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ORIGINAL ARTICLE

A successful compartmental approach for the treatment of breast cancer brain metastases

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Abstract

Background Brain metastases are challenging daily practice in oncology and remain a compartmental problem since most anti-cancer drugs do not cross the blood–brain barrier at relevant pharmacological concentrations.

Methods In a young woman with HER2-overexpressing breast cancer resistant to standard treatments, at the time of brain metastases progression, a ventricular reservoir was implanted for intrathecal drug injections and detailed pharmacokinetic studies.

Results A first association of intrathecal trastuzumab with intravenous cisplatin was offered to the patient. For trastuzumab, the mean cerebrospinal fluid trough concentration of 53.4 mg/L reached relevant levels, enabling the stabilization of the metastases. Adding intravenous cisplatin was not beneficial, since the cerebrospinal fluid exposure was almost undetectable under 0.08 mg/L. We then offered the patient an intrathecal combination of trastuzumab and methotrexate, because of their in vitro synergic cytotoxicity. The cerebrospinal fluid peak of methotrexate was 1037 µmol/L at 2 h, and the concentrations remained above the theoretical therapeutic concentration. After 2 months of this drug combination, we obtained an excellent response on the brain metastases.

Conclusion Our preliminary study supports the interest of a compartmental approach through a direct administration of drugs into the cerebrospinal fluid for the treatment of breast cancer brain metastases.

Keywords HER2-overexpressing breast cancer · Brain metastasis · Intrathecal trastuzumab · Intrathecal methotrexate · Cerebrospinal fluid

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Introduction

Brain metastases are challenging daily practice in oncology, with a median survival under 11 months [1]. In women with metastatic HER2-overexpressing breast cancer, targeting HER2 is associated with high response rates and 50% of long-term survivors [2]. Most patients with disease progression will develop brain metastases, mainly due to an inadequate passage of drugs through the blood–brain barrier.

Trastuzumab, an anti-HER2 antibody, and the leading drug for the treatment of HER2-overexpressing breast cancer [3], does not efficiently cross the blood–brain barrier [4]. In a pilot pharmacological study, we demonstrated the benefit of the direct intrathecal administration of trastuzumab to halt the progression of HER2-overexpressing breast cancer brain metastases [5]. However, trastuzumab monotherapy is associated with limited responses and usually requires combination with a cytotoxic drug to reach full efficacy [6].

Here, in a young woman with HER2-overexpressing breast cancer brain metastases resistant to standard treatments, we explored the benefit of combining intrathecal trastuzumab with either intravenous cisplatin or intrathecal methotrexate.

Materials and methods

Assessment of *HER2* copy number on tissue samples using droplet-digital PCR

HER2 copy number was assessed on three different tumor samples: the primary tumor, an axillary lymph node metastasis at the time of initial diagnosis, and a skin metastasis at the time of first progression. All three samples were processed for laser-microdissection using a Zeiss Microdissection and Pressure Catapulting system (Zeiss, Munich, Germany), to select cancer cells. Total DNA was extracted from the microdissected cells using DNeasy-Micro-Kit (Qiagen, Courtaboeuf, France) and concentrated in a final volume of 10 µL. Total DNA from HER2-overexpressing BT474 and non-HER2-overexpressing MDA231 cell lines were used as positive and negative controls, respectively.

On the different DNA samples, droplet digital Polymerase Chain Reaction (ddPCR) was performed using the QX100 ddPCR workflow system (Biorad, Hercules, CA, USA). The mix contained 20 ng of genomic DNA from microdissected cells or cancer cell lines, 10 µL of So Fast Eva Green Supermix (Bio Rad), 1 µL of *HER2* probes (Hs00223586_cn, Life Technologies, Foster City, USA), and 1 µL *RnaseP* probes (Taqman® copy number Reference Assay, 4403326, Life Technologies) per well. The final volume for the reaction was 20 µL. Droplets were generated by a QX200 Droplet Generator (Biorad). PCR was carried out on the CFX96 Real Time System (Bio Rad). There was an initial denaturing step at 95 °C for 10 min, followed by 40 cycles of denaturing (95 °C for 15 s), and annealing (60 °C for 1 min). A post-amplification melting curve program was initiated by heating to 98 °C for 10 min and then cooling to 12 °C. Each PCR run included a no-template control. The results of the ddPCR were generated using QX100 Droplet Reader (Biorad), and analysed using QuantaSoft software (Biorad). The ratio of *HER2*-positive droplets to *RnaseP*-positive droplets was calculated. A ratio of 0.8–1.2 was considered as a normal copy number for the *HER2* gene.

Intrathecal administration of trastuzumab and methotrexate

We used an Ommaya reservoir, and for each injection, the volume of cerebrospinal fluid removed was identical to the volume of drug injected. For trastuzumab, the dose of 50 mg per injection corresponded to a total volume injected of 3 mL. For methotrexate, the dose of 15 mg per injection corresponded to a total volume of 1 mL.

Each drug was injected directly in less than 30 s, and when we co-administered trastuzumab and methotrexate, trastuzumab was administered first and methotrexate immediately after. In these cases, we used the same reservoir, and the total volume of cerebrospinal fluid removed before injection of drugs was 4 mL.

Immediately after the end of drug infusion, 1 mL of saline serum was flushed to ensure complete drug delivery without significant increase of CSF pressure.

Assessment of trastuzumab concentrations

Cerebrospinal fluid samples were collected to measure trastuzumab trough concentrations before each trastuzumab infusion. Trastuzumab concentrations were determined using a validated ELISA test, as previously described [7].

Assessment of cisplatin concentrations

On the first day of cycle 2 (day 21), a detailed pharmacokinetic study was performed to assess cisplatin concentrations in both the plasma and the cerebrospinal fluid. Cerebrospinal fluid and blood samples were collected before cisplatin infusion, and at 15, 30 min and 1, 2, 4, 6, 24 h after the end of infusion. Blood samples were immediately centrifuged at 15,700×*g* for 10 min to obtain plasma, which was then stored at − 80 °C until analysis [8]. Cisplatin concentrations

in the cerebrospinal fluid and in the blood were determined using inductively coupled plasma-mass spectrometry as previously described [9].

The measurement of trastuzumab and cisplatin serum concentrations was carried out on the CePiBAc platform. Centre Pilote de Suivi Biologique des traitements par Anticorps (CePiBAc) is a pharmacological platform directed by Prof. Gilles Paintaud at University Hospital of Tours (France) and mostly dedicated to the assessment of therapeutic antibody concentrations for clinical purpose.

Assessment of methotrexate concentrations

At day 14 of cycle 3, a detailed pharmacokinetic study was performed to assess methotrexate concentrations in both the blood and in the cerebrospinal fluid. Cerebrospinal fluid and blood samples were collected before methotrexate infusion, at 30 min, and 1, 2, 4, and 24 h after the end of infusion. Samples were protected from light until processing. The method was a Syva enzyme multiplied immunoassay technique (EMIT), using a COBAS c501 device (Roche). Reagents were provided by Syva-SIEMENS. The method is based on an immune-metric method using sheep anti-methotrexate antibodies, and quantifying total methotrexate (i.e. free and bound forms), but not its 7-OH metabolite. The calibration values range from 0.2 to 2 µmol/L. Biological samples were diluted in TRIS buffer under a sequential dilution procedure to obtain a reliable concentration in the range 0.2–2 µmol/L [10].

Case study and findings

Breast cancer with liver, bone, and brain metastases, including two cerebellar localizations, was diagnosed in a 30-year-old woman. The histological diagnosis was ductal invasive carcinoma overexpressing HER2, without expression of estrogen or progesterone receptors. The patient received a combination of docetaxel, trastuzumab, and pertuzumab for 6 months with complete metabolic response on localizations outside the central nervous system. She had additional whole-brain radiation therapy at 30 Gy with partial response on the two cerebellar metastases. Trastuzumab and pertuzumab were maintained for three additional months. Then, a new brain imaging showed rapid progression with numerous metastases. The patient also had local progression with skin metastases on the breast, which were biopsied. Tissue analyses using immunostaining showed the persistence of HER2 overexpression (Fig. 1a) and a strong gene amplification with 30 copies of the *HER2* gene using digital droplet PCR on laser-microdissected cancer cells (Fig. 1b). We assumed that the *HER2* genotype was identical in the brain metastases and thus decided to administer trastuzumab directly into the cerebrospinal fluid (CSF).

With the patient's informed consent, a ventricular reservoir was implanted for further intrathecal drug injections and pharmacokinetic studies.

Because of the reported efficacy of cisplatin on breast cancer brain metastases [11, 12], we offered the patient an association of intrathecal trastuzumab [5] and intravenous cisplatin (Fig. 2a). A detailed pharmacokinetic study was performed to assess trastuzumab and cisplatin concentrations in the CSF and the blood. The mean CSF trough concentration of trastuzumab was 53.4 mg/L, ranging from 7.6 to 102.9 mg/L, i.e. above the clinically relevant concentration of 40 mg/L (Fig. 2b). Serum concentration of trastuzumab was assessed at four time-points per week during the two first cycles. As previously reported in our pilot study [5], the mean serum trough concentration was 48 mg/L despite the absence of intravenous administration of trastuzumab, indicating an important drug efflux from the CSF to the blood. For cisplatin, a peak plasma concentration of 4.1 mg/L was observed at 15 min after intravenous administration, and it remained high at 24 h, at 2.3 mg/L. In contrast, in the CSF, cisplatin concentrations were almost undetectable, below 0.08 mg/L (Fig. 2c).

After two cycles of this regimen, a new brain MRI showed stable disease. Because of the very low exposure of the CSF to cisplatin, we concluded that this stabilization of brain metastases resulted solely from the intrathecal trastuzumab. To overcome the limitation of the blood–brain barrier passage from blood to brain, we then decided to administer a cytotoxic drug directly into the CSF. We chose methotrexate because of its in vitro synergic cytotoxicity in combination with trastuzumab [13]. Again, a pharmacokinetic study was performed to assess methotrexate concentrations in the CSF and the plasma (Fig. 3a). In the CSF, a peak of 1037 µmol/L occurred 2 h after injection and decreased rapidly, with concentrations above the theoretical therapeutic concentration of 1 µmol/L at 24 h [14]. In contrast, the serum concentration remained very low after a single injection, not exceeding 0.3 µmol/L (Fig. 3b). After 2 months of intrathecal methotrexate and trastuzumab, we obtained a 74% response on the brain metastases according to RECIST criteria (Fig. 3c) [15].

Discussion

Brain metastases are an increasing cause of death from cancer because of drug inadequacy to cross the blood–brain barrier. The treatment of brain metastases thus requires a compartmental approach.

Intrathecal administration of trastuzumab has been used since 2001, mainly for the treatment of women with HER2 overexpressing leptomeningeal carcinomatosis from breast cancer origin [16–20]. Most case studies have

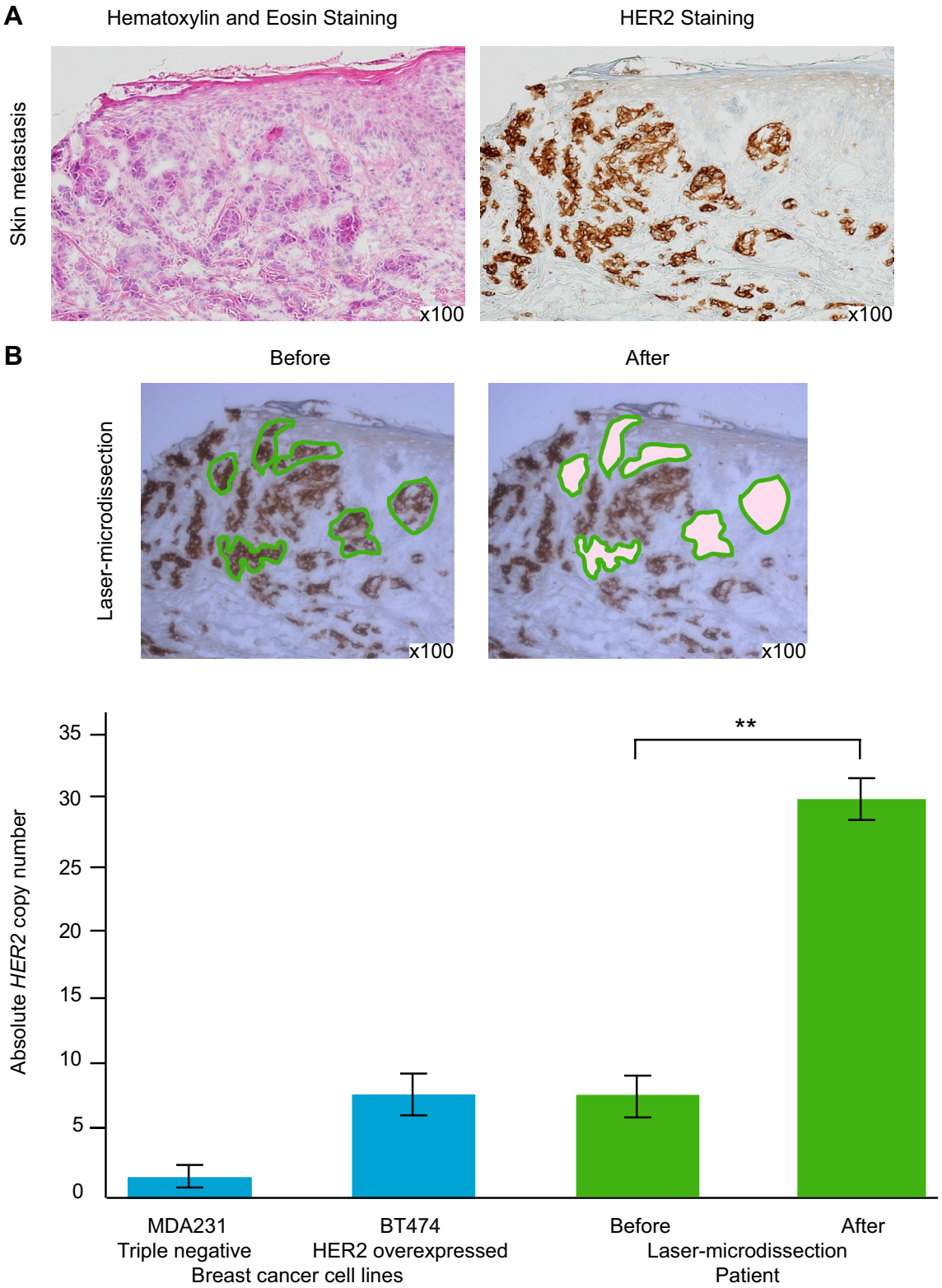

Fig. 1 Histological and molecular findings. **a** Representative histological analysis of the skin biopsy shows islets of cancer cells in the dermis, using hematoxylin–eosin (left panel). Cancer cells strongly overexpressed HER2, using immunostaining (right panel). **b** Laser-microdissection of HER2-overexpressing cancer cells (upper panel). *HER2* absolute copy number is very high in laser-microdissected cancer cells, significantly higher than in the whole skin biopsy (**$P < 0.01$)

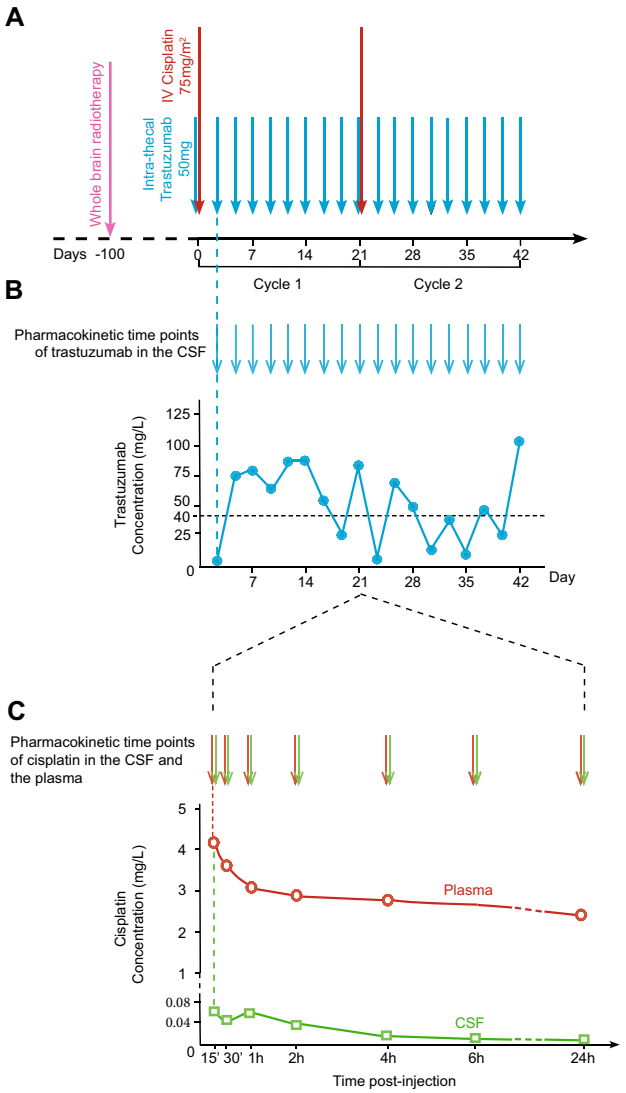

Fig. 2 Therapeutic protocol and pharmacokinetics of trastuzumab and cisplatin. **a** Therapeutic protocol for cycles 1 and 2. **b** Pharmacokinetic time points for trastuzumab and concentrations in the cerebrospinal fluid (CSF) during cycles 1 and 2. **c** Pharmacokinetic time points for cisplatin on the first day of cycle 2 (day 21) and concentrations in the CSF and in the plasma. Cisplatin concentrations in the CSF are almost undetectable, below 0.08 mg/L

been using empirical doses of trastuzumab with no associated pharmacological studies. In 2018, a phase I study has tested increasing doses of intrathecal trastuzumab for the treatment of 16 women with HER2 overexpressing breast cancer and leptomeningeal carcinomatosis. They have shown the feasibility of weekly injections of 150 mg of trastuzumab, but with a limitant injected volume of 7.2 mL and sub-optimal trough concentrations of trastuzumab with important intra- and inter-patient variabilities. However, they had included patients with both leptomeningeal and parenchymal brain localizations, with some radiological and clinical responses on both sites [20]. We had previously conducted a pilot pharmacological study and obtained the proof of concept for direct intrathecal administration of trastuzumab to halt the progression of HER2-overexpressing brain metastases, via relevant pharmacological concentrations of trastuzumab in the CSF [5].

We confirmed this here, but we failed to gain in efficacy with the concomitant administration of intravenous cisplatin. This was coherent with a very low CSF exposure to the drug in our patient and also with historical pharmacological data on humans and monkeys (Table 1). While intravenous cisplatin induces radiological response on cancer brain metastases, this might not mean that the drug crosses the blood–brain barrier but possibly that the response results from an anti-angiogenic effect on tumor vessels [21, 22].

As previously reported in our pilot study [5], we also confirmed the important efflux of trastuzumab from the CSF to the blood after intrathecal administration in our patient, since the mean serum trough concentration was 48 mg/L despite the absence of intravenous administration of trastuzumab. Such an efflux had been described for trastuzumab with cynomolgus monkeys [27], but also for rituximab, an anti-CD20 antibody, in a phase I study with patients treated for brain lymphomas [28]. This efflux may be linked to the presence of FcRn receptors at the surface of endothelial cells of the blood–brain barrier [29].

In a compartmental approach associating trastuzumab and methotrexate in the CSF, we obtained an excellent response on brain metastases. Unlike what was observed with trastuzumab, we did not detect methotrexate in the blood, and this was probably due to a blood dilution effect from drug efflux of the low total dose of 15 mg injected in the CSF. This effect was also attributable to the diffusion and high concentration of methotrexate in the brain parenchyma, including metastases [30].

Innovative therapeutic approaches are being developed to facilitate the passage through the blood–brain barrier of anticancer agents administered intravenously: (1) the engineering of bi-specific antibodies or peptide–drug conjugates [31]; (2) the co-administration of osmotic component such as mannitol to permeabilize the blood–brain barrier [32–34]. Another approach could be to engineer Fab fragment antibodies to limit the efflux from brain to blood after intrathecal administration.

Conclusion

Pending successful innovative treatments, our study supports the interest of a compartmental approach through direct administration of drugs into the cerebrospinal fluid for the treatment of HER2 breast cancer brain metastases.

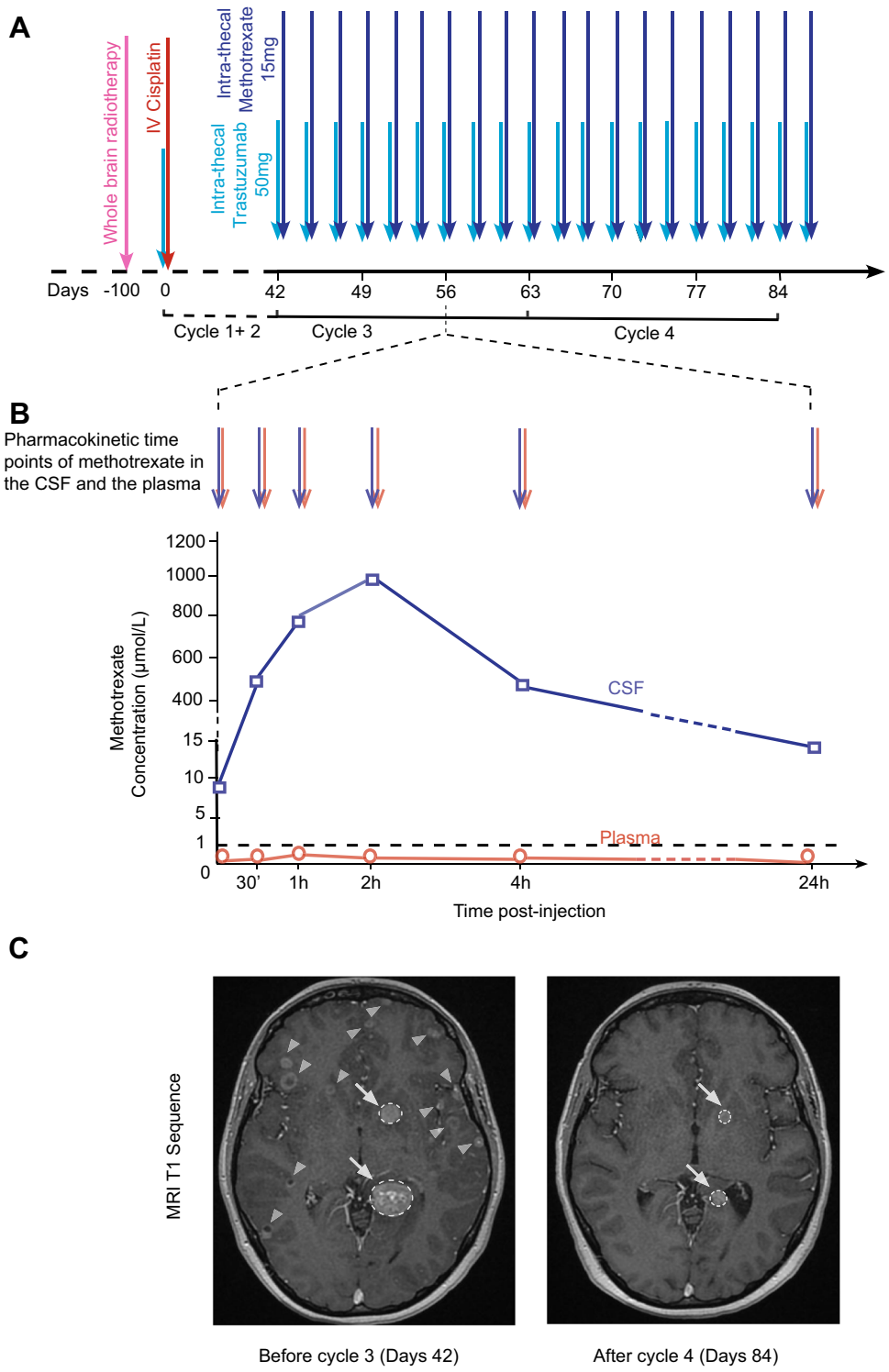

Fig. 3 Therapeutic protocol and pharmacokinetics of methotrexate. **a** Therapeutic protocol for cycles 3 and 4. **b** Pharmacokinetic time points for methotrexate at day 14 of cycle 3 and concentrations in the CSF and in the plasma. CSF concentrations are above the theoretical therapeutic concentration of 1 µmol/L. The serum concentration does not exceed 0.3 µmol/L. **c** Axial T1-weighted magnetic resonance imaging (MRI) of brain metastases, with gadolinium injection. Before cycle 3 (day 42), metastases are numerous (arrowheads), the largest measuring 20 mm in the left temporal horn (arrow). After the end of cycle 4 (day 84), there is an excellent response with almost a disappearance of all metastases

Table 1 CSF exposition to cisplatin in data on human and monkeys

Species	*N*	Tumor type	Dose of cisplatin (mg/m^2)	Chemotherapy regimen	Administration	Ratio of concentration of cisplatin in CSF:plasma (%)
Male rhesus monkeys [21]	3	NA	40	Cisplatin	Intravenous	3.6
Male rhesus monkeys [23]	1	NA	200	Cisplatin	Intravenous	4.3
	1	NA	200	Cisplatin	Intravenous	5.4
Human [24]	1	Glioblastoma	80	Cisplatin	Intravenous	< 4
Human [25]	1	Neuroblastoma	120	Cisplatin	Intravenous	< 3.3
Human [26]	6	Meningeal carcinomatosis	60	Cisplatin–etoposide	Intravenous	2.5
	8	Metastatic brain tumor	60	Cisplatin–etoposide	Intravenous	2.5
	9	Metastatic brain tumor	100	Cisplatin–etoposide	Intravenous	2.9
	7	Malignant glioma	60	Cisplatin–etoposide	Intracarotid	15
	7	Metastatic brain tumor	60	Cisplatin–etoposide	Intracarotid	5.4
Our study	1	Metastatic brain tumor	75	Cisplatin	Intravenous	0.31–1.94

NA not applicable

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Author contributions TTN conceived and designed the study, provided the study material or patient, collected and assembled the data, provided data analysis and interpretation, and drafted the manuscript. EA provided data analysis and interpretation. FD provided data analysis and interpretation, provided the study material, provided administrative support and located financial support. QTN provided the study material and provided administrative support. CD provided the study material and provided administrative support. MR provided the study material and provided administrative support. ON provided the study material and provided administrative support. PN provided the study material, provided administrative support, provided data analysis and interpretation. QVL provided the study material and provided administrative support. SW provided the study material and provided administrative support. M-CP collected and assembled the data. LZ collected and assembled the data. GP provided the study material, provided administrative support, provided data analysis and interpretation. AJ conceived and designed the study, provided the study material, provided administrative support, provided data analysis and interpretation, drafted the manuscript and located financial support. GB conceived and designed the study, provided the study material, provided administrative support, collected and assembled the data, provided data analysis and interpretation, drafted the manuscript and located financial support.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Informed consent Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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