Management of Leptomeningeal Metastases: When and How to Treat?

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Neuro-Oncology and Radiation Oncology Departments
• Conflict of interest disclosure

  – **Mundipharma:**
    Honoraria-consultancy-travel grants

  – **Roche**
    Honoraria-consultancy-travel grants
TREATMENT GOALS

• Improve or stabilize the neurological status
• maintain neurological quality of life and prevent neurologic death
• prolong survival

• EARLY TT based on an EARLY diagnosis of LM
• BEFORE appearance of fixed and disabling neurological deficits
• BEFORE appearance of bulky disease

• Should target the entire neuraxis and systemic disease
• Bulky disease and malignant cells floating in CSF
Which Patients?

Decision based on PROGNOSIS
Prognosis in LM

- **Histological type +++**
  - BC > NSCLC > Melanoma
- gender (tumor type)

- **Performance Status (PS) at LM diagnosis**
- age at LM diagnosis
- **time from diagnosis of primary tumor to diagnosis of LM**
- **Bulky CNS disease- encephalopathy- CSF flow blockade**
- **Status of systemic disease**
- **initial CSF protein level**

- **treatment modality (administration of systemic therapy- addition of local therapy)**
- **Short-term therapeutic response to LM treatment (MA)**

Prognostic factors
LM from Breast Cancer

- **Histological characteristics**
  - histological grade and hormone receptor status,
  - Non triple-negative status in primary

- **CSF**:
  - CSF cyfra 21-1 level

- **Between PS and treatment modalities**
  - number of prior chemotherapy regimens,
  - coadministration of systemic chemotherapy, intra-CSF chemotherapy
  - initial response to treatment of LM
  - cytologic response to treatment of LM

Prognostic factors
LM from NSCLC

• CSF:
  - high initial WBC count (poor)

• treatment modality
  - systemic therapy ++
  - EGFR-TKI in pts with sensitive EGFR mutations
  - Intra-CSF chemotherapy
  - VP shunt operation
  - impact of whole brain radiotherapy is unclear

• clinical improvement after intra-CSF chemotherapy

Prognostic factors
LM from Melanoma

- Primary lesion on the trunk: shorter OS

- Treatment related:
  - intra-CSF chemotherapy: longer OS

**Median OS**

**All types:** 1mo- 5.8mo  
**Breast:** 7wks-8mo  
**Melanoma:** 10wks-4mo  
**NSCLC:** 5wks-14mo

<table>
<thead>
<tr>
<th>Type of the primitive tumor</th>
<th>References</th>
<th>Recruitment of the patients</th>
<th>Median overall survival (Min-Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All types</td>
<td>Wassermström et al., 1982</td>
<td>50 patients from 1975 to 1980</td>
<td>5.8 months (1-29)</td>
</tr>
<tr>
<td></td>
<td>Hitchins et al., 1987</td>
<td>44 patients</td>
<td>8 weeks</td>
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<td>Liaw et al., 1992</td>
<td>41 patients from 1984 to 1990</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td>Grossman et al., 1993</td>
<td>52 patients</td>
<td>14.1-15.9 weeks</td>
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<td></td>
<td>Chamberlain et al., 2002</td>
<td>22 patients from 1995-2001</td>
<td>16 weeks</td>
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<td></td>
<td>Grant et al., 1999</td>
<td>61 patients from 1994 to 1996</td>
<td>76-105 days</td>
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<td></td>
<td>Kim et al., 2003</td>
<td>55 patients from 1995 to 2002</td>
<td>11.5 weeks (2.7-28.7)</td>
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<td></td>
<td>Hertlinger et al., 2004</td>
<td>155 patients from 1980 to 2002</td>
<td>4.8 months</td>
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<tr>
<td></td>
<td>Lessman et al., 2006</td>
<td>32 patients from 1999 to 2003</td>
<td>19.5 weeks (2.9-135.4)</td>
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<td></td>
<td>Groves et al., 2008</td>
<td>62 patients from 2001 to 2006</td>
<td>15 weeks (95% CI 13-24w)</td>
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<td></td>
<td>Waki et al., 2009</td>
<td>85 patients from 1995 to 2005</td>
<td>51 days (3-759 days)</td>
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<tr>
<td></td>
<td>Clarke et al., 2010</td>
<td>187 patients from 2002 to 2004</td>
<td>2.4 months (95% IC 1.9-3.1)</td>
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<tr>
<td></td>
<td>Oeschke et al., 2010</td>
<td>135 patients from 1989 to 2005</td>
<td>2.5 months</td>
</tr>
<tr>
<td></td>
<td>Jimenez-Mateos et al., 2011</td>
<td>37 patients from 1990 to 2008</td>
<td>12.6 weeks</td>
</tr>
<tr>
<td></td>
<td>Gani et al., 2012</td>
<td>27 patients</td>
<td>8.1 weeks</td>
</tr>
<tr>
<td></td>
<td>Segura et al., 2012</td>
<td>19 patients</td>
<td>43 days (95% IC 28-57.3)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Boogerd et al., 2004</td>
<td>35 patients from 1991 to 1998</td>
<td>18.3-30.3 weeks</td>
</tr>
<tr>
<td></td>
<td>Grossman 1982</td>
<td>52 patients</td>
<td>14.1-15.8 weeks</td>
</tr>
<tr>
<td></td>
<td>Clamon et al., 1987</td>
<td>22 patients</td>
<td>21-150 days</td>
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<tr>
<td></td>
<td>Boogerd 1991</td>
<td>58 patients</td>
<td>12 weeks</td>
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<tr>
<td></td>
<td>Jayson 1994</td>
<td>35 patients</td>
<td>77 days</td>
</tr>
<tr>
<td></td>
<td>Chamberlain 1997</td>
<td>32 patients</td>
<td>7.5 months (1.5-16)</td>
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<td></td>
<td>Jaekle 2001</td>
<td>43 patients from 1994 to 1999</td>
<td>7 weeks</td>
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<td></td>
<td>Regier 2008</td>
<td>27 patients from 1998 to 2005</td>
<td>9 weeks</td>
</tr>
<tr>
<td></td>
<td>Rudnicka et al., 2007</td>
<td>67 patients from 2000 to 2005</td>
<td>16 weeks (1-402)</td>
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<td></td>
<td>De Armas et al., 2011</td>
<td>60 patients from 2003 to 2009</td>
<td>3.3 months (0.03-90.4)</td>
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<td></td>
<td>Clotot 2009</td>
<td>24 patients</td>
<td>150 days (9-561)</td>
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<td></td>
<td>Gauthier et al., 2010</td>
<td>91 patients from 2000 to 2007</td>
<td>4.5 months (0.5-3)</td>
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<tr>
<td></td>
<td>Lee et al., 2011</td>
<td>68 patients from 1995 to 2008</td>
<td>4.1 months (2.2-5.8 months)</td>
</tr>
<tr>
<td></td>
<td>Kim et al., 2012</td>
<td>30 patients from 1991 to 2009</td>
<td>8 months</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Chamberlain et al., 1996</td>
<td>16 patients from 1986-1995</td>
<td>4 months</td>
</tr>
<tr>
<td></td>
<td>Harstad 2008</td>
<td>110 patients from 1944 to 2002</td>
<td>10 weeks (95% IC, 8-14)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Rosen et al., 1982</td>
<td>60 patients from 1969 to 1980</td>
<td>7 weeks</td>
</tr>
<tr>
<td></td>
<td>Chamberlain et al., 1998</td>
<td>32 patients</td>
<td>5 months (1-12)</td>
</tr>
<tr>
<td></td>
<td>Hammerer et al., 2005</td>
<td>26 patients</td>
<td>57 weeks (NA)</td>
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<tr>
<td></td>
<td>Sud et al., 2006</td>
<td>37 patients from 2001 to 2005</td>
<td>106 days (10-392)</td>
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<tr>
<td></td>
<td>Chuang et al., 2008</td>
<td>34 patients from 1992 to 2002</td>
<td>5.1 weeks (1 day-82 weeks)</td>
</tr>
<tr>
<td></td>
<td>Morris 2012</td>
<td>50 patients from 2003 to 2009</td>
<td>3 months (95% CI, 2.0-4.0)</td>
</tr>
<tr>
<td></td>
<td>Park 2012</td>
<td>125 patients from 2002 to 2009</td>
<td>4.3 months (1.5-6.7)</td>
</tr>
</tbody>
</table>

*From Le Rhun et al, 2013, SNI*
Which Patients?

• Decision based on prognosis
• Remains challenging

• *NCCN CNS guidelines (version 1.2012)*
  between
  – patients reasonably considered for treatment
  vs.
  – those patients in whom supportive care is most appropriate
### Risk categories in patients with LM

<table>
<thead>
<tr>
<th>Poor risk group</th>
<th>Good risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low KPS (&lt;60%)</td>
<td>High KPS (≥60%)</td>
</tr>
<tr>
<td>Multiple, serious, or major neurological deficits</td>
<td>No major neurological deficits</td>
</tr>
<tr>
<td>Extensive systemic disease with few treatment options</td>
<td>Minimal systemic disease</td>
</tr>
<tr>
<td>Bulky CNS disease</td>
<td>Reasonable systemic treatment options</td>
</tr>
<tr>
<td>LM-related encephalopathy</td>
<td>No CSF block</td>
</tr>
</tbody>
</table>

KPS: Karnofsky performance status, CNS: Central nervous system

*Le Rhun et al, SNI, 2013*

*adapted from CNS National Comprehensive Cancer Network Guidelines*
Therapeutic Strategy

• Combined treatment approach
  ▪ systemic CT or targeted TT adapted to primary
  ▪ intra-CSF chemotherapy
  ▪ site specific radiotherapy
  ▪ Surgery

+ Symptomatic / palliative approach
  • in poor prognosis patients
  • in every symptomatic patient with quality of life interfering fixed neurologic deficits independent of main TT
Surgery

- ventriculo-peritoneal shunting (VPS) : symptomatic hydrocephalus

- ventricular (rarely lumbar) access device
  with post-implantation CT check of intraventricular placement before use for TT

- When both a VPS and ventricular access device are needed : on-off valve

  DeAngelis 1998, Lin 2011
Radiation Therapy
Involved-field
Site Specific Radiation Therapy

• **Indications**
  • focal symptomatic lesions
  • bulky disease on MR
  • CSF blockade sites
  • Cauda equina compression: LS RT *regardless of MRI findings*
  • Cranial nerves palsy: skull-base RT *regardless of MRI findings*
  • Encephalopathy: WBRT 30 Gy/10
  • Hydrocephalus: WBRT 30 Gy/10

• **Impact**
  • effective relief of pain
  • mostly stabilizes neurological symptoms

• **on OS not clearly established**
  even in radiosensitive cancers
  contradictory results
  reflecting the limited survival of patients with LM (<15% survive 1 year)
  heterogeneity of pts /prognosis factors in retrospective cohorts

*Morris 2012, Park 2012*
Radiation Therapy
Techniques

• **Involved-field Site Specific**

• **Craniospinal axis irradiation (CSI):**
  - entire neuraxis
  - too toxic in adults with solid tumor-related LM
  - previously irradiated
  - poor bone marrow reserve

  – alternative methods of CSI To be assessed in the future:
    • tomotherapy and proton radiotherapy
    • improved precision in radiation dosing and targeted volumes
    • less hematological toxicity

• **intra-CSF administration of radioisotopes or radiolabeled monoclonal antibodies**
  - experimental

Systemic TT

• **Only one-third** of patients with LM **will die from LM**
• systemic therapy against systemic disease is most often required
• Choice based

upon the ability of drug to achieve effective concentrations in the CSF
HD- MTX and CYTARABINE , TMZ (BC and NSCLC LM)

AND

upon the histological type of the primary
Intra-CSF treatment

Intralumbar / IT
Intraventricular / IVe
Intra-CSF chemotherapy

- MAINSTAY of treatment for LM
- although its superiority / systemic CT
- never been proven in randomized trials

- Nevertheless
- Recent retrospective data in NSCLC
- Suggest a positive impact on survival of IT chemotherapy
- In cytological responders
  - Median survival 5.5 vs 1.4 mo in non responders (p=0.075) Park 2011
• ITS GOAL is to bypass the blood-CSF barrier only partially disrupted in LM
• To maximize drug exposure in the CSF
• To achieve higher intra-CSF C while using smaller dose
• Thus reducing systemic toxicity

• HOWEVER, ITS LIMITED INTRATUMORAL DIFFUSION (2-5 mm)
• Unable to treat bulky disease
Practice guidelines for IT chemotherapy before treatment

• Should be avoided if any obstruction
  • Increased local toxicity
  • Decreased efficacy

• Radiation therapy to areas of obstruction
  – Even if blocks not seen on MRI
  – Can reverse flow abnormality

• CSF flow assessment is critical
  – Abnormal in 2/3 of patients
  – Often with normal CNS MRI
  – BUT variable availability / centers
  – At least in clinical trials (RANO/LANO rec)

• Re check CSF flow after RT, before IT treatment


• Radionuclide CSF flow study: 111-indium DTPA
Randomized clinical trials for intra-CSF CT in LM

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Response</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hitchon 1997 (14)</td>
<td>N=44</td>
<td>IT MTX vs. IT MTX + Ara-C: RR*: 61% vs. 45% Median survival: 12 vs. 7 wk</td>
<td>IT MTX vs. IT MTX + Ara-C: NV: 38% vs. 50% Septicemia: neutropenia: 5% vs. 15% Mucoptysis: 14% vs. 10% Panocytophenia: 9% vs. 10%. AEs related to reservoir: Bocled drainage: 17% Intracranial hemorrhage: 11%</td>
</tr>
<tr>
<td>Grossman 1993 (15)</td>
<td>N=59</td>
<td>IT MTX vs. IT Eloxate: Neurological improvements: none Median survival: 16.0 vs. 14.1 wk</td>
<td>IT MTX vs. Eloxate: Serious toxicity (47%) similar between groups Mucoptysis and neurological complications more common in IT MTX group</td>
</tr>
<tr>
<td>Glanz 1999 (30)</td>
<td>N=28</td>
<td>Iveno DacOx vs. Iveno Ara-C: TTP*: 77.5 vs. 42 d OS*: 99.5 vs. 63 d RR*: 71% vs. 15%</td>
<td>Iveno DacOx vs. Iveno Ara-C: Headache: 27% vs. 2% Nausea: 9% vs. 2% Fever: 6% vs. 4% Pain: 5% vs. 4% Confusion: 7% vs. 6% Somnolence: 6% vs. 4%</td>
</tr>
<tr>
<td>Glanz 1999 (18)</td>
<td>N=28</td>
<td>Iveno DacOx vs. Iveno MTX: RR*: 29% vs. 29% OS*: 106 vs. 70 d TTP*: 53 vs. 30 d</td>
<td>Iveno DacOx vs. MTX: Sensory motor: 4% vs. 10% Altered mental status: 5% vs. 2% Headache: 4% vs. 2% Malaise: 10% vs. 3%</td>
</tr>
<tr>
<td>Beopend 2004 (22)</td>
<td>N=35</td>
<td>Systemic therapy and involving radiotherapy with IT MTX vs. no IT MTX: Improved stabilization: 59% vs. 67% TTP*: 23 vs. 24 wk</td>
<td>Systemic therapy and involving radiotherapy with IT MTX vs. no IT MTX: Treatment complications: 47% vs. 6%</td>
</tr>
<tr>
<td>Shapiro 2006 (21)</td>
<td>Solid tumors: N=103</td>
<td>Iveno DacOx vs. Iveno MTX+Ara-C: PFS*: 35 vs. 43 d</td>
<td>Iveno DacOx vs. Iveno MTX+Ara-C: Drug-related AEs: 49% vs. 60% Serious AEs: 68% vs. 77%</td>
</tr>
<tr>
<td></td>
<td>DeplaCyt, MTX</td>
<td>Iveno DacOx vs. Iveno MTX: PFS*: 35 vs. 37.5 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymohomas, N=24</td>
<td>Iveno DacOx vs. Iveno Ara-C: CR*: 33.3% vs. 16.7%</td>
<td></td>
</tr>
</tbody>
</table>
Leptomeningeal metastasis: a Response Assessment in Neuro-Oncology critical review of endpoints and response criteria of published randomized clinical trials.
Neuro Oncol. 2014 Sep;16(9):1176-85.

The RANO group in LM or LANO

Made a critical review of endpoints and response criteria

lack standardization with respect to response assessment
In LM clinical trials
Endpoints in randomized studies
heterogeneous across trials

Primary endpoints

- overall survival
- neurological response rate
- time to neurological progression
- progression free survival

Secondary endpoints

- Overall survival
- neurological response rate
- time to neurological progression
- LM-specific survival
- cause of death
- safety and toxicity profile
  - 4 studies, CTC
- KPS over time
- quality of life assessment
- evaluation of prognostic and predictive factors
Evaluation Criteria in Randomized Studies

Definition varied from one study to another:

- Time to progression
- Response criteria
  - Clinical assessment only
  - Based on significant neurological improvement not previously defined of at least one symptom/sign and stability of others
  - Based on cytology
  - Based on MRI without predefined MR criteria
  - Without detailed MR
<table>
<thead>
<tr>
<th>Drug</th>
<th>Description of drugs</th>
<th>CSF half life</th>
<th>Description of regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>folate anti-metabolite, cell cycle specific drug</td>
<td>4.5-8 hours</td>
<td><strong>Standard regimen</strong> 10-15 mg twice weekly (total, 4 wks), then 10-15 mg once weekly (total, 4 wks) then 10-15 mg once a month</td>
</tr>
<tr>
<td></td>
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<td></td>
<td><strong>High dose regimen</strong> 15 mg/d (d1-d5) every other wk</td>
</tr>
<tr>
<td>DepoCyt</td>
<td>pyrimidine nucleoside analogue, cell cycle specific</td>
<td>14-21 days</td>
<td>50 mg every 2 weeks (total, 8 wks) then 50 mg once weekly</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>alkylating ethyleneimine compound, cell cycle non-specific drug</td>
<td>3-4 hours</td>
<td>10 mg twice weekly (total, 4 wks) then 10 mg once weekly (total, 4 wks) then 10 mg once a month</td>
</tr>
</tbody>
</table>

Main IT agents
Liposomal Ara-C

Liposomal Ara-C is approved only for lymphomatous LM in most countries. Widely used off label for solid tumor-related LM.

In solid tumor-related LM, a randomized trial comparing intra-CSF liposomal ara-C to MTX:

- increased median time to neurologic progression (58 vs. 30 days, \( P = 0.0068 \))
- greater quality-adjusted survival (SS)
  - non SS for median survival (105 vs. 78 days, NS)

Main side effect arachnoiditis
### Intra-CSF chemotherapy regimens in breast cancer

SNI Le Rhun 2013

<table>
<thead>
<tr>
<th>Agent/referenc</th>
<th>Recruitment of the patients</th>
<th>Population characteristics</th>
<th>Associated treatment</th>
<th>Clinical, MRI and cytologic response</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>STD MTX</td>
<td>67 patients from 2000 to 2005</td>
<td>Median age: 49 Median initial IC&gt; 60: 41% CL: 33%-IDC: 34% HR+: 55% HER2+: Not stated Triple negative: Not stated</td>
<td>Systemic CT*: 61% CNS RT: 64%</td>
<td>Clinical response: NS MRI response: NS Cytol. response: NS Overall response: 76%</td>
<td>4 months</td>
</tr>
<tr>
<td>STD MTX</td>
<td>60 patients from 2003 to 2009</td>
<td>Median age: 46 Median initial PS: Not stated IDC: 78.3% ER+: 51.7%-PR+: 43.3% HER2+: 15% Triple negative: Not stated</td>
<td>Systemic CT: 43% CNS RT: 36.7%</td>
<td>Clinical response: NS MRI response: NS Cytol. response: NS</td>
<td>3.3 months</td>
</tr>
<tr>
<td>Int MTX</td>
<td>24 patients from 1999 to 2008</td>
<td>Median age: 49 Median initial PS: 2 (0-2: 71%) CL: 29%-IDC: 58% HR+: 58% HER2+: 29% Triple negative: Not stated</td>
<td>Systemic CT: 46% CNS RT: 46%</td>
<td>Clinical response: 96% MRI response: NS Cytol. response: 46%</td>
<td>5 months</td>
</tr>
<tr>
<td>Int MTX</td>
<td>80 patients from 2000 to 2007</td>
<td>Median age: 53 Median initial PS: Not stated CL: 28%-IDC: 63% ER+: 70%-PR+: 4% HER2+: 21% Triple negative: 21%</td>
<td>Systemic CT: 78% CNS RT: 29%</td>
<td>Clinical response: 73% MRI response: NS Cytol. response: 20%</td>
<td>4.5 months (0-53)</td>
</tr>
<tr>
<td>Lip CYT.</td>
<td>103 patients from 2007 to 2011</td>
<td>Median age: 48 (25-78) Median initial PS: 2 (0-2: 61%) ILC: 28.7%-IDC: 71.3% ER+: 61.1%-PR+: 44.6% HER2+: 12.6% Triple negative: 23.3%</td>
<td>Systemic CT: 58.2% Whole brain RT: 13.5%</td>
<td>Clinical response: 56.8% MRI response: 62.5% Cytol. response: 30.6%</td>
<td>3.9 months (1 day-33.33 months)</td>
</tr>
</tbody>
</table>

ILC: Invasive lobular carcinoma, IDC: Invasive ductal carcinoma, ER: Estrogen receptors, PR: Progesterone receptors, CT: Chemotherapy, RT: Radiotherapy, NS: Not stated
Route of administration of intra-CSF TT

• Advantages of IVe route:

- **Efficacy**: for short half-life drugs such as MTX: site of injection is clinically relevant (PFS) *Glantz, 2010*
- *safe* (site of injection) *Zairi, 2014*
- better distribution (PK studies)
- less painful and more convenient, avoidance of repeated LP
- possible use in case of thrombopenia
- CxT schedule *Bleyer, 1978*

<table>
<thead>
<tr>
<th>Drug</th>
<th>PFS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal Cytarabine ITL</td>
<td>29</td>
<td>0.35</td>
</tr>
<tr>
<td>Liposomal cytarabine IV</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Methotrexate ITL</td>
<td>19</td>
<td>0.048</td>
</tr>
<tr>
<td>Methotrexate IV</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

Randomized study *Glantz 1999*

Liposomal cytarabine n=52; MTX n=48
No SS difference in PFS: 35 vs 37.5 days ($p=0.79$)
Intra-CSF TT: thiotepa

- Thiotepa as 1st line TT

  randomized trial in 52 LM pts (solid tumors)
efficacy and toxicity prospectively compared with intra-CSF MTX
Comparable median OS 14 vs. 16 wks
CSF cytological clearance rate with T: 30%
Fewer neurological toxicities with T  
  *Grossman, JCO 1993*

- Thiotepa as salvage TT

  Retrospective single institution series: 24 BC LM pts
  after failure with intra-CSF liposomal cytarabine
  median ECOG status was 3 (range 1-4)
  median PFS = 3.1 mo (range 3 d-2 y)
  median survival = 4 mo (range 6 d-2.5 y)
  Median OS from LM dg = 9.5 mo (range 1.3 mo-2.7 y).
  No grade 3 toxicity  
  *Le Rhun, Anticancer drug, s 2013*
### Promising IT cytotoxic and radiotherapeutic treatments

<table>
<thead>
<tr>
<th>Study author (yr) [agent/design]</th>
<th>Induction IT dose and frequency</th>
<th>Response</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamberlain (2006) <em>Etoposide</em> Phase II N=27</td>
<td>0.5 mg daily x 5d, EOW x 8 wk</td>
<td>26% CSF clearance 11% 6mo-PFS 4% 1-yr survival</td>
<td>18% mild arachnoiditis</td>
</tr>
<tr>
<td>Groves et al (2008) <em>Topotecan</em> Phase II N=62</td>
<td>0.4 mg BIW x 6 wk</td>
<td>21% CSF clearance 30% 13wk-PFS 19% 6mo-PFS 15-wk median survival</td>
<td>32% mild arachnoiditis</td>
</tr>
<tr>
<td>Wong et al (2006) <em>131I-sodium iodide</em> Phase I N=31</td>
<td>120 mCi x single dose, MTD not reached</td>
<td>29% CSF clearance And improved neurocognitive tests</td>
<td>All less than grade 2</td>
</tr>
<tr>
<td>Kramer et al (2007) <em>131I-iodine-labeled monoclonal Ab 3F8</em> (<em>131I-3F8</em>) Phase I N=13</td>
<td>MTD 10 mCi x single dose</td>
<td>23% CSF or MRI responses</td>
<td>Self-limited headache, fever, vomiting</td>
</tr>
</tbody>
</table>

Adapted from Groves
IT trastuzumab
IT Trastuzumab

• LM involvement still a relatively rare manifestation of HER2 (3-5%)

• High level of concordance in HER2 status between primary tumors and metastatic cancer cells in the CSF (Park 2010)

• CSF concentrations 300 times lower /serum C after IV trastuzumab (Pestalozzi 2000)
IT trastuzumab

• Preclinical data

• Animal models- toxicology studies- weekly IT- Braen 2010, Gutierrez 2011-

• PK study:
  rapid clearance from CSF with high serum C
  possible role of FcRn-membrane receptors of brain endothelium:
  reverse transcytosis of Igs

  further engineering of Fab fragment of hum MAB targeting HER2
  to overcome a IgG-FcRn bond

IT trastuzumab

- Clinical data
  - Mostly cases reports (5-100 mg)
  
  Occasional prolonged survival (>72 mo)
  Complete response (necropsy) Oliveira 2011
  with IT MTX and IT Thiotepa, Ferrario 2009, Mego 2011

- Systematic review and pooled analysis N = 17 pts (13 articles)
  - Safe (no SAE 88.2%)
  - Significant clinical improvement In 68.8%
  - CSF response 66.7%
  - Median OS 13.5 months
  - Median CNS-PFS 7.5 months
  - Clinical improvement and CSF response associated with longer CNS-PFS

Phase I/II trials ongoing
NCT01325207 (US) and NCT01373710 (France)

French Phase I HIT
first results
Gutierrez SABCS 2014
Final results of the phase I "HIT" study: A multicenter Phase I-II study evaluating trastuzumab administered by intrathecal injection for leptomeningeal meningitis of HER2+ metastatic breast cancer (MBC)

Maya Guzman, Myriam Zouari, Emmanuel Mouren Fournier, Myriam Zouari Institute, F. Le Roux, M. Phurum, O. Trehan, M. Haners, V. Vigneron, D. Duras, Myriam Zouari Institute, Patrice Troc, Myriam Zouari Institute, Fauzia Mert, Myriam Zouari Institute, Isabelle Turbier, MS, Curie Institute, M. Phurum, D. Duras, Céline Desguermes, Ph. Traissac, G. Couzi, C. Seigneur, G. Pailhaux, M. Phurum, Ph. Traissac

**Main objective**

- To evaluate the safety and efficacy of IT Tゾト in MBC.

**Primary objective**

- Tゾト dose (MTD) of Tゾト + hemicraniectomy for CSF concentration close to the concentration (30 μg/ml).

**Primary endpoint**

- Events or serious adverse events (SAEs) of Tゾト in CSF.

**Study design**

- Systematic treatment authorized except lapatinib
- Systematic steroids 3 days before IT injection
- Blood + CSF samples
- IT Tゾト: 
  - Samples W1 to W4 for evaluation
  - IV Tゾト: authorized if Tゾト maintains under control extra cranial disease
  - IV Tゾト: authorized if Tゾト maintains under control extra cranial disease

**First results Phase I**

19 patients were included May 2011 to February 2014: 16 evaluable for toxicity (3 had not received the treatment).

- 12 patients evaluable for PK with 103 samples LCR & 107 serum.
- The MTD was not reached and the treatment appears to have been well tolerated by the patients. Neither Grade 3 toxicity nor neurological toxicity related to IT Tゾト was observed.
- The Tゾト target-concentration in the CSF was reached at DL4 and the recommended Tゾト dose for the Phase II trial is 150 mg.
- Five patients have experienced a evident clinical benefit and received more than 8 weekly injections with an average of 23 [12-40].
- Extended data on clinical outcome and PK will be presented.

**Concl**

- The Phase II study will involve 150 mg and possible dose of 250 mg.

- Intrathecal or IT injection dose of 150 mg and possible dose of 250 mg.

This trial was performed...
- Planned treatment
- Phase I
- 1 IT injection per week by lumbar puncture or Ommaya- 8 weeks
- Dose escalation study of TZT: 30-60-100-150 mg
- maximum of 24 patients: 3-6 patients at each DL

- Phase I primary objective:
- To determine the maximum tolerated dose (MTD) of TZT
- achieving a TZT target-C in CSF close to the standard therapeutic plasma C (30 μg/mL)

- Phase I Primary endpoint:
- Neurological MTD and pharmacokinetics of TZT in CSF
- MTD
RESULTS

- 19 patients
- MTD not reached
- Good tolerance profile
- No Grade ≥3 toxicity nor neurological toxicity related to IT
- Target-concentration in the CSF was reached at DL4
- Recommended dose in Phase II is 150 mg (I EP= NPFS @2mo)
- 5 patients have experimented an evident clinical benefit and received more than 8 weekly injections with an average of 23 [12-40]
New Therapeutic Approaches

INVESTIGATIONAL SYSTEMIC TREATMENT

Breast Cancer

limited number data-case reports
small retrospective series
Prolonged response and survival (>12 mo, m=21 mo)
role remains to be confirmed

Capecitabine
Vinorelbine
Hormonal treatment
tamoxifen, letrozole, anastrozole, and megestrol

Le Rhun 2015
New Therapeutic Approaches
Investigational systemic treatment
Breast Cancer and NSCLC

Bevacizumab
IV or intra-CSF
Bevacizumab: Rationale and Data

- CSF levels and CSF/serum indices of (VEGF) have been measured in several studies
- significantly higher in LM patients
- possible role of angiogenesis in LM
- VEGF negatively correlated with LM patients survival
  

- Bev safe in CNS metastases
  
  Besse 2010, Besse 2015
Bevacizumab: Rationale and Data

• Reported cases of prolonged response and functional restoration in advanced LM BC
  – with IV bev in combination with CT
  – capecitabine or vinorelbine  

  \textit{Le Rhun 2015, Vincent 2013}

• Intra-CSF bev under evaluation in LM in NSCLC \textit{De Braganca 2010, Groves 2011}

• Pilot study (n = 15):
  – bev significantly decreases CSF VEGF levels over time
  – clinical, imaging and CSF responses or stable disease in 54-73% of LM patients \textit{Groves 2011}
New Therapeutic Approaches
INVESTIGATIONAL SYSTEMIC TREATMENT
NSCLC

Combined modality approach
Retrospective data
Mostly from single institution and retrospective
Suggest that CT as part of a combined therapy (+TKI) approach improves survival
OS remains low (median 3-6 mo)

- In n=22 pts, median OS 11.5 vs. 1.4 months, $P < 0.001$  
  Park 2011

- In n=30 adenok pts, median OS from LM diagnosis was 6 months (95% CI, 3-12)
  With a decreased hazard of death ($hazard\ ratio\ [HR], 0.24; \ P = .007$)  
  Riess 2014

- In n=6 adenok pts, median OS = 9 mo (8-15)  
  Yang 2014
New Therapeutic Approaches
Investigational systemic treatment
NSCLC

Chemotherapy:
any CT targeting the type of primary
pemetrexed (multi-targeted anti-folate agent) alone or in combination (cisplatin) +++
Riess 2014, Kumthekar 2013, Yang 2014

EGFR TK inhibitors:
• Gefitinib-erlotinib
  case-reports
  So 2009
  3 large retrospective series
  Park 2012, Morris 2012, Xu 2014

• long lasting remission (11-12 months) from erlotinib and gefitinib if an EGFR mutation is present

• long-lasting response can occur under erlotinib after PD under gefitinib and conversely
  Katayama 2009, Xing 2014, Masuda 2008

• Optimal dosage of erlotinib and gefitinib is not clear
  Clarke 2012, Dhruva 2009
• based on the hypothesis that higher C in the CSF can be reached by higher systemic C
• potential advantage
  of high dose of gefitinib
  Groves 2011, Jackman 2006
  of intermittent (pulsatile) schedule of erlotinib (1000-1500 mg/week)
  Clarke 2012, Grommes 2011, Kuiper 2013
<table>
<thead>
<tr>
<th>Population</th>
<th>Patients characteristics</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
</table>
| N=50 2003-2009 | 25 F/25 M  
Median age =62.5  
M T NSCLC to LM = 10.4 m | MS=4.3 m  
PS 1-2 (n=35): MS 5,5 mo vs 0,7 mo for PS 3-4 (p <0,001)  
IT (n=48 ):  
52% cytol response  
MS if cytol response 5,5 mo vs 1,4 mo (p=0,075)  
Impact of RT-IT conco MS= 5,5 vs 1,5 m) (n=22) (p=0,053)  
with Chemo or TKI (n=22 ): MS 11,5 m vs 1,4 mo (p<0,001)  
With TKI (n=14 ): MS= 19,2 mo | Park et al. 2011. Lung Cancer |
| N=125 2002-2009 | 80 F/45 M  
Median age= 59  
M T NSCLC to LM = 10.4 m | MS=3 m  
No impact of WBRT (n=46) MS (p=0,84)  
Impact With IT (n=7): MS= 18 mo (p=0,001)  
impact TKI and EGFR mut + (n=9 ): MS= 14 mo | Morris et al. 2011. J Thorac Oncol |
| N= 108 2006-2013 | 55 F/53 M  
Median age= 61  
M T NSCLC to LM<12 m = 72.2%  
M T NSCLC to LM>12 m = 27.8% | MS= 5.3 m  
PS 1-2 (n=87): MS 6.8 mo vs 2.8 mo for PS 3-4 (p <0,001)  
Impact WBRT(n=49) :6.4 mo vs 4.3 mo (p=0.022)  
No impact syst chemo  
Impact TKI: 11.1 vs 4.4 mo (p<0.01)  
Impact Conco WBRT-TKI:1MS=2.3 mo | Xu et al. 2014. Thoracic Cancer |
New Therapeutic Approaches
Investigational systemic treatment
NSCLC

• Afatinib
  • Irreversible ErbB Family Blocker EGFR- TKI
  • Seems to penetrate into the CNS with C high enough to have clinical effect on CNS Mets
  • Effective first-line TT in EGFR-mutated NSCLC
  • Activity in patients progressing on EGFR-TKIs

• Assessed in pretreated CNS mets (BM + LM ) : n=100 / 74% EGFR mut
  • CNS response = 35% - 16% exclusively response CNS
  • TTP for CNS =3.6 mo (same matched extra-CNS mets pts)
  • CNS disease control =66%


New Therapeutic Approaches

Investigational systemic treatment

Melanoma

- **Limited efficacy of Intra-CSF and systemic chemotherapy**
- **Systemic**: temozolomide, dacarbazine, fotemustine
- **Poor prognosis**, with a median survival 10 wks-3.8 mo (Harstad 2008, Papadopoulos 2002)

- **Encouraging clinical results observed in intraparenchymal brain mets**
- With **anti-CTLA4 monoclonal antibody ipilimumab**
- and
- **targeted therapies targeting mutated BRAF such as vemurafenib and dabrafenib**
- Suggest LM pts may benefit from this approach


Leptomeningeal involvement may also be addressed with these new therapies as illustrated by case reports of treating melanoma-related LM with ipilimumab and dabrafenib.

Bot I, Blank CD.


Challenges and Controversies

• **LM presents substantial challenges for clinicians in everyday practice and in clinical research**
  Diagnostic criteria are not standardized
  Treatment effectiveness is low
  No generally accepted criteria define patient subgroups that might benefit from therapy
  Often heavily pretreated patients with refractory concomitant systemic metastatic disease

• **Several factors contribute to the difficulty in evaluating new therapies for LM**

• **Traditional survival endpoints are difficult to apply in LM**
  – Often simultaneous progression of both systemic and CNS disease
  – Difficult to establish the cause of death (neurological vs. systemic vs. both vs. neurotoxicity vs. intercurrent disease)
  – The best criteria of evaluation may be the time to neurological progression
Challenges and Controversies

- **LACK STANDARDIZATION WITH RESPECT TO RESPONSE ASSESSMENT AND SURVIVAL ENDPOINTS**

- **New clinical signs** and symptoms may reflect:
  - Co-existent parenchymal disease
  - Treatment related toxicities
  - Concurrent disease
  - Systemic PD
  - Paraneoplastic sd

- **New clinical signs** and symptoms may be transient – should not define PD

- MRI: One-dimensional **RECIST criteria** are not appropriate
  - Most LM imaging features not measurable
  - For most solid tumors, no reduction in LM enhancement with intra-CSF or systemic chemotherapy
  - No agreed upon radiologic criteria

- **Lack of sensitivity of CSF cytological analysis**
  - Up to 55% at 1st assessment
  - Detection of malignant cells varies from CSF sample to sample
LANO recommends that all patients enrolling in LM clinical trials undergo a CSF analysis,
including cytology in all cancers and flow cytometry in hematologic cancers
complete contrast-enhanced neuraxis (brain and spine) MRI
and radioisotope CSF flow studies (if intra-CSF therapy only)

WORK ON PROGRESS:
3 recognized elements of TT response in LM
Standardized Neurological Examination [with NANO]
CSF Cytology or Flow Cytometry
CNS Radiology
Thank you!