

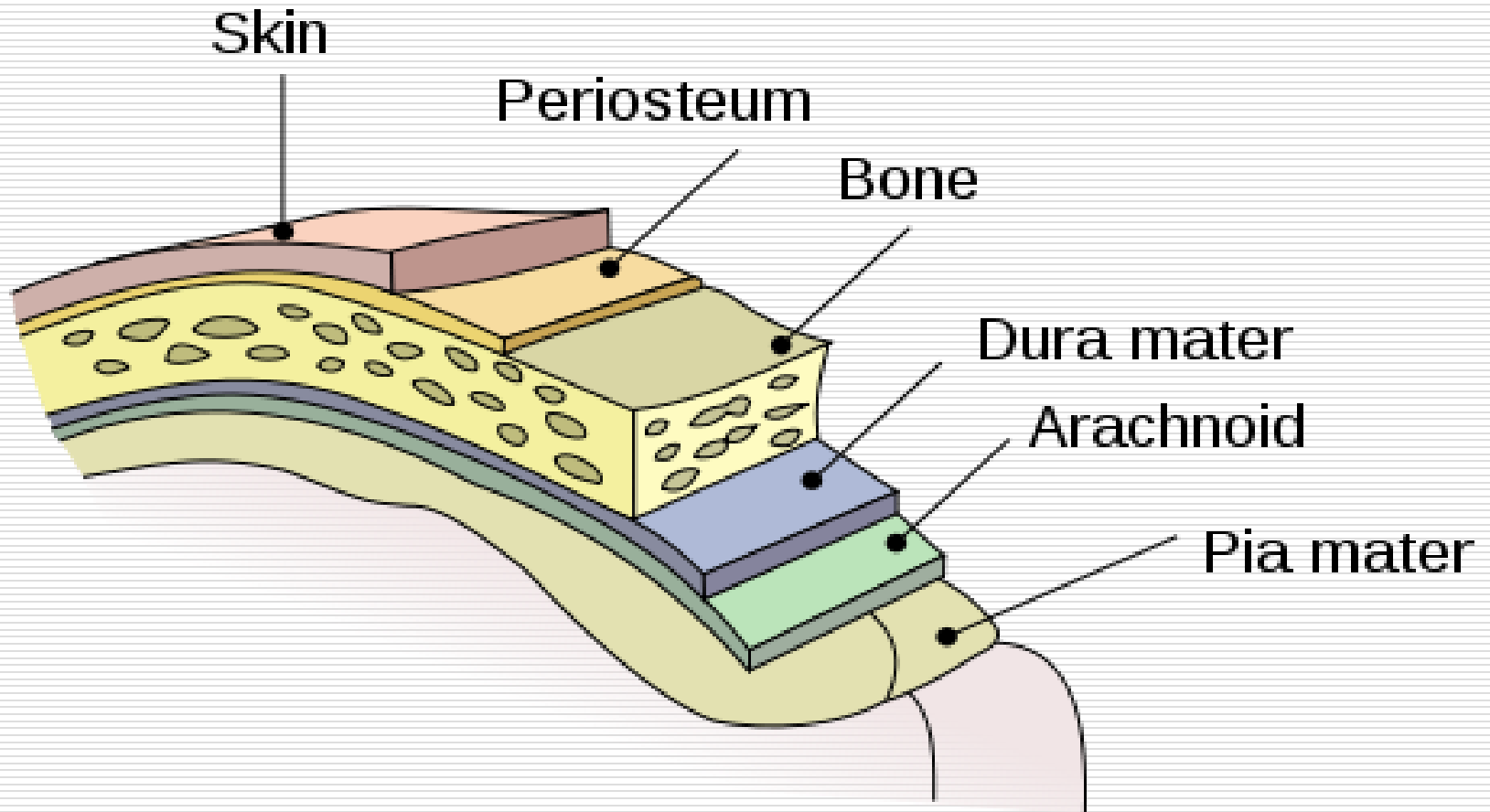
INTRATHECAL APPLICATION OF MONOCLONAL ANTIBODIES

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AGENDA

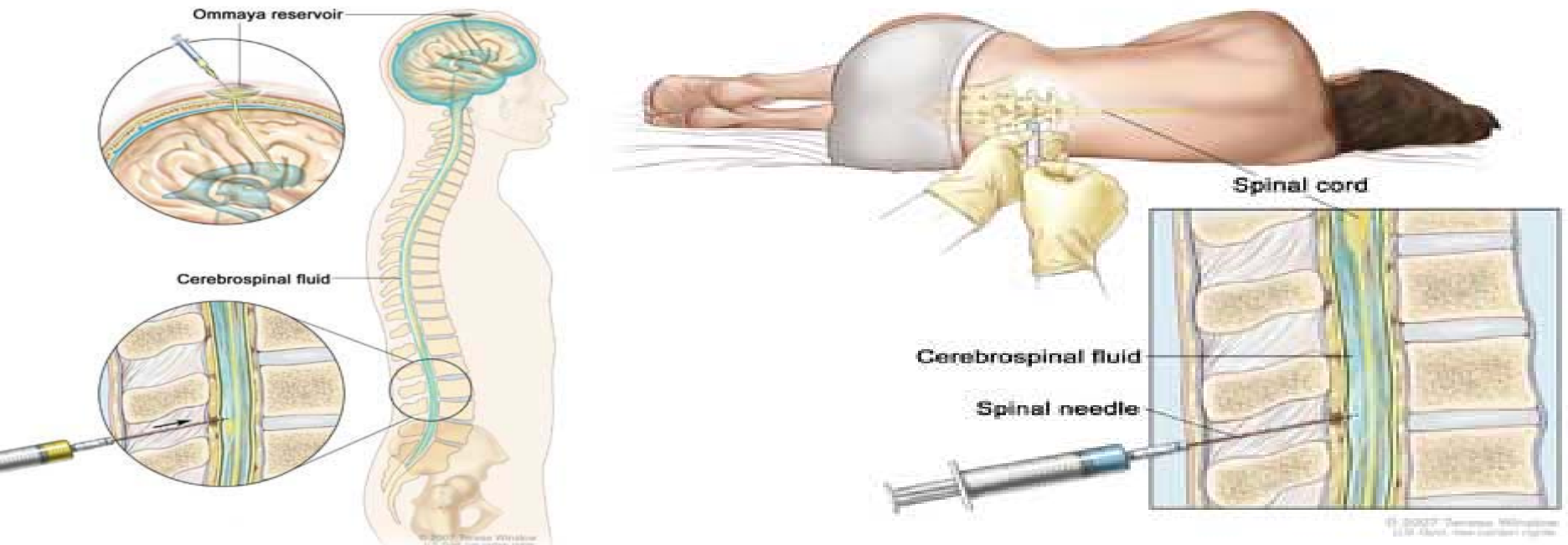
- 1. INTRATHECAL APPLICATION**
 - 2. MONOCLONAL ANTIBODIES**
 - 3. MALIGNANT CARCINOMATOSIS**
 - 4. INTRATHECAL TRASTUZUMAB**
 - 5. INTRATHECAL RITUXIMAB**
 - 6. CONSIDERATIONS**
 - 7. ADMINISTRATION**
 - 8. PREPARATION**
 - 9. CONCLUSION**
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PHYSIOLOGY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



INTRATHECAL APPLICATION

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

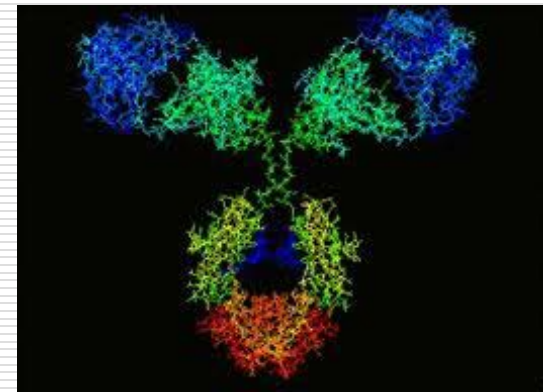


MONOCLONAL ANTIBODY

□ Diagnostic/therapeutic treatment

□ Big molecule – 150 kDa

□ Usually intravenous application (sometimes intramuscular or subcutaneous)



Intrathecal application?

➤ Clinical Pharmacokinetics of Therapeutic Monoclonal Antibodies. *Clin Pharmacokin* 2010; 49(8):493-507.

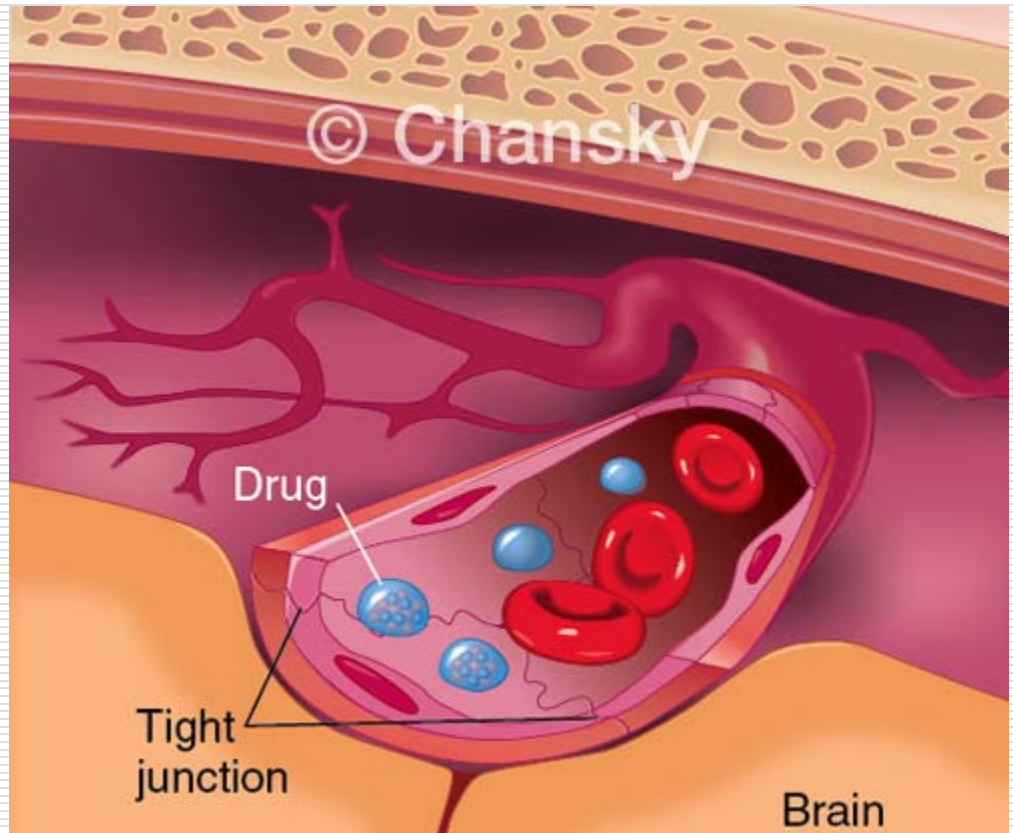
LEPTOMENINGEAL CARCINOMATOSIS

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

➤ Leptomeningeal carcinomatosis. *Cancer Treat Rev* 1999, 25:103-119.

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

- Breast Cancer Metastasis to the Central Nervous System. *Am J Pathol* 2005;167:913-920.
- Central Nervous System Metastases in HER-2 – Positive Metastatic Breast Cancer Patients Treated with Trastuzumab: Incidence, Survival, and Risk Factors. *The Oncologist* 2007;12:766-773.
- Trastuzumab in CSF (letter). *J Clin Oncol* 2000;18:2349-2351.

Summary of reports using intrathecal application of trastuzumab

Role of Intrathecal Rituximab and Trastuzumab in the Management of Leptomeningeal Carcinomatosis. *Ann Pharmacother* 2010;44:1633-40.

Report	Patients (n)	Dose	Doses (n)	Other i.t. medicines	Systemic therapy	Survival after first i.t. trastuzumab
1.	1	20 mg	4	Methotrexate	Yes	39 days
2.	1	5-20 mg	4	Methotrexate, thiotepa	Yes	66 days
3.	1	12,5 mg	23	/	Yes	>72 months
4.	1	5-20 mg	4	/	Yes	>5 months
5.	1	20-50 mg	29	Methotrexate, thiotepa	Yes	>2 years
6.	1	20-100 mg	6	/	/	5 months
7.	1	20-25 mg	46	Prednisone, thiotepa	Yes	>21 months
8.	1	25 mg	6	/	/	>6 weeks
9.	16	20-60 mg	4	/	/	4 weeks to >14 weeks

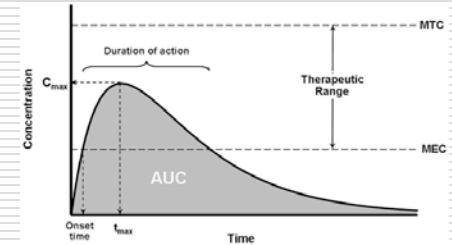
INTRATHECAL TRASTUZUMAB – CLINICAL FINDINGS

- 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

➤ Role of Intrathecal Rituximab and Trastuzumab in the Management of Leptomeningeal Carcinomatosis. *Ann Pharmacother* 2010;44:1633-40.

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

➤ Relatively low CSF concentration

} higher doses?



higher 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

➤ Lymphomatous meningitis. Hematologica reports 2005;1:108-109.

➤ Rituximab therapy for CNS lymphomas: targeting the leptomeningeal compartment. Blood 2003;101:466-468.

Summary of report using intrathecal application of rituximab

Role of Intrathecal Rituximab and Trastuzumab in the Management of Leptomeningeal Carcinomatosis. *Ann Pharmacother* 2010;44:1633-40.

Report	Patients (n)	Dose	Doses (n)	Other i.t. medicines	Systemic therapy	Survival after first i.t. rituximab
1.	1	25 mg	5	/	Yes	>25 months
2.	1	10-40 mg	8	/	Yes	>7 months
3.	1	40 mg	12	Methotrexate, cytarabine, Prednisone	Yes	>16 months
4.	1	10-40 mg	4	/	No	4 months
5.	1	20-30 mg	6	/	No	>3,5 years
6.	1	10-35 mg	4	/	No	>15 months
7.	1	20 mg	4	/	Yes	>28 months
8.	6	10-40 mg	4-10	/	Yes	2-14 months
9.	7	10 mg	4	/	Yes	7 to >24 months
10.	10	10-50 mg	1-9	/	No	1,1 week to >134 weeks

INTRATHECAL RITUXIMAB – CLINICAL FINDINGS

- ❑ 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.

➤ Role of Intrathecal Rituximab and Trastuzumab in the Management of Leptomeningeal Carcinomatosis. *Ann Pharmacother* 2010; 44:1633-40.

INTRATHECAL RITUXIMAB – CLINICAL FINDINGS Phase I

- 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

➤ Phase I study of intraventricular administration of rituximab in patients with recurrent CNS and intraocular lymphoma. *J Clin Oncol* 2007;25:1350-6.

INTRATHECAL RITUXIMAB - CONCLUSION

- ❑ 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?**
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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
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ADMINISTRATION

- ❑ Monoclonal antibodies should be administered immediately after preparation
 - ❑ Intrathecal injections administered over a period of 1-5 minutes
 - ❑ Method of delivery → lumbar puncture or Ommaya reservoir
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CONCLUSION

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

Further research is warranted!
