Incontri Oncologici
Triveneto

Metastasi Cerebrali da Carcinoma Mammario HER2-positivo

NEGRAR 7 OTTOBRE 2014

12° INCONTRO ONCOLOGICO DEL TRIVENETO

Caso clinico: il dosaggio nel liquor dei farmaci anti-HER2 si correla all'attività antitumorale a livello cerebrale?

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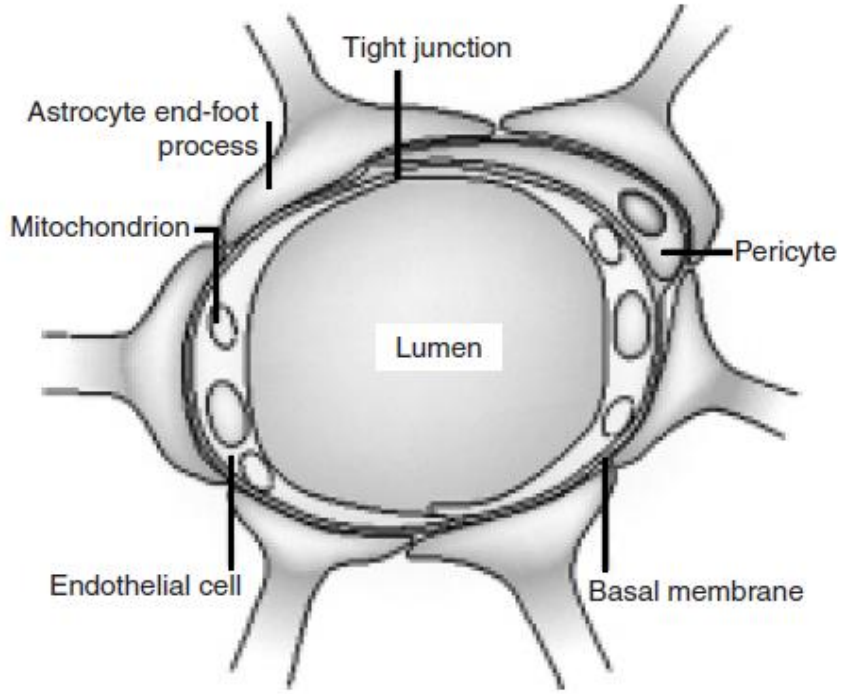
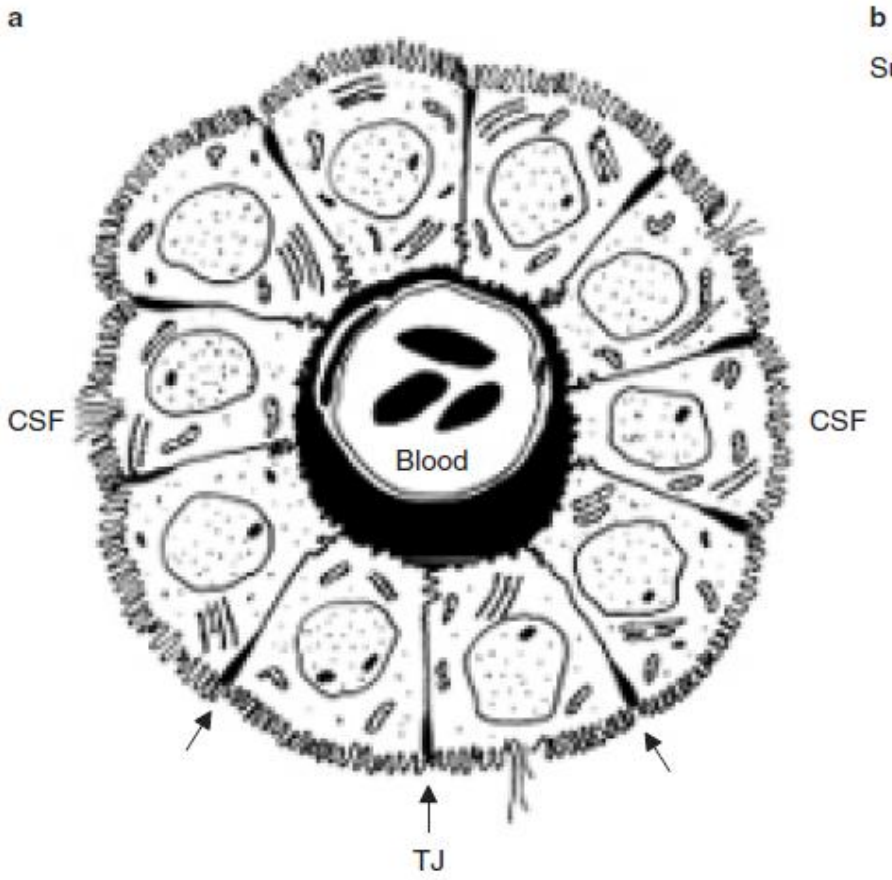
Drug concentrations in CSF

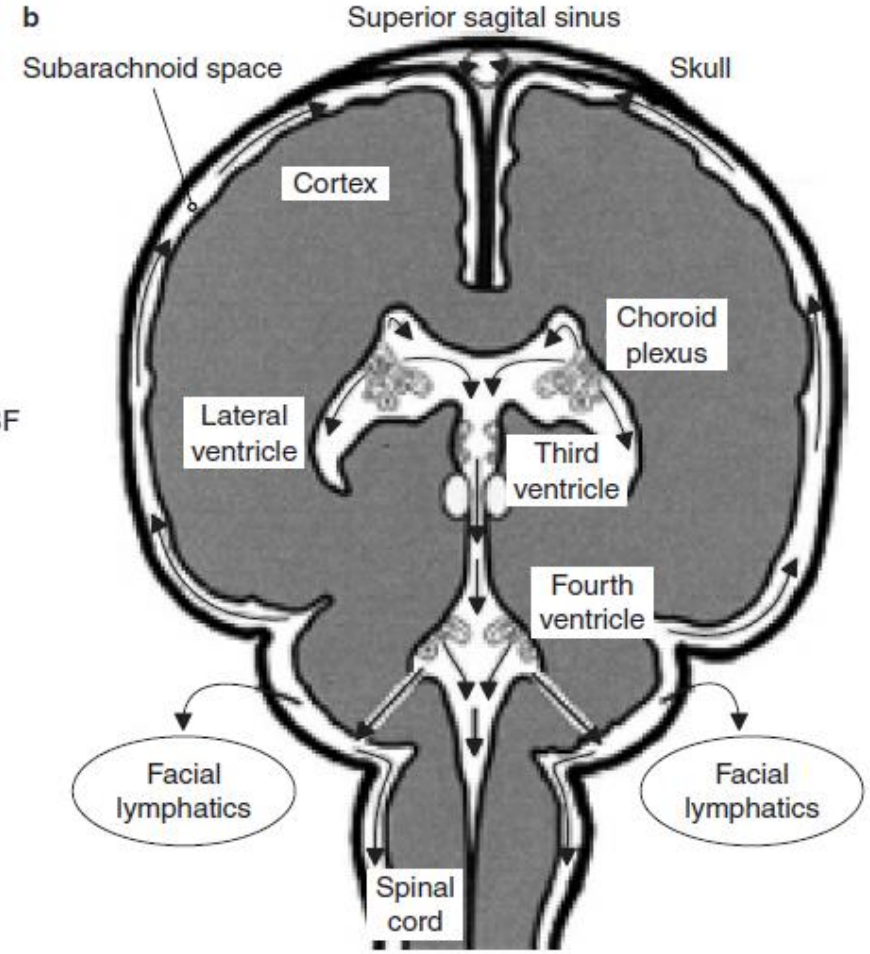
- Drug concentration in CSF is generally considered a surrogate for predicting concentration in the brain
- A high ratio of CSF/plasma drug concentration indicates a high distribution in the brain, whereas a low ratio means poor penetration through BBB and possibly lack of activity within CNS

Blood Brain Barrier



Blood Cerebrospinal-fluid Barrier





Trastuzumab in CSF

Trastuzumab in CSF

To the Editor: Trastuzumab is a recombinant humanized monoclonal antibody used to treat breast cancer patients overexpressing the *HER2* proto-oncogene. Its half-life in serum is 8.3 ± 5 days.[1] It is unknown whether and to what extent trastuzumab can cross the blood-brain barrier. Therefore, we measured CSF and concomitant serum levels of trastuzumab in a 62-year-old patient with meningeal carcinomatosis treated with weekly intravenous trastuzumab.

A few hours after trastuzumab infusion, serum levels achieved were as expected in the range of 10,000 to 100,000 ng/mL.[1] Concomitant CSF levels were 300-fold lower (Table 1). Despite a possibly leakier blood-brain barrier in this patient with meningeal carcinomatosis, only minimal amounts of trastuzumab penetrated the CSF. Therefore, it is unlikely that intravenous trastuzumab would be useful to treat meningeal or cerebral disease of breast cancer.

Table 1. CSF and Concomitant Serum Levels of Trastuzumab

Trastuzumab Dose (mg)	Delay* (minutes)	Trastuzumab in Serum† (ng/mL)	Trastuzumab in CSF† (ng/mL)
240 (week 1)	NA	ND	ND
120 (week 2)	210	61,392	210
120 (week 3)	140	70,326	212

Abbreviations: NA, not applicable; ND, not determined.

*Time interval from the end of the 30-minute infusion of trastuzumab to sampling.

†A serum sample was collected at the same time the CSF was collected.

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Journal of Clinical Oncology, Vol 18, No 11 (June), 2000

Lapatinib in CSF

Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study

Thomas Bachelot, Gilles Romieu, Mario Campone, Véronique Diéras, Claire Cropet, Florence Dalenc, Marta Jimenez, Emilie Le Rhun, Jean-Yves Pierga, Anthony Gonçalves, Marianne Leheurteur, Julien Domont, Maya Gutierrez, Hervé Curé, Jean-Marc Ferrero, Catherine Labbe-Devilliers

Our study had several limitations. First, it was a single-arm phase 2 study and we cannot rule out some selection bias. In particular, more than 95% of our patients had an ECOG status of lower than 2, and 43% of the patients had asymptomatic brain metastases. Extrapolation of our findings to the general population could, therefore, be difficult. Second, no direct comparison can be made with other therapeutic regimens, such as monotherapy, other combination treatments, and WBRT.[32] Third, we did not measure lapatinib or capecitabine concentrations in the cerebrospinal fluid, and we therefore could not assess penetration of the blood–brain barrier. Finally, we did not assess quality of life or the effect of treatment on the neurocognitive functions.

Lancet Oncology 2013

An Unexpected Synergist Role of P-Glycoprotein and Breast Cancer Resistance Protein on the Central Nervous System Penetration of the Tyrosine Kinase Inhibitor Lapatinib (*N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine; GW572016)

Joseph W. Polli, Katie L. Olson, John P. Chism, Lisa St. John-Williams, Russell L. Yeager, Sesha M. Woodard, Vicky Otto, Stephen Castellino, and Victoria E. Demby

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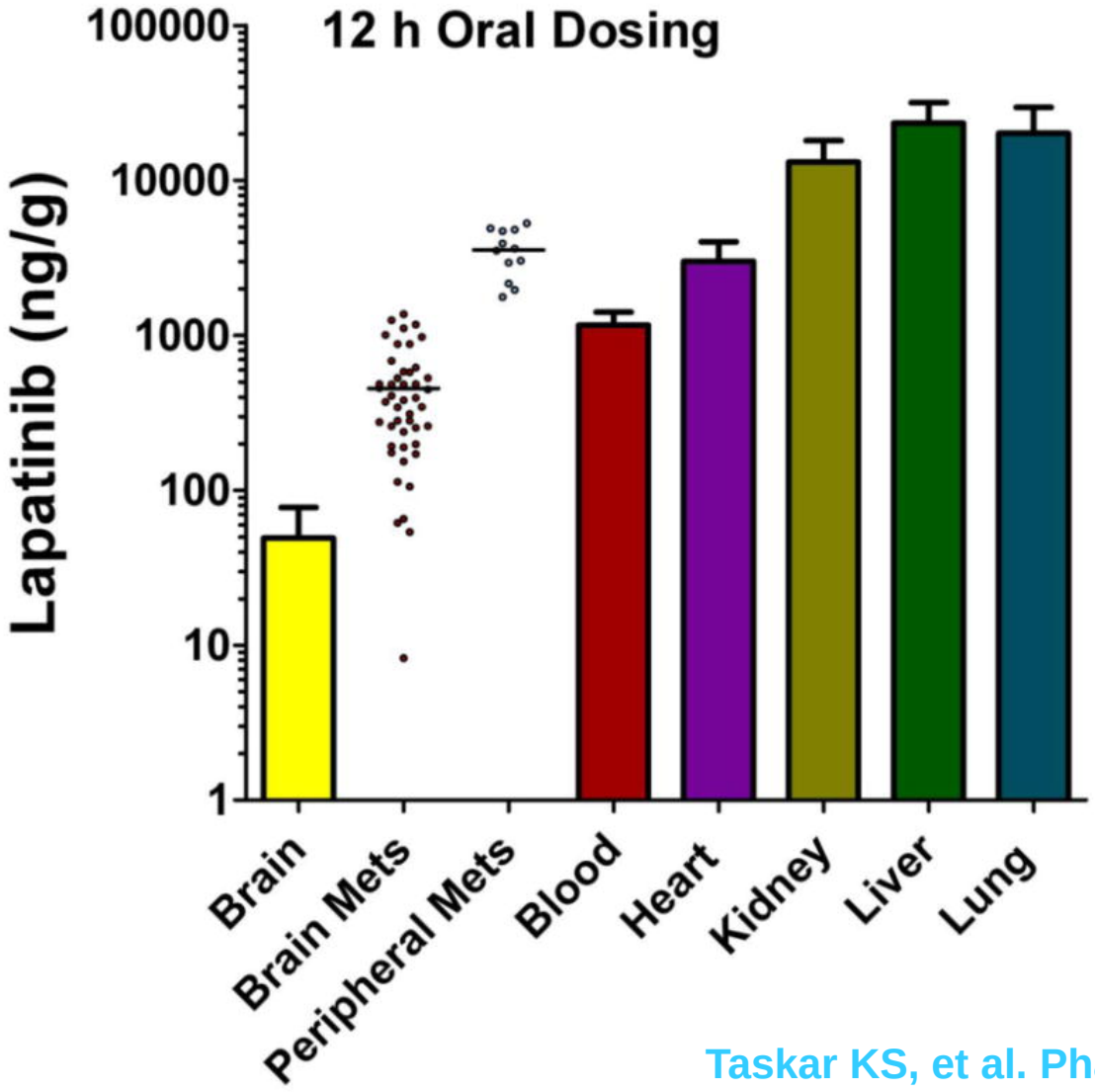
Summary of the plasma and brain concentrations and plasma clearance of lapatinib in Mdr1a/1b(−/−), Bcrp1(−/−), and Mdr1a/b(−/−)/Bcrp1(−/−) knockout mice and FVBn (wild-type) mice after a constant-rate intravenous infusion of lapatinib at 0.3 and 3 mg/kg/h

Data are presented as the mean ± S.D. Statistical difference was declared when $p \leq 0.05$.

Genotype	Mice per Group	Lapatinib Infusion Rate: 0.3 mg/kg/h			
		Plasma C_{ss}	Brain Concentration	Brain-to-Plasma Ratio	Plasma Clearance
		ng/ml	*ng/ml*		*ml/min/kg*
FVBn	5	730 ± 410	18 ± 9.1	0.03 ± 0.01	13 ± 6.1
Mdr1a/b(−/−)	4	239 ± 43[a,b]	21 ± 3.3[c]	0.09 ± 0.02[a,b,c]	31 ± 4.2[a,b]
Bcrp1(−/−)	5	394 ± 74[a]	17 ± 3.1[d]	0.04 ± 0.01[a,d]	20 ± 4.6[a]
Mdr1a/b(−/−) /Bcrp1(−/−)	5	296 ± 150[a]	319 ± 67[a]	1.2 ± 0.42[a]	28 ± 13[a]
FVBn	4	5097 ± 2729	194 ± 65	0.04 ± 0.02	20 ± 13
Mdr1a/b(−/−)	3	4463 ± 811[c]	732 ± 421[a,b,c]	0.16 ± 0.06[a,b,c]	15 ± 2.3[c]
Bcrp1(−/−)	5	6447 ± 2731[d]	253 ± 23[a,d]	0.04 ± 0.01[d]	13 ± 4.4[d]
Mdr1a/b(−/−) /Bcrp1(−/−)	5	2840 ± 867	4938 ± 1823[a]	1.7 ± 0.50[a]	23 ± 6.2

[a] FVBn compared with *Mdr1a/b(−/−)*, *Bcrp1(−/−)*, or *Mdr1a/b(−/−)/Bcrp1(−/−)*.
[b] *Mdr1a/b(−/−)* compared with *Bcrp1(−/−)*.
[c] *Mdr1a/b(−/−)/Bcrp1(−/−)* compared with *Mdr1a/b(−/−)*.
[d] *Mdr1a/b(−/−)/Bcrp1(−/−)* compared with *Bcrp1(−/−)*.

Lapatinib distribution in HER2 overexpressing experimental brain metastases of breast cancer



Taskar KS, et al. Pharm Res. 2012

Lapatinib concentration in cerebrospinal fluid in two patients with HER2-positive metastatic breast cancer and brain metastases

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METASTASI CEREBRALI DA CARCINOMA MAMMARIO HER2-POSITIVO

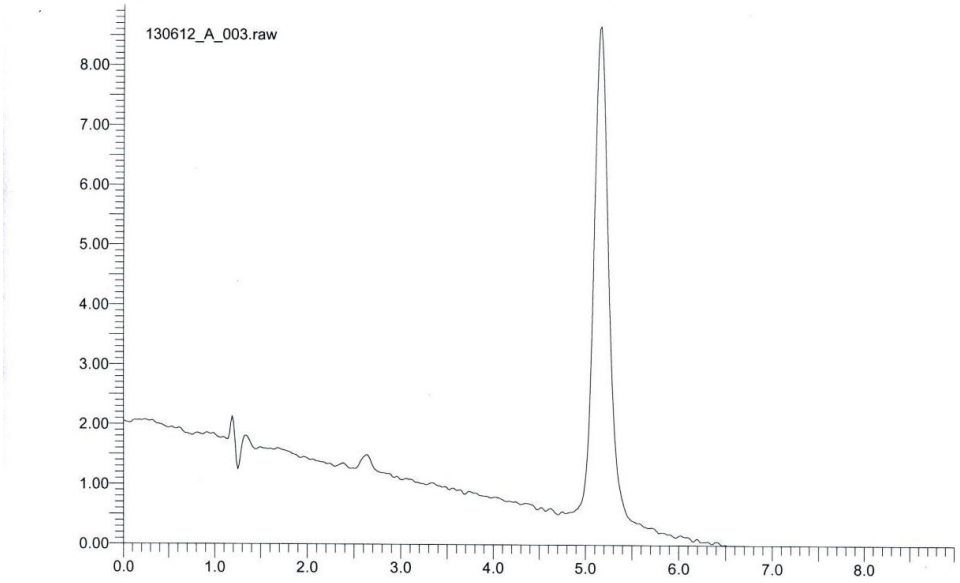
Table 1. Characteristics of two patients with 'de novo' HER2-positive metastatic breast cancer and lapatinib concentrations in cerebrospinal fluid and in plasma

	Patient #1	Patient #2
Age, years	36	37
Biological features	Ductal carcinoma HR negative HER2 positive (IHC 3+) Grade 2 Ki67, 40%	Ductal carcinoma HR positive HER2 positive (IHC 3+) Grade 3 Ki67, 60%
Surgery for primary tumor	No	Yes
Time to brain metastases development, months	0	15
Number of brain metastases	1	2
Maximum size of brain metastases, mm	5	13
CNS symptoms	No	No
Extracranial sites of metastasis	Lung, mediastinal lymph nodes	Mediastinal lymph nodes, bone
Previous systemic therapy	-Carboplatin + Paclitaxel + Trastuzumab -Vinorelbine + Trastuzumab -Liposomal Doxorubicin + Trastuzumab	-Anthracycline-based→ Paclitaxel + Trastuzumab -Tamoxifen + Leuprorelin
Previous RT for brain metastases		
Stereotactic radiosurgery, Gy	21	18
WBRT	No	No
Best Response to capecitabine + lapatinib		
Brain metastases	Stable disease	Stable disease
Extracranial disease	Partial response	Partial response
Intracranial progression-free survival (from starting lapatinib + capecitabine), months	14	19
Overall survival (from starting lapatinib + capecitabine), months	15	22+

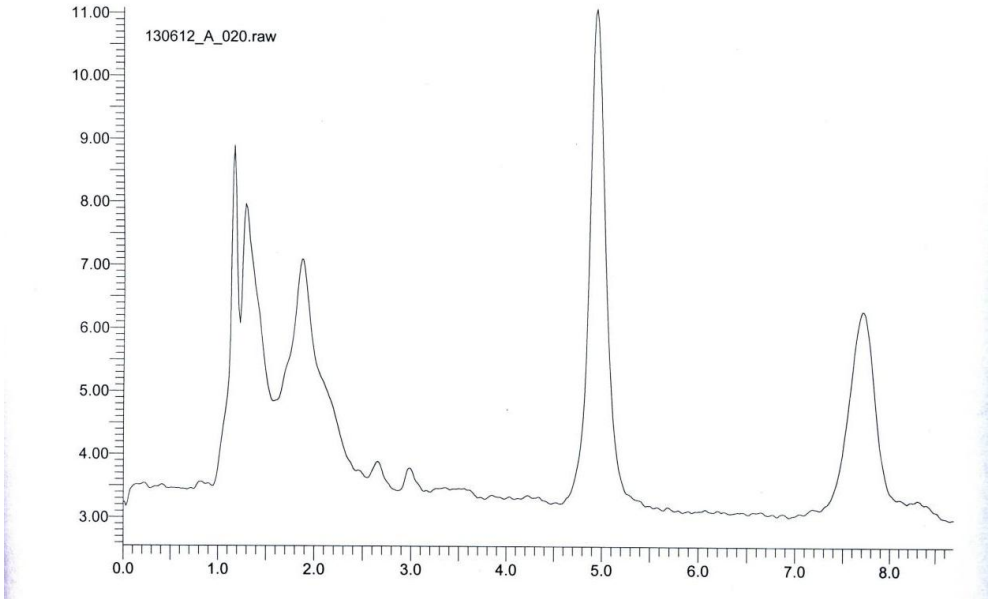
RT, radiotherapy; WBRT, whole-brain radiotherapy; CSF, cerebrospinal fluid; CNS, central nervous system.

Lapatinib plasma assay (HPLC/UV)

Standard



Plasma



Lapatinib CSF assay (HPLC/MS)

Dosaggio lapatinib in liquor: paragone EIC tra standard a 50 ng/ml e 10 ng/ml e campioni (concentrati 5 volte)

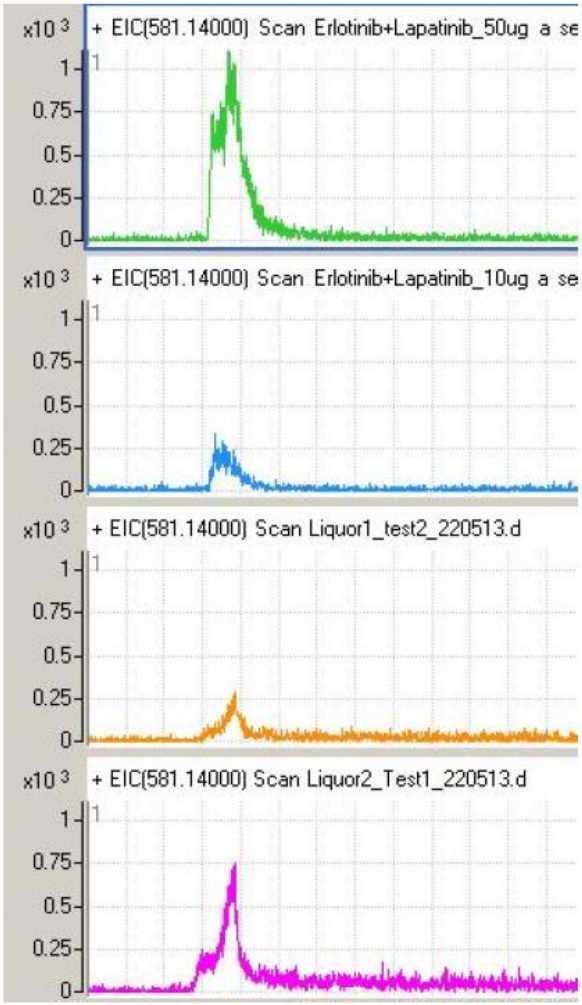


Table 1. Characteristics of two patients with 'de novo' HER2-positive metastatic breast cancer and lapatinib concentrations in cerebrospinal fluid and in plasma

	Patient #1	Patient #2
Concentration of lapatinib, ng/ml		
Plasma	1515	3475
CSF	1.3	4.5
'CSF concentration/plasma concentration' ratio, ‰	0.9	1.3
Concentration of proteins, g/l		
Plasma	69.1	70.6
CSF	0.21	0.43

RT, radiotherapy; WBRT, whole-brain radiotherapy; CSF, cerebrospinal fluid; CNS, central nervous system.

Gori S et al., Ann Oncol 2014, 4:912-913

Clinical pharmacokinetics of tyrosine kinase inhibitors

Nielka P. van Erp[a,*], Hans Gelderblom[b], Henk-Jan Guchelaar[a]

Pharmacokinetic parameters of the individual tyrosine kinase inhibitors.

Name	F (%)	Protein binding (%)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-24} (μg h/mL)	V_d/F (L)	Cl/F (L/h)	C_{trough} (ng/mL)	Reference
Imatinib	98	~95	2–4	18	40.1	295	11.8	1215.8	[15,26,34]
Gefitinib	60	~91	3–7	48	5.6	1400	35.7	60	[36,39,153]
Erlotinib	60–100	~93	4	36.2	26.5	232	5.3	1168	[40,41]
Sorafenib	Unknown	~99.5	3	25–48	143.4	Unknown	Unknown	Unknown	[46,47]
Sunitinib	Unknown	~95	6–12	40–60	1.11	2230	34–62	44	[49,93]
Dasatinib	Unknown	~96	0.5–6	3–5	Unknown	2505	Unknown	Unknown	[51]
Lapatinib	Unknown	>99	3–4	24	14.3–36.2	>2200	Unknown	300	[53,79,154,155]
Nilotinib	Unknown	~98	3	17	36.0	579	29.1	900.2	[57,156]

Abbreviations: F, absolute bioavailability; T_{max}, time to peak concentration; $t_{1/2}$, elimination half life; AUC, area under the concentration–time curve; V_d/F, apparent volume of distribution; Cl/F, apparent oral clearance; C_{trough}, trough concentration.

logP lapatinib = 5.4

Cancer Treatment Reviews 35 (2009) 692–706

Preclinical data are consistent with the results of a clinical trial showing clinically relevant concentrations of lapatinib in BMs from HER2+ breast cancer

Table 3. Lapatinib concentrations: brain metastases (BM) and serum at time of BM resection (μM) and BM to serum ratio

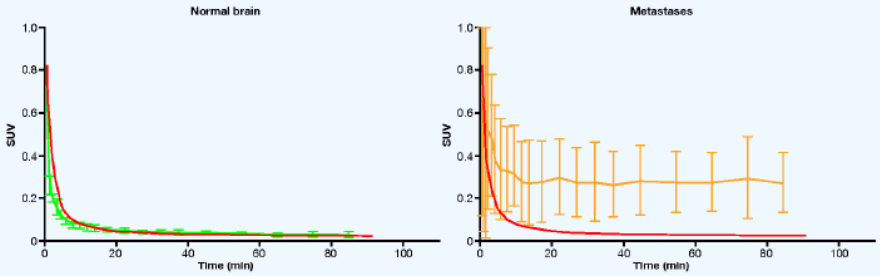
Patient	Preop doses	BM Conc average* & range (μM)	Serum conc (μM)	BM to serum ratio
2	5	63.6 (43.9-77.2)	6.5	9.8
10	3	14.6 (11.7-22.2)	2.4	6.0
11	3	18.6 (11.3-31.0)	3.5	5.3
12	2	1.0 (0.7-1.5)	5.3	0.2

*Brain metastases average concentrations were calculated based on average of multiple samples from a single collected lesion, and ranges of concentrations are shown.

Morikawa A et al. Clinical evidence for drug penetration of capecitabine and lapatinib uptake in resected brain metastases from women with metastatic breast cancer. J Clin Oncol 2013; 15(Suppl): 514.

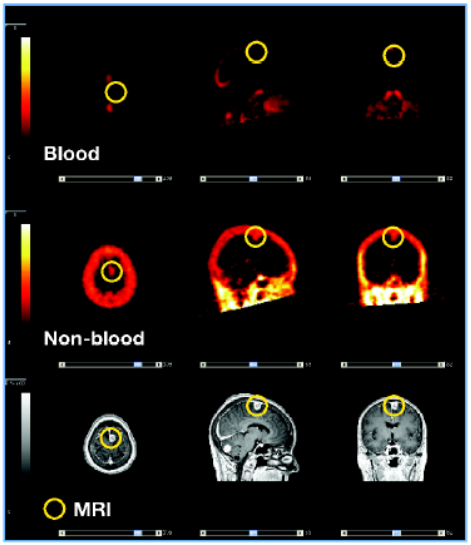
Uptake of [^{11}C]-Lapatinib was observed in brain metastases indicating that lapatinib could enter the brain through a disrupted BBB

Figure 7. Uptake in normal brain and metastases compared with scaled whole blood



Mean time-activity curves (TACs) for tumor and normal tissue from all scans. Baseline and the Day 8 TACs were combined in the plots shown. The blood TAC (red line) has been scaled to represent a 5% blood volume representing a 'null hypothesis model' which assumes that no [^{11}C]lapatinib enters the tissue from the blood.

Figure 8. Signal dissection



- Image data for Subject 10 separated into blood and non-blood components. The position of a brain metastasis is highlighted with a yellow circle. The corresponding contrast-enhanced MRI is also shown for anatomical reference. This image shows that the uptake of radioactivity in the brain metastases is over and above that contributed from a model-fitted blood volume. This suggeststhat the observed uptake of [^{11}C]lapatinib in brain metastases of HER2 over-expressing subjects cannot be attributed to a blood volume effect alone.

Saleem A et al. Brain and tumor penetration of carbon-11-labeled lapatinib ([11C]Lap) in patients (pts) with HER2-overexpressing metastatic breast cancer (MBC). J Clin Oncol 2013; 15(Suppl): 635.

Conclusions

- We found low concentrations of lapatinib in CSF
- CSF/plasma ratio was low for both patients
- Our findings are consistent with the poor solubility of the drug in watery environment and with the low concentration of proteins in the CSF
- Lapatinib concentration in CSF may not be a reliable surrogate of its distribution in brain metastases

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