prognostic in our little cohort. Stabilisation of MC was observed in patients with HER2-BC MC at all dose levels. Clinical and/or radiological meningeal responses were detected only at the 100 mg and 150 mg dose levels. However, few patients in the 30 mg cohort received concurrent systemic chemotherapy. We observed prolonged survival for some patients, as the median OS after inclusion was 7.3 months, with a maximum of 27.9 months. This is almost twice the 16-week median OS described in the literature [1]. Eleven of the 16 patients received concurrent systemic chemotherapy, and all patients received general corticosteroid therapy in addition to IT corticosteroids before the IT trastuzumab injection. It is noteworthy to observe that all patients receiving a new line of systemic chemotherapy at inclusion had regressive or stable disease clinically. Although most of these systemic therapies have only limited CNS penetration, it is possible that either the concurrent systemic therapy or the concomitant IT injection of corticosteroids could be confounding factors for evaluation of response in this study. The addition of IT methotrexate 4 weeks after trastuzumab for disease progression without discontinuing trastuzumab treatment could have been questionable. However, no patient received this treatment except one, out of the protocol during the first 2 weeks. This patient displayed a progressive disease and did not bias our optimistic results. Our results will need to be compared to those of another phase I clinical trial evaluating IT trastuzumab in MC of HER2-BC ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT01325207) when they will be published.

This study demonstrated for the first time in a clinical trial the interest and feasibility of IT trastuzumab. There is little information about other anti-HER2 therapies in the literature. Lapatinib, a tyrosine kinase inhibitor, can pass the blood-meningeal barrier when it is altered because of its low molecular weight and permissive membrane transporters [23]. However, its efficacy on brain metastases is poor in monotherapy, and a regimen including capecitabine is required to increase the rate of objective response [24,25]. There are only two case reports in the literature suggesting a response of MC to lapatinib administration [26,27]. IT administration of trastuzumab emtansine (T-DM1) or IT administration of pertuzumab could also be interesting options. However, they have not been tested yet. In a retrospective exploratory analysis of the EMILIA trial, the rate of CNS progression among patients with advanced HER2-BC was similar in patients treated with i.v. T-DM1 or with lapatinib plus capecitabine [28]. In our cohort, patient No. 15 developed MC while she was receiving the T-DM1 regimen. There is no published report specifically addressing MC cases treated with either T-DM1 or pertuzumab.

5. Conclusions

In conclusion, this study demonstrated the safety and feasibility of administering IT trastuzumab to HER2-BC patients with MC. The RD of IT trastuzumab administered with IT corticosteroids is 150 mg. Promising evidence of antitumour activity of IT trastuzumab in HER2-BC MC was observed. Our group is currently recruiting for a phase II trial to further assess the response and toxicity profile of IT trastuzumab for treatment of HER2-BC with MC.

Conflict of interest statement

Claire Bonneau, Coraline Dubot, Céline Desvignes, Patricia Tresca, Isabelle Turbiez, Jacques Li, Christophe Passot, Fawzia Mefti, Emmanuelle Mouret-Fourme and Maya Gutierrez certify that there are no actual or potential conflicts of interest in relation to this article. Emilie Le Rhun gets research funding to disclose from Mundipharma and Amgen. Véronique Dieras has been a consultant for Pfizer, Roche, Novartis, Allovie and Lilly. Gilles Paintaud has been a consultant for Laboratoire Français du Fractionnement et des Biotechnologies (LFB) and Pierre Fabre Laboratories. His research team has received grants from Roche Pharma, Chugai, Pfizer, MSD, Genzyme and Novartis. Olivier Tredan has been a consultant for Laboratoire Roche. Sophie Taillibert has been a consultant for Mundipharma EDO.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejca.2018.02.032>.

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