Controversial treatments for CNS Metastases

Intra-CSF pharmacotherapy for leptomeningeal metastasis: pro!

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Levels of evidence in leptomeningeal metastasis

- No standards for:

➢Neurological examination
➢Neuro-imaging assessment
➢Cerebro-spinal fluid cytological diagnosis

- No trial on systemic treatment
- No trial on radiotherapy
- Only 6 randomized trials on intrathecal therapy….

Trial	Design	Population	Primary endpoint	Efficacy	Safety
Grossman 1993	IT MTX versus IT thiotepa	Solid tumors (n=40), CUPS (n=1) and lymphomas (n=10)	Neurological response rate	IT MTX vs. IT thiotepa Neurological response rate: none Neurological stabilization: 32% vs. 12.5% Survival: 15.9 weeks vs. 14.1 weeks	IT MTX vs. IT thiotepa Serious toxicities similar in both group Mucositis (p=0.04) and neurological complications (p=0.008) more frequent in MTX arm
Hitchins 1997	IT MTX versus IT MTX + cytarabine	Solid tumors (n= 30), cancers of unknown primaries (n=7) and lymphomas (n=7)	Response rate	IT MTX vs. MTX + cytarabine Response rate : 61 vs. 45% (p<0.05) Median survival : 12 vs. 7 weeks (p<0.05)	IT MTX vs. MTX + cytarabine Nausea and vomiting : 36% vs. 50% Septicemia, neutropenia : 9% vs. 15% Mucositis : 14% vs. 10% Pancytopenia : 9% vs. 10%
Glantz 1999	IT liposomal cytarabine versus IT MTX	Solid tumors (n=61)	Neurological response rate at the end of the induction period	IT liposomal cytarabine vs. IT MTX Responses rate : 26% vs. 20% (p = 0.76) Median survival : 105 days vs. 78 days (p P = 0.15) Time to neurological progression : 58 vs. 30 days (p = 0.007) Neoplastic meningitis-specific survival : 343 vs. 98 days (p = 0.074)	IT liposomal cytarabine vs. IT MTX Sensory/motor dysfunction : 4% vs. 10% (p = 0.021) Visual impairment 0% vs. 13% (p = 0.066) Chemical meningitis of any grade : 23% vs. 19% (p=0.57)
Boogerd 2004	IT MTX versus no IT	Breast cancers (n=35)	Overall survival: time from randomization until death	IT MTX vs. no IT Overall survival :18.3 weeks vs. 30.3 weeks (p = 0.32) Neurological improvement or stabilisation : 59% vs. 67% (p = NR) Median time to progression of 23 weeks and 24 weeks (p = NR)	IT MTX vs. no IT Neurological complications : 47% vs 6% (p = 0.0072)
Shapiro 2006	solid tumors: IT liposomal cytarabine versus IT MTX (lymphomas: IT liposomal cytarabine versus IT aracytine)	Solid tumors (n=103) and lymphomas (n=25)	Progression free survival: randomized to neurological progression or death	IT liposomal cytarabine versus IT MTX or aracytine Median progression free survival: 35 vs. 43 days (p=0.7321)	IT liposomal cytarabine versus IT control Drug related AE: 48% vs. 60% of the serious AE: 86 vs. 77%

Pros & Cons

Limitations of intra-CSF therapy	In favor of intra-CSF therapy
No randomized trial has demonstrated that intra-CSF therapy prolongs survival in LM patients	Used by a large majority of physicians in addition to systemic treatments across Europe (only 11% of physicians never use intra-CSF therapy) Recent prospective safety data have shown a good tolerance of liposomal cytarabine
The compounds routinely used for intra-CSF treatment do not have a key role as single agents for systemic treatment of common cancers causing LM	Compounds with systemic efficacy are currently under evaluation as intra-CSF agents in clinical trials
Intra-CSF therapy has only a limited penetration (1-3 mm) into solid tumor lesions Intra-CSF therapy may be inefficient and toxic in case of CSF flow blocks	Rationale for the treatment of floating tumor cells in the CSF in the setting of little or no blood CSF barrier dysfunction Rationale for the treatment of linear diffuse or ependymal spread not yet accompanied by blood brain barrier dysfunction Circumvention of systemic toxicity

DEPO-SEIN (NCT01645839)

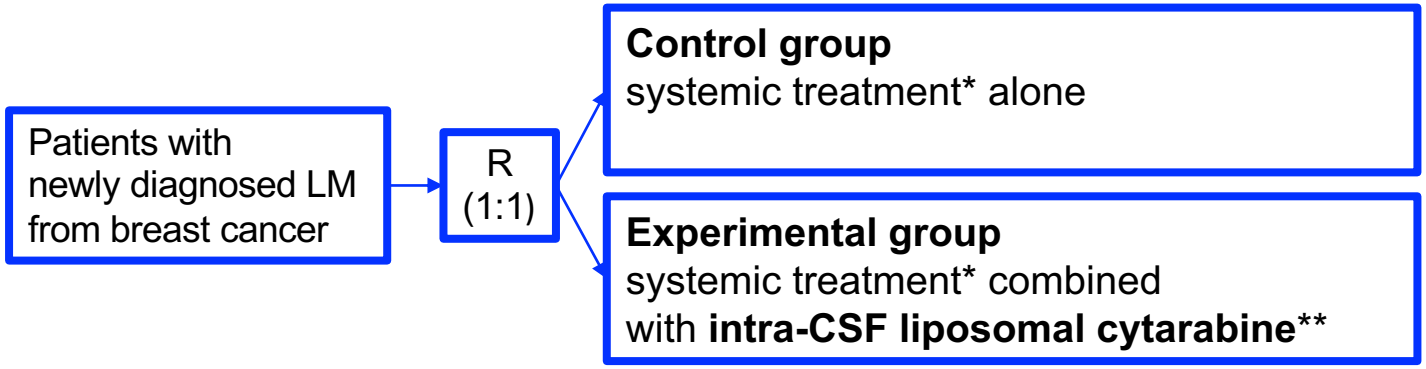
Phase III randomised controlled open-label trial

Main inclusion criteria

Breast cancer patients requiring systemic treatment at inclusion, ECOG PS: 0-2
Diagnosed with LM (CSF positive cytology; combination of typical clinical and MRI findings)
Leptomeningeal metastases <0.5 cm (or >0.5 if treated by SRS/SRT)
Asymptomatic brain metastases permitted
Whole brain radiotherapy not allowed
Untreated CSF blockade not allowed

Main objective

To compare the **leptomeningeal metastases progression free survival** (clinical and imaging criteria) between the 2 groups

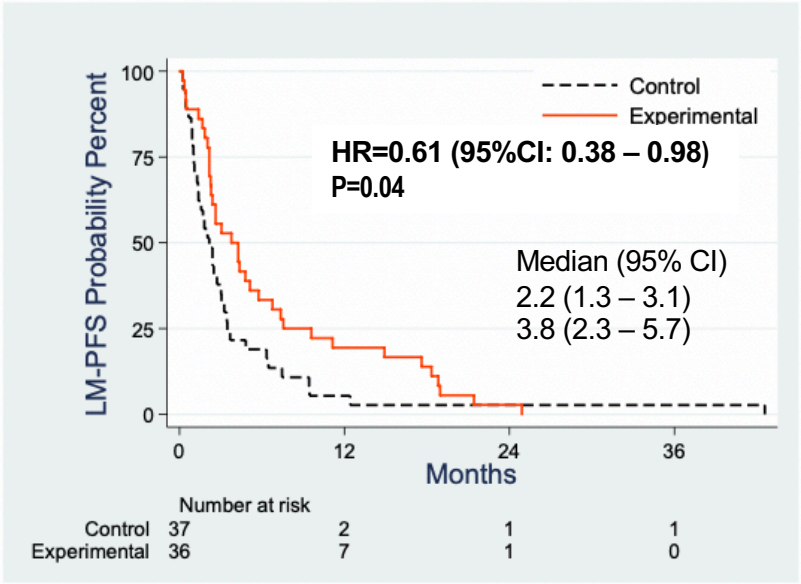


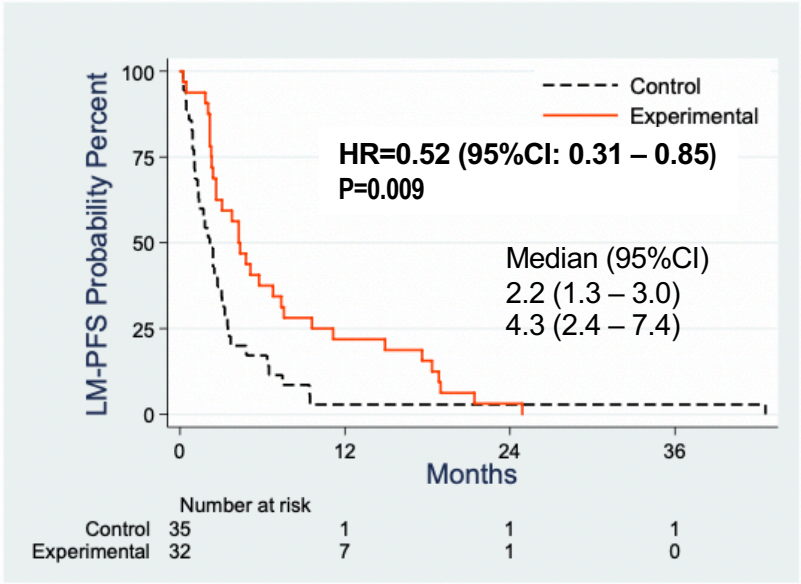
* In both groups: systemic treatment selected by the treating physician prior to randomisation
** Intra-CSF liposomal cytarabine: 50 mg every 14 days for 2 months (5 injections) followed by monthly injections of 50 mg until progression, unacceptable toxicity or for a total of one year. Oral steroids recommended for 5 days from the day of intra-CSF injection to prevent chemical meningitis. In case of severe toxicity, the dose of cytarabine could be reduced to 25 mg.

Intent to treat

Per protocol

LM-PFS





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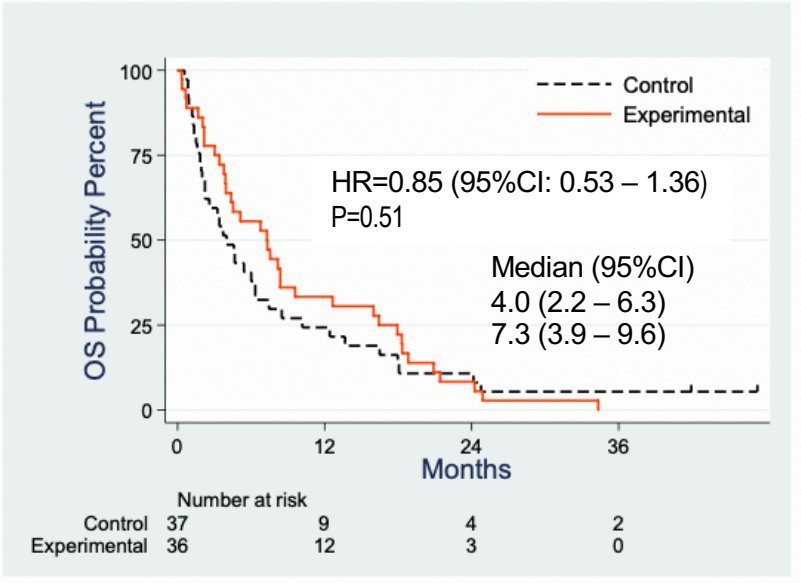

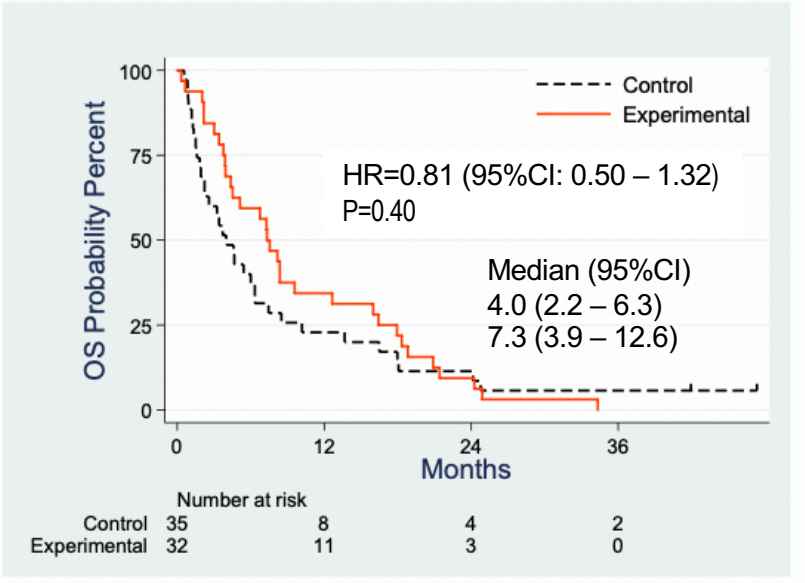


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DISORIENTED
UNCLEAR