INTRATHECAL APPLICATION
OF MONOCLONAL ANTIBODIES

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AGENDA

1. INTRATHECAL APPLICATION
2. MONOCLONAL ANTIBODIES
3. MALIGNANT CARCINOMATOSIS
4. INTRATHECAL TRASTUZUMAB
5. INTRATHECAL RITUXIMAB
6. CONSIDERATIONS
7. ADMINISTRATION
8. PREPARATION
9. CONCLUSION
PHYSIOLOGY OF CNS

- Skin
- Periosteum
- Bone
- Dura mater
- Arachnoid
- Pia mater
INTRATHECAL APPLICATION

- Application in the subarachnoid space
- Indications
- Administration of analgesia/chemotherapy
- Intrathecal injection/Ommaya reservoir
MONOCLONAL ANTIBODY

- Diagnostic/therapeutic treatment
- Big molecule – 150 kDa
- Usually intravenous application (sometimes intramuscular or subcutaneous)

Intrathecal application?

LEPTOMENINGEAL CARCINOMATOSIS

- Leptomeningeal carcinomatosis – neoplastic meningitis
- Incidence of leptomeningeal carcinomatosis – 5%
- Survival
- Treatment

TREATMENT CONSIDERATIONS

- Tight barriers
- Adverse effects
- Trastuzumab
- Rituximab
TRASTUZUMAB

☐ Adjuvant/metastatic setting

☐ Incidence of breast cancer brain metastasis: **10-16%**

☐ Incidence of HER2+ breast cancer brain metastasis: **25-50%**

☐ Trastuzumab concentration: serum levels 300 – 400-fold higher vs. cerebrospinal fluid

### Summary of reports using intrathecal application of trastuzumab


<table>
<thead>
<tr>
<th>Report</th>
<th>Patients (n)</th>
<th>Dose</th>
<th>Doses (n)</th>
<th>Other i.t. medicines</th>
<th>Systemic therapy</th>
<th>Survival after first i.t. trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1</td>
<td>20 mg</td>
<td>4</td>
<td>Methotrexate</td>
<td>Yes</td>
<td>39 days</td>
</tr>
<tr>
<td>2.</td>
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<td>5-20 mg</td>
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<td>Methotrexate, thiotepa</td>
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<td>66 days</td>
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<tr>
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<td>12.5 mg</td>
<td>23</td>
<td>/</td>
<td>Yes</td>
<td>&gt;72 months</td>
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<tr>
<td>4.</td>
<td>1</td>
<td>5-20 mg</td>
<td>4</td>
<td>/</td>
<td>Yes</td>
<td>&gt;5 months</td>
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<tr>
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<td>20-50 mg</td>
<td>29</td>
<td>Methotrexate, thiotepa</td>
<td>Yes</td>
<td>&gt;2 years</td>
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<tr>
<td>6.</td>
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<td>20-100 mg</td>
<td>6</td>
<td>/</td>
<td>/</td>
<td>5 months</td>
</tr>
<tr>
<td>7.</td>
<td>1</td>
<td>20-25 mg</td>
<td>46</td>
<td>Prednisone, thiotepa</td>
<td>Yes</td>
<td>&gt;21 months</td>
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<tr>
<td>8.</td>
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<td>25 mg</td>
<td>6</td>
<td>/</td>
<td>/</td>
<td>&gt;6 weeks</td>
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<tr>
<td>9.</td>
<td>16</td>
<td>20-60 mg</td>
<td>4</td>
<td>/</td>
<td>/</td>
<td>4 weeks to &gt;14 weeks</td>
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</table>
INTRATHECAL TRASTUZUMAB – CLINICAL FINDINGS

- Relief of clinical symptoms in 7 out of 8 patients
- Decrease or disappearance of brain lesions on MRI
- Duration of response: 39 days to 72 months
- 6 patients surviving > 5 months
- Response is dose related

INTRATHECAL TRASTUZUMAB - PHARMACOKINETICS

- Intrathecal therapy → increase in cerebrospinal fluid (CSF) concentration of trastuzumab
- CSF concentration still lower than serum concentration of trastuzumab
  - Maximum dose 20 mg higher
  - Relatively low CSF concentration doses?
INTRATHECAL TRASTUZUMAB - CONCLUSION

- Intrathecal trastuzumab appears to be a promising therapy

- Survival: 4 weeks to > 7 years after first trastuzumab intrathecal dose

- Most patients: resolution of leptomeningeal carcinomatosis symptoms no clinical toxic effects

- Optimal dose?
- Optimal schedule?
- Place in therapy?
RITUXIMAB

- Indolent/aggressive Non-Hodgkin's lymphoma (NHL)
- Incidence of lymphomatous meningitis: **5%** of diffuse large B-cell lymphoma patients
- Most NHLs that involve the CNS express CD20
- Rituximab concentration: CSF concentration approximately 0.1% serum concentration

Summary of report using intrathecal application of rituximab

<table>
<thead>
<tr>
<th>Report</th>
<th>Patients (n)</th>
<th>Dose</th>
<th>Doses (n)</th>
<th>Other i.t. medicines</th>
<th>Systemic therapy</th>
<th>Survival after first i.t. rituximab</th>
</tr>
</thead>
<tbody>
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<td>25 mg</td>
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<td>/</td>
<td>Yes</td>
<td>&gt;25 months</td>
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<tr>
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<td>10-40 mg</td>
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<td>Yes</td>
<td>&gt;7 months</td>
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<tr>
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<td>40 mg</td>
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<td>Methotrexate, cytarabine, Prednisone</td>
<td>Yes</td>
<td>&gt;16 months</td>
</tr>
<tr>
<td>4.</td>
<td>1</td>
<td>10-40 mg</td>
<td>4</td>
<td>/</td>
<td>No</td>
<td>4 months</td>
</tr>
<tr>
<td>5.</td>
<td>1</td>
<td>20-30 mg</td>
<td>6</td>
<td>/</td>
<td>No</td>
<td>&gt;3,5 years</td>
</tr>
<tr>
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<td>1</td>
<td>10-35 mg</td>
<td>4</td>
<td>/</td>
<td>No</td>
<td>&gt;15 months</td>
</tr>
<tr>
<td>7.</td>
<td>1</td>
<td>20 mg</td>
<td>4</td>
<td>/</td>
<td>Yes</td>
<td>&gt;28 months</td>
</tr>
<tr>
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<td>10-40 mg</td>
<td>4-10</td>
<td>/</td>
<td>Yes</td>
<td>2-14 months</td>
</tr>
<tr>
<td>9.</td>
<td>7</td>
<td>10 mg</td>
<td>4</td>
<td>/</td>
<td>Yes</td>
<td>7 to &gt;24 months</td>
</tr>
<tr>
<td>10.</td>
<td>10</td>
<td>10-50 mg</td>
<td>1-9</td>
<td>/</td>
<td>No</td>
<td>1,1 week to &gt;134 weeks</td>
</tr>
</tbody>
</table>
Case reports (7 patients): 7 patients showed tumour cell clearance, 4 symptomatic improvements

7 paediatric patients: 5 patients in complete response after 2 years, only one had neurologic complications

Adverse effects: infusion reactions (without long-lasting effect)

Doses above 40 mg may increase the likelihood of adverse effects.

8 patients receiving 10-25 mg rituximab had no signs of major toxicity

2 patients receiving 50 mg suffered from toxicities → resolved within 20 minutes

Survival: 1-134 weeks

Rituximab cerebrospinal fluid (CSF) concentration similar to serum concentration

CSF $t_{1/2} = 25$ hours, serum $t_{1/2} = 22$ days

Intrathecal rituximab appears to be a promising therapy.

Survival: 2 months to > 3.5 years after first rituximab intrathecal dose.

Toxicity has been described, majority for doses above 40 mg.

Toxicities were manageable.

More frequent administration? Optimal dose/schedule?
PREPARATION

- Preparation of trastuzumab – necessary to use sterile water for injection

- 440 mg vial (supplied in the USA) – supplied with bacteriostatic water for reconstitution → contains 1.1% benzyl alcohol

- Products that contain preservatives should not be administered intrathecally
ADMINISTRATION

- Monoclonal antibodies should be administered immediately after preparation.

- Intrathecal injections administered over a period of 1-5 minutes.

- Method of delivery → lumbare puncture or Ommaya reservoir.
CONCLUSION

- Poor prognosis of malignant carcinomatosis
- Remarkable efficacy
- Favourable toxicity profile

Further research is warranted!