Terapia medica delle metastasi cerebrali : chemiosensibilità e barriera ematoencefalica

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Chemotherapy of brain metastases: factors influencing the efficacy

- Sensitivity of neoplastic cells
- Drug exposure
  - Drug properties
    (liposolubility, molecular weight)
  - blood-brain barrier
    (including P-glycoprotein)

TABLE 6.2. Brain capillary permeability of chemotherapeutic agents[a]

High	Intermediate		Low
•Nimustine	•Temozolomide	•Etoposide/Teniposide	•Doxorubicin
•Carmustine	•Cytarabine	•Cisplatin/Carboplatin[b]	•Vincristine
•Lomustine	•Topotecan	•Irinotecan[b]	•Taxanes
•Procarbazine	•Hydroxyurea	•Bleomycin	•Gemcitabine[b]
•Thiotepa		•Methotrexate	•Proteins (e.g., interferon-alpha, Trastuzumab)

[a] Information based on Refs. 9, 14, 15, 24, 39, 53, 54, 69, 73, 74, 79, 108, 110, and 111.
[b] These relationships were surmised based on physical size and hydrophobicity of these drugs.

Peerebom, 2005

BLOOD-BRAIN BARRIER

The blood-brain barrier within brain metastases is at least partially disrupted (as demonstrated by enhancement on CT/MRI) → many chemotherapeutic agents, although unable to penetrate an intact barrier, may achieve therapeutic levels in the center of the tumor.

The periphery is virtually impermeable → tissue adjacent to the tumor receives subtherapeutic concentrations of drugs

Micrometastases hide behind an intact blood-brain barrier → the brain can be a pharmacological sanctuary→ high CNS relapse rates in patients treated with otherwise effective systemic chemotherapy (i.e trastuzumab in HER2+ breast cancer patients)

PITFALLS REGARDING CHEMOTHERAPY IN BRAIN METASTASES

- Few randomized trials have been performed
- Survival is often limited by death from systemic disease, which can occur in patients free of neurological progression
- Many patients progress through multiple chemotherapies, thus finding an effective and well tolerated regimen is a major challenge
- Many studies include heterogeneous tumor types

Conventional single agents or combination regimens with activity in brain metastases from NSCLC

- cisplatin; carboplatin
- etoposide; teniposide
- cisplatin and etoposide
- carboplatin and etoposide
- cisplatin and paclitaxel with either vinorelbine or gemcitabine
- carboplatin, vinorelbine and gemcitabine
- topotecan

Kleisbauer et al, 1988-1990; Malacarne et al, 1996; Boogerd et al, 1999; Franciosi et al, 1999; Bernardo et al, 2002; Cortes et al, 2003; Guerrieri et al, 2004; Wong and Berkenblit, 2004; Lorusso et al, 2006

Conventional single agents or combination regimens with activity in brain metastases from breast cancer

- cyclophosphamide, fluorouracil, prednisone
- cyclophosphamide, fluorouracil, prednisone, methotrexate and vincristine
- cyclophosphamide, methotrexate and fluorouracil
- cyclophosphamide, doxorubicin and fluorouracil
- cisplatin and etoposide
- high-dose methotrexate
- megestrol acetate; tamoxifen

Rosner et al, 1986; Pors et al, 1991; Salvati et al, 1991; Boogerd et al, 1999; Franciosi et al, 1999; Lassman et al, 2006;

Fotemustine in brain metastases from melanoma

- Response rates of 12%-25% as single agent (*Jacquillat et al, 1990; Kleeberg et al, 1995*)
- Longer neurological progression-free survival when combined with radiotherapy (*Mornex et al, 2003*)

LESSONS FROM CLINICAL STUDIES

- Response rates of brain metastases reflect the sensitivity of the primary tumor: relatively high response rates in SCLC (30-80%), intermediate rates in breast cancer (30-50%) and NSCLC (10-30%) and low rates in melanoma (10-15%)
- Higher response rates are observed in newly-diagnosed chemotherapy-naive patients
- Response in the brain does not always parallel that in the extracranial sites
- It is still uncertain if the response to chemotherapy of brain metastases from mostly chemosensitive tumors is of the same order of that observed after radiotherapy

Van den Bent, 2003
Soffietti et al, 2005
Seute et al, 2006

ASSOCIATION OF CHEMOTHERAPY AND RADIOTHERAPY

Few randomized studies have compared chemotherapy plus WBRT with chemotherapy or WBRT alone (in patients with metastases from SCLC, NSCLC and melanoma)

As a general conclusion: even in case of higher response rate and/or longer progression-free survival after combined treatment → overall survival not different

Postmus et al 2000; Robinet et al, 2001; Delaunay et al, 2003; Guerrieri et al, 2004; Kocher et al 2005

TEMOZOLOMIDE AS SINGLE AGENT IN BRAIN METASTASES

Salvage treatment

Christodolou et al, 2001	4 % PR	1 PR in a NSCLC
Abrey et al, 2001	6 % PR	All PR_s in NSCLC
Friedman et al, 2003	6 % PR	2 PR_s in NSCLC, 1 PR in melanoma
Giorgio et al, 2005	10% PR	NSCLC

TEMOZOLOMIDE AS SINGLE AGENT IN BRAIN METASTASES

First line treatment

Dziadziuszko et al, 2003	0% CR + PR	NSCLC
Siena et al, 2003	24 % PR + SD	melanoma 40%; NSCLC 24%; breast 19%
Agarwala et al, 2004	7 % CR + PR	melanoma

COMBINATION OF TEMOZOLOMIDE WITH OTHER CHEMOTHERAPEUTICS

TMZ + CDDP (**Christodolou et al, 2005**)	31% CR+PR	Responses in NSCLC, breast, melanoma
TMZ + CDDP (**Cortot et al, 2006**)	16% CR+PR	NSCLC
TMZ + THALIDOMIDE (**Hwu et al, 2005**)	12% CR+PR	Melanoma
TMZ + PLD (**Carrglia et al, 2006**)	37% CR+PR	Responses in breast and colon
*TMZ + VINORELBINE (**Omuro et al, 2006**)	NA	Responses in NSCLC and melanoma

**** Phase I study***

TEMOZOLOMIDE PLUS WBRT

Author	CR + PR	Outcome
Antonadou et al[1], 2002	96% TMZ+WBRT 67% WBRT	No difference in OS
Verger et al[2], 2005	32% TMZ+WBRT 32% WBRT	PFS 90 days 72% PFS 90 days 54% No difference in OS
Dardoufas et al, 2001	55%	CR+PR 86% in lung cancer
Martines-Cedillo et al[3], 2003	44%	-------

[1)] 84% lung cancer; [2)] 49% lung cancer; [3)] 100 % breast cancer

GEFITINIB (ZD1839, IRESSA) IN BRAIN METASTASES FROM NSCLC: BACKGROUND

- An oral tyrosine kinase inhibitor of EGFR
- Respose rates of 11-18% in pretreated patients with NSCLC (IDEAL1 and IDEAL2 trials)
- Therapeutic activity against brain tumors in mice
- Low molecular weight and excellent cell penetration, but lack of pharmacokinetic and clinical data on the ability to cross the intact BBB in humans

Helmberger et al, 2002; Fukuota et al, 2003; Kris et al, 2003

GEFITINIB IN BRAIN METASTASES FROM NSCLC: CLINICAL RESULTS

- Response rates (CR+PR) of 10-33% (prospective studies) and 40-60% (retrospective studies) with a median duration of response ranging from 8 to 13.5 months
- Rapid tumor regression on CT/MRI (more frequently after 1 month of treatment) and improvement of neurological symptoms
- Responses both in previously irradiated and non-irradiated patients
- Responses both in brain and extracranial metastases
- Sensitivity to gefitinib influenced by WBRT? Age, histology, sex, skin toxicity predict response?

Ceresoli et al, 2004 (prospective study); Chiu et al, 2005 (prospective study); Stemmler at al 2005; Nishi et al, 2006; Matsuyama et al, 2006

Table 2. Treatment with gefitinib, evaluation of the efficacy of gefitinib, and *EGFR* gene status[a]

Patient	Interval[b] (months)	Objective Tumor Response/ Months	Efficacy of Gefitinib	Duration of Gefitinib Treatment (months)	Extracranial Lesions/ Treatment	Efficacy for Extracranial Lesions	Steroid Therapy/ Weeks	Survival[c] (months)	*EGFR* Gene Status
1	0	No	Noneffective	9	Lung LN/RTX, CTX	Noneffective	Yes/10	>13*	Wild type
2	2	Yes/16	**Effective**	11	Pleural dissem./ CTX	Not assessable	No	19	**del E746–A750**
3	12	Yes/18	**Effective**	18	Bone/RTX	Not assessable	No	>18**	**del E746–A750**
4	12	Yes/12	**Effective**	12	Bone/RTX	Not assessable	No	>14*	**pm L858R**
5	3	No	Noneffective	2	—	—	Yes/10	2	Wild type
6	7	No	Noneffective	2	Bone/RTX	Noneffective	No	8	Wild type
7	5	Yes/10	Not assessable	10	Lung/CTX	Not assessable	Yes/16	>9*	**pm G719C**
8	4	Yes/4	Not assessable	4	Liver, bone/ CTX	Effective	Yes/8	4	**pm L858R**

Abbreviations: CTX, chemotherapy; del, deletion; LN, lymph node; pm, point mutation; RTX, radiotherapy.

[a]Boldface indicates a possible relationship between efficacy of gefitinib and *EGFR* gene status.

[b]Interval indicates the interval between the completion of last radiotherapy and the initiation of gefitinib.

[c]Survival was calculated from the day of initiating gefitinib treatment. A number with an asterisk means that the patient was still alive at the time of this study, and the number with double asterisks means that the case was not followed up in the course of this study.

Shimato et al, Neuro-Oncology 8,137-144, 2006

Erlotinib in brain metastases from NSCLC: case reports

- 5 responders (1 CR, 4 PR) reported so far
- In all patients rapid responses (within 2-4 weeks) along with neurological improvement
- In 1 patient a point mutation in the EGFR gene

Abigerges et al, 2006
Lai et al, 2006
Popat et al, 2007

Association of chemotherapy and radiotherapy: ongoing clinical trials in patients with brain metastases from NSCLC

- Eligibility criteria:

  similar (brain metastases not eligible for surgical resection or radiosurgery and no prior WBRT or radiosurgery; systemic disease stable or not requiring immediate therapy; PS 0-1)

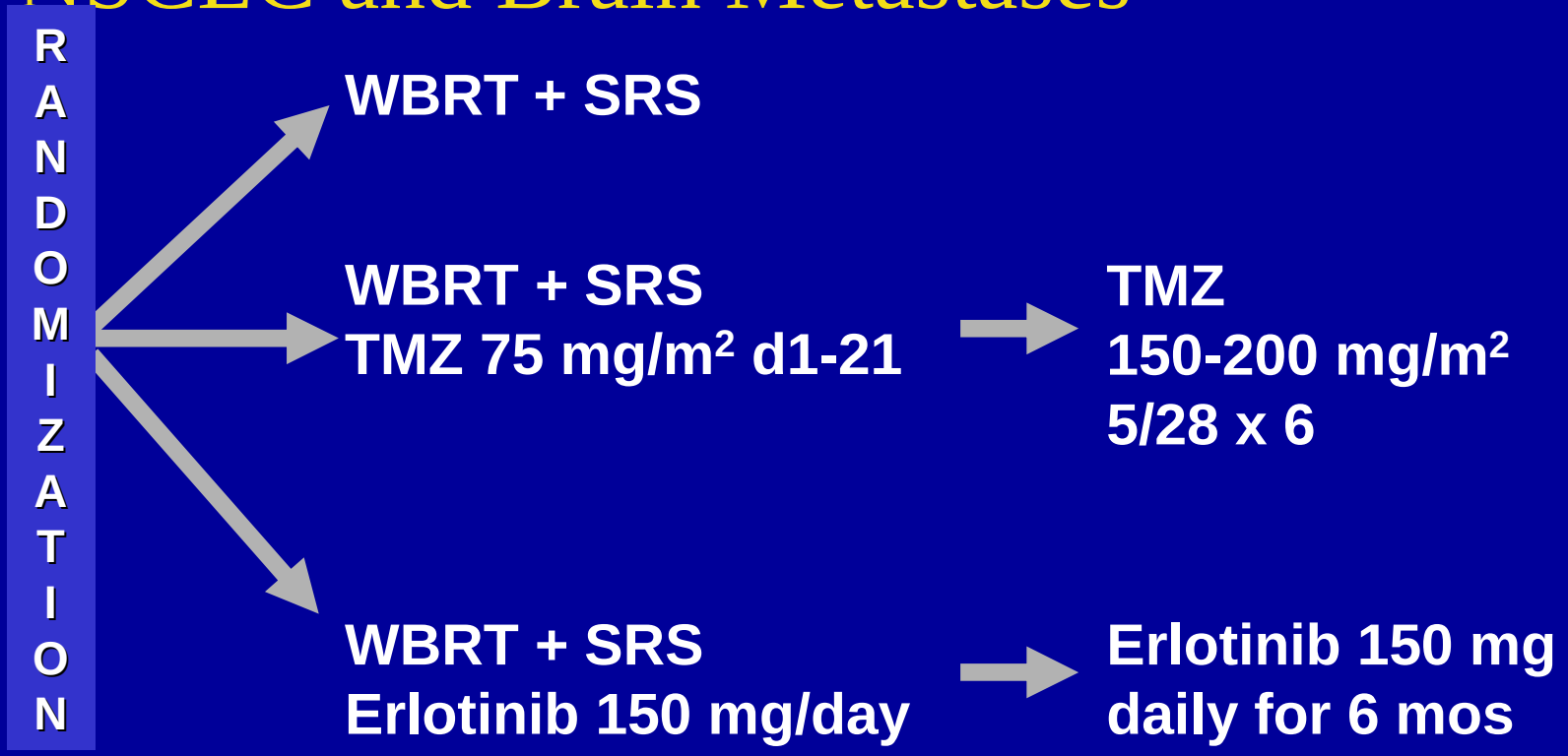
- Primary end-point:

  depending on the type of study (overall survival; CNS response rate)

RTOG 0320: Phase III Randomized Study of WBRT and SRS +/- TMZ or Erlotinib in Patients With NSCLC and Brain Metastases

Stratification Factors:

- **RPA Class**
- **# met**
- **Extracranial disease**



WBRT 2.5 Gy x 15 fractions

Target n = 381

Treatment until PD

www.clinicaltrials.gov

SAKK 70/03: Randomized Phase II trial of WBRT + gefitinib or TMZ for brain metastases from NSCLC

Stratification Factors:

- **Systemic disease**
- **# brain mets**
- **Prior chemo**
- **PS**
- **Institution**

RANDOMIZATION

WBRT
TMZ 75 mg/m²
day 1-21

→ **TMZ**
75 mg/m²
21/28 x 6

WBRT
Gefitinib 250 mg
daily

→ **Gefitinib 250 mg**
daily for 6 mos

Treatment until PD

WBRT 3 Gy x 10 fractions day 1-14

Target n=86

www.clinicaltrials.gov

SP 03247: Randomized trial of TMZ and WBRT vs. WBRT Alone in Brain Metastasis from NSCLC

Stratification Factors:

- **Extracranial mets**
- **Controlled systemic disease**

n = 95

RANDOMIZATION

WBRT
TMZ 75 mg/m² day 1-28
→ **Additional tx beginning day 35***

WBRT
→ **Additional tx beginning day 21***

WBRT 3 Gy x 10 fractions day 1-14

***At investigator's discretion**

www.clinicaltrials.gov

ECOG E1F03: Phase II Study of Temozolomide and WBRT in Patients With Brain Metastasis Secondary to NSCLC

Treatment

- Course 1: TMZ + WBRT

WBRT 3Gy x 10
TMZ 75 mg/m^2/day x 14

- Course 2-6:
  - TMZ 150 mg/m^2 x 5 days q 28 days
  - concurrent chemotherapy for systemic disease allowed

Target Accrual: 53

www.clinicaltrials.gov

New drugs for brain metastases from NSCLC

- gimatecan (a novel oral camptothecin)
- premetrexed disodium (antifolate compound)
- patupilone (microtubule stabilizer)

Targeted molecular drugs for brain metastases from NSCLC: future directions

- bevacizumab (anti-VEGF monoclonal antibody)
- bevacizumab in combination with pemetrexed
- bevacizumab in combination with erlotinib
- VEGF Trap (fusion molecule of VEGFR extracellular domain and Fc portion of Ig G1)
- multitarget TK inhibitors: ZD6474 (VEGFR and EGFR inhibitor); sorafenib (VEGFR, Raf Kinase and PDGFR inhibitor); sunitinib malate (VEGFR, PDGFR and c-Kit inhibitor)

Capecitabine for brain metastases from breast cancer

- An oral prodrug for 5-fluorouracil with activity against anthracycline- and taxane-pretreated metastatic breast cancer
- Case reports with durable responses in both brain metastases and neoplastic meningitis from breast cancer (*Wang et al, 2001; Giglio et al, 2003; Rogers et al, 2004; Fabi et al, 2006; Hikino et al, 2006; Tham et al, 2006; unpublished Turin data, 2007*)
- Limited ability to cross an intact BBB
- Risk of central neurotoxicity?

Phase I study of TMZ + Capecitabine in pts with Multiple Brain Metastases from Breast Ca

- n=24:
  - 14 newly dx brain mets, 10 recurrent after WBRT
  - 17 had at least 2 prior chemo regimens
- Dose level reached:
  - Capecitabine 2000mg/m2/day + TMZ 150mg/m2/d, d1-5, 8-12 every 21 days
  - no DLT observed
- ORR: 18% (1 CR, 3 PR) Disease control: 68%
- Median Response Duration: 8 wk
- TTP (brain): 12 wk

Rivera E, et al. *Cancer* 2006, 106(6):1348.

Phase II trial of lapatinib for brain metastases in patients with HER2+ breast cancer

- lapatinib (GW-572016): an oral TK inhibitor of EGFR and HER 2
- 39 pts with new or progressive brain metastases while receiving trastuzumab
- 2 PR (lasting 158 and 347 days) and 5 SD $\geq$ 16 wks (according to Recist)
- Volumetric analysis in 20 pts: a 15-30% decrease in volume in 40% of pts
- Mild toxicity

Lin N et al, J.C.O. 2006, 24/18s; 503

BRAIN METASTASES FROM BREAST CANCER: ONGOING TRIALS AND FUTURE DIRECTIONS

- Phase II trials on lapatinib in HER2+ patients (alone, in association to radiotherapy, in association to capecitabine)
- Pan-erb B receptor inhibitors (CI-1033)
- VEGFR inhibitors (PTK 787)
- Bevacizumab (Mab against VEGF) + cytotoxic agents
- Aromatose inhibitors (letrozole)

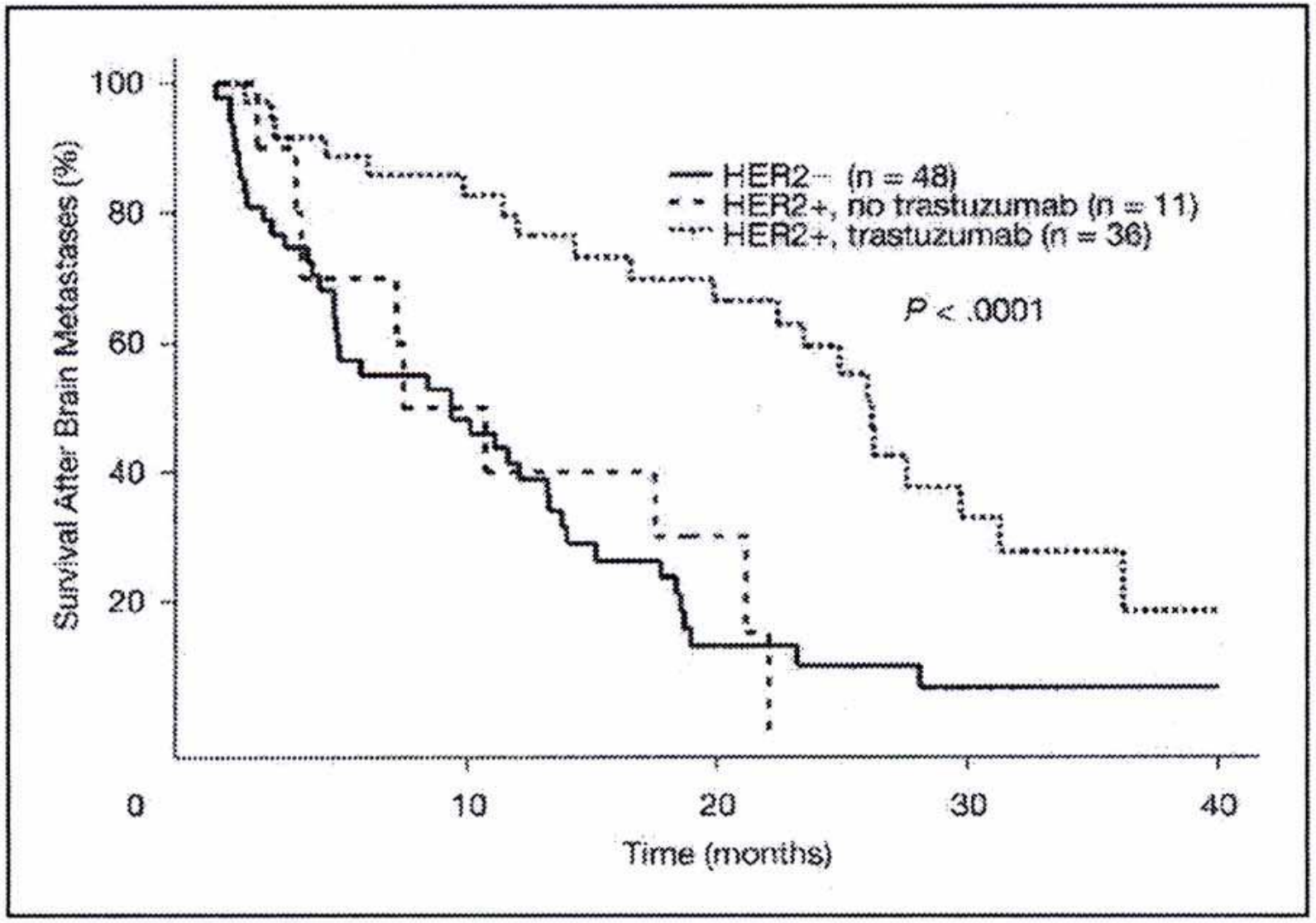


Fig 1. Overall survival from diagnosis of brain metastases by HER2 status and treatment with trastuzumab.

Kirsch et al, JCO, April 2005

Brain and leptomeningeal metastases

- Brain metastases can be associated with leptomeningeal metastases (neoplastic meningitis) (14-32%), being autoptic rates higher than the clinical ones
- Brain metastases can preceed, coexist with or even follow neoplastic meningitis

Phase II trial of depocyte plus capecitabine for the treatment of CNS leptomeningeal and parenchymal metastases in breast cancer patients

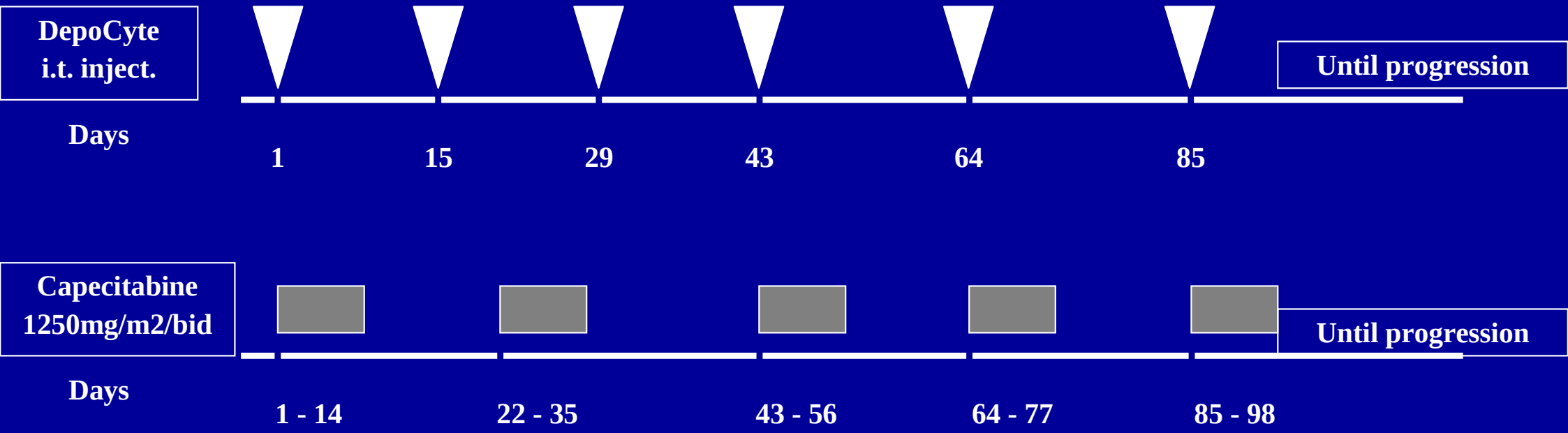
Induction Phase:

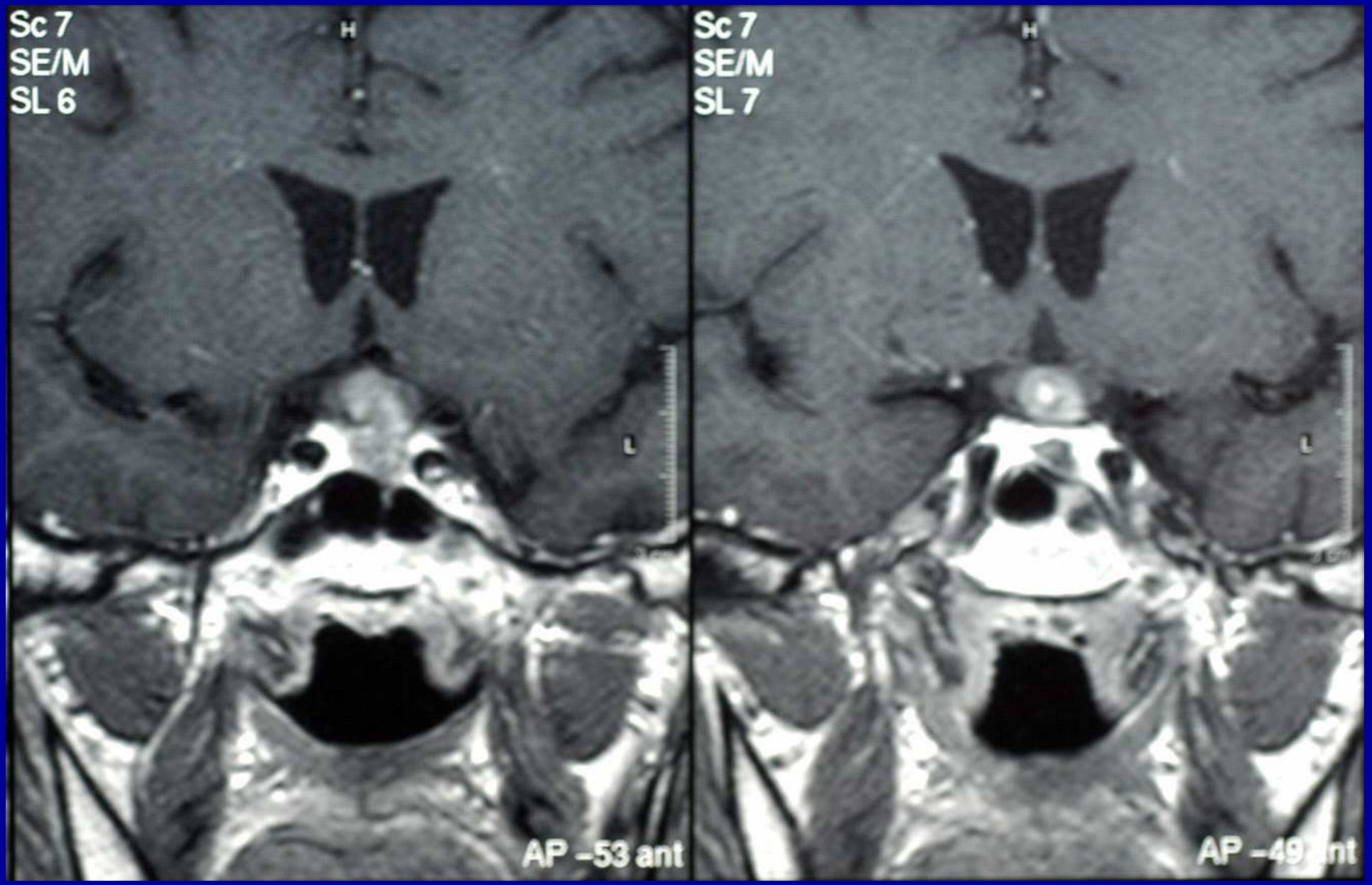
Capecitabine + DepoCyte 4 x q2w

Maintenance:

Capecitabine + DepoCyte q3w

Until progression or death




Sc 7
SE/M
SL 6
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L
AP -53 ant
Sc 7
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SL 7
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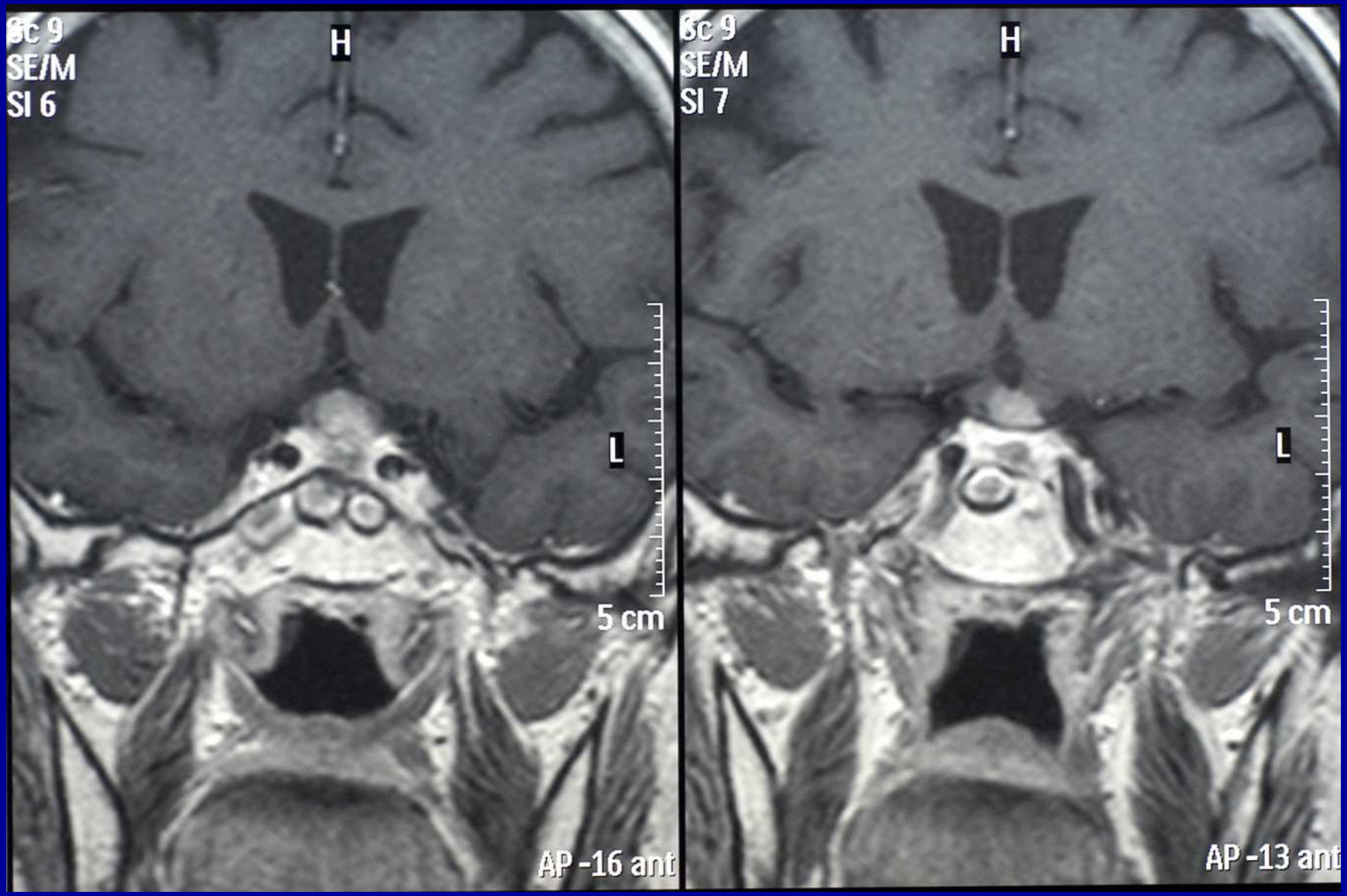
AP -49 ant


Sc 9
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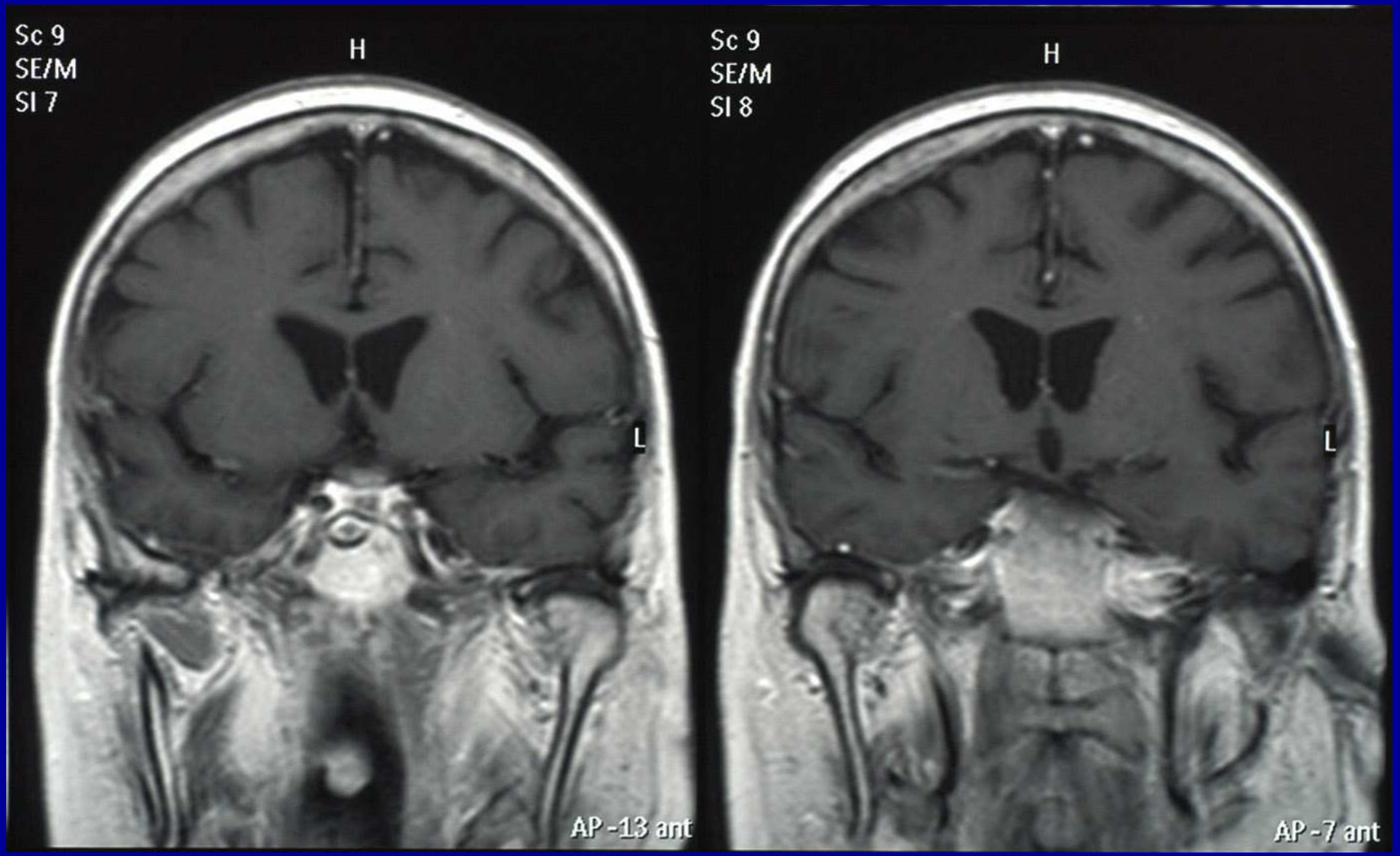
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Leptomeningeal relapse after treatment of brain metastases

- At the time of diagnosis of both clinically evident and occult brain metastases, a microscopic seeding in the leptomeninges and/or CSF can coexist
- The frequency of meningeal relapse after surgery and/or radiosurgery and/or WBRT of brain metastases in the literature is highly variable (from 5% to 66%), being the highest rates reported after surgery for posterior fossa lesions (33%-66%)

TECHNIQUES TO CIRCUMVENT THE BLOOD-BRAIN-BARRIER

- Intraarterial chemotherapy
- Disruption of the BBB combined with chemoterapeutics, biological agents or radiotherapy
- Use of convection-enhanced delivery (CED)
- Direct drug delivery with drug-impregnated polymer wafers
- Carrier-mediated transport
- Nanoparticle technology

Newton, 2006; Doolittle et al, 2006

TABLE 6.6. Patients with recurrent or new brain metastases treated with surgery and carmustine wafer implants with or without whole-brain radiotherapy[a]

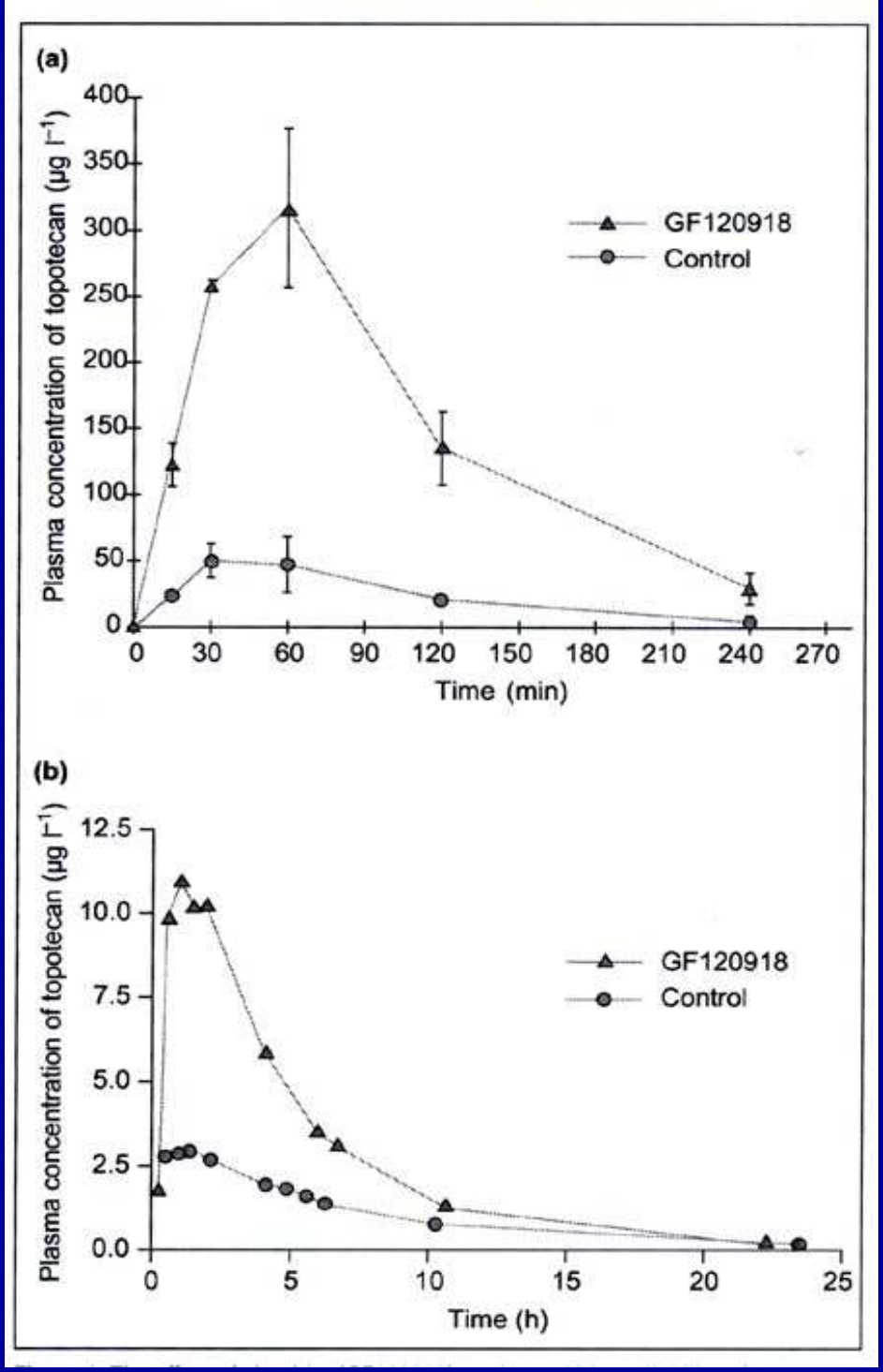
	Ewend et al. (40)[b]	Golden et al. (51)	Brem et al. (20)[b]
No. of patients	25	36[c]	42[d]
Local recurrence (n)	0	0	0
Distant recurrence (n)	4	7	3
Median/mean survival (mo)	14.2[f]	NR	16.8
Cause of death (n)			
Neurological disease	NR	NR	23
Systemic disease	NR	NR	3

[a] NR, not reported.
[b] Ten patients were enrolled in both studies.
[c] Follow-up data were available for 27 patients.
[d] Follow-up data were available for 41 patients.
[e] Patients with newly diagnosed metastases (n = 34).
[f] Patients with more than 1 year of follow-up (n = 16).

Peerebom, 2005

MODULATION OF CHEMORESISTANCE

- Continous TMZ schedules to deplete MGMT → problem: large variability in the distribution of MGMT among different primary tumors and brain metastases, thus more data are needed
- PARP-1 and PARG inhibitors + TMZ (*Tentori et al, 2005; Plummer et al, 2006*)
- P-glycoprotein and BCRP inhibitors (*Breedveld et al, 2006*)



Breedveld et al, TRENDS in Pharmacological Sciences 27/1, 17-24, 2006

EGFR sequence variations and real-time quantitative polymerase chain reaction analysis of gene dosage in brain metastases of solid tumors

Franco-Hernandez C, Martinez-Glez V, Arjona D. et al.

Cancer Genetics and Cytogenetics 173:63-67; 2007.

ADVANCES IN MANAGEMENT OF BRAIN METASTASIS

Identification of patients at higher risk of developing brain metastases

by means of :

Epidemiological studies

Gene expression profiling

Careful radiological monitoring

Radiotheraphy / Chemotherapy as prophylaxis

Back to guidelines: the role of chemotherapy

Chemotherapy may be the initial treatment for patients with brain metastases from chemosensitive tumors, like small cell lung cancers, lymphomas, germ cell tumors and breast cancers, especially for chemo-naive patients or if an effective chemotherapy schedule for the primary is still available (Good Pratice Point). Radiation therapy, with or without chemotherapy, is still the treatment of choice for patients needing a palliation of neurological symptoms (Good Pratice Point).

EFNS Guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force – *European Journal of Neurology, 2006, 13: 674-681*

R. Soffietti, P. Cornu, J.Y. Delattre, R. Grant, F. Graus, W. Grisold, J. Heimans, J. Hildebrand, P. Hoskin, M. Kalljo, P. Krauseneck, C. Marosi, T. Siegal and C. Vecht

ANTIEPILEPTIC DRUGS AND CHEMOTHERAPY

- Phenobarbital, phenytoin and carbamazepine are metabolized by the cytocrome P450, and thus may accelerate the clearance of chemotherapeutics that are metabolized by same system (paclitaxel, CPT-11, vinorelbine, cyclophosfamide, ifosfamide, doxorubicin, etoposide, teniposide, vinca alkaloids) and reduce their efficacy
- Molecular agents such as TK inhibitors (gefitinib, erlotinib, imatinib) are metabolized through the P450 → interactions
- Non-inducing antiepileptic drugs (valproate, gabapentin, topiramate, levetiracetam, lamotrigine) must be choosen

COGNITIVE DYSFUNCTIONS AFTER RADIOTHERAPY: NEW APPROACHES

- Treatment of cognitive dysfunctions after radiotherapy with neuroactive compounds (donepezil, memantine) (*Shaw et al, 2006; Closed trial in Torino*)

- New form of brachytherapy after surgical resection (Gliasite System) (*Rogers et, al 2006*)