

**Involved-field Radiotherapy Combined With
Concurrent Intrathecal-MTX Versus Intrathecal-Ara-C
for Leptomeningeal Metastases From Solid Tumor: A
Randomized Phase II Clinical Trial**

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Study Protocol

Objective:

This study was designed to investigate the efficacy and safety of concurrent involved-field radiotherapy and intrathecal chemotherapy for patients with leptomeningeal metastases from solid tumors. Furthermore, another purpose of the study is to compare the two intrathecal chemotherapy drugs in the concomitant therapeutic modality.

Design:

It is a prospective, randomized controlled, parallel group, and phase II clinical trial. The study participants were newly diagnosis patients with leptomeningeal metastases from solid tumors. Patient with hematological malignancy (e.g., leukemia and lymphoma) or primary brain tumor was excluded.

In our previous study ^[1], it has been proved that concurrent radiotherapy and intrathecal methotrexate (MTX) for leptomeningeal metastases (LM) from solid tumors with adverse prognostic factors showed great effectiveness and safety. This treatment regimen improved the prognosis of LM patients from solid tumors with adverse prognostic factors for the first time. The findings suggest that the concomitant regimen could be an optimal treatment option for LM. MTX and cytarabine (ara-C) are conventional cytotoxic drugs, which are the most frequently used agents for intrathecal chemotherapy. The common regimen of intrathecal dose of MTX and ara-C was 15mg and 50mg, respectively.

This study was approved by the Ethic Committee of The First Hospital of Jilin University on February 1, 2017. All procedures were compliant with the Declaration of Helsinki. The study plan and regimen schema is provided in

Figure 1,2. The patients were randomly divided into two groups, who will accept the treatment of involved-field radiotherapy (RT) combined with concurrent intrathecal-MTX or intrathecal-ara-C, respectively. Concomitant regimen consisted of intrathecal chemotherapy (via lumbar puncture, MTX 15 mg, plus dexamethasone 5 mg, or ara-C 50mg, plus dexamethasone 5 mg, once per week, 4 weeks in total) and RT. RT consisted of fractionated, conformal radiation given at a daily dose of 2 Gy. The planning volume consisted of sites of symptomatic disease, bulky disease observed on MRI, including the whole brain and basis cranii received 40 Gy in 20 fractions and/or segment of spinal canal received 40-50 Gy(the first lumbar vertebra and the above segments were given 40 Gy in 20 fractions; the first lumbar vertebra and the inferior segments were given 40/50 Gy in 20 fractions). Patients with Karnofsky performance status score (KPS) of ≤ 40 and irradiation intolerance were required to receive induction intrathecal chemotherapy (MTX 15 mg, or ara-C 50mg, plus dexamethasone 5 mg, twice per week). Then these patients were allowed to receive concomitant therapy upon neurologic improvement and radiotherapy tolerance.

The primary endpoint was clinical response rate (CRR). The secondary endpoints were safety and overall survival (OS).

Methods:

We adopted the criteria of evaluation for clinical response established in our previous study based on improvement of neurologic symptoms/signs and changes of KPS ^[1]. The criteria have been proved associated with the prognosis of LM patients and suitable for clinical application. The clinical response was evaluated by at least two experienced neuro-oncologists. The evaluation consists of 5 layers, including complete response (CR), obvious response (OR), partial response (PR), stable disease (SD) and progressive disease (PD) (Table 1). Clinical evaluation was performed once per week from the beginning of LM-related therapy, till 2 weeks later after salvage therapy.

Clinical response was defined as continuous presence of CR, OR or PR within an interval of at least 1 week. SD and PD were defined as ineffective. Adverse events (AEs) were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). Events of grade 3~5 was defined as moderate and severe adverse events. Survival time was measured from the enrollment of the study until death or the last follow-up.

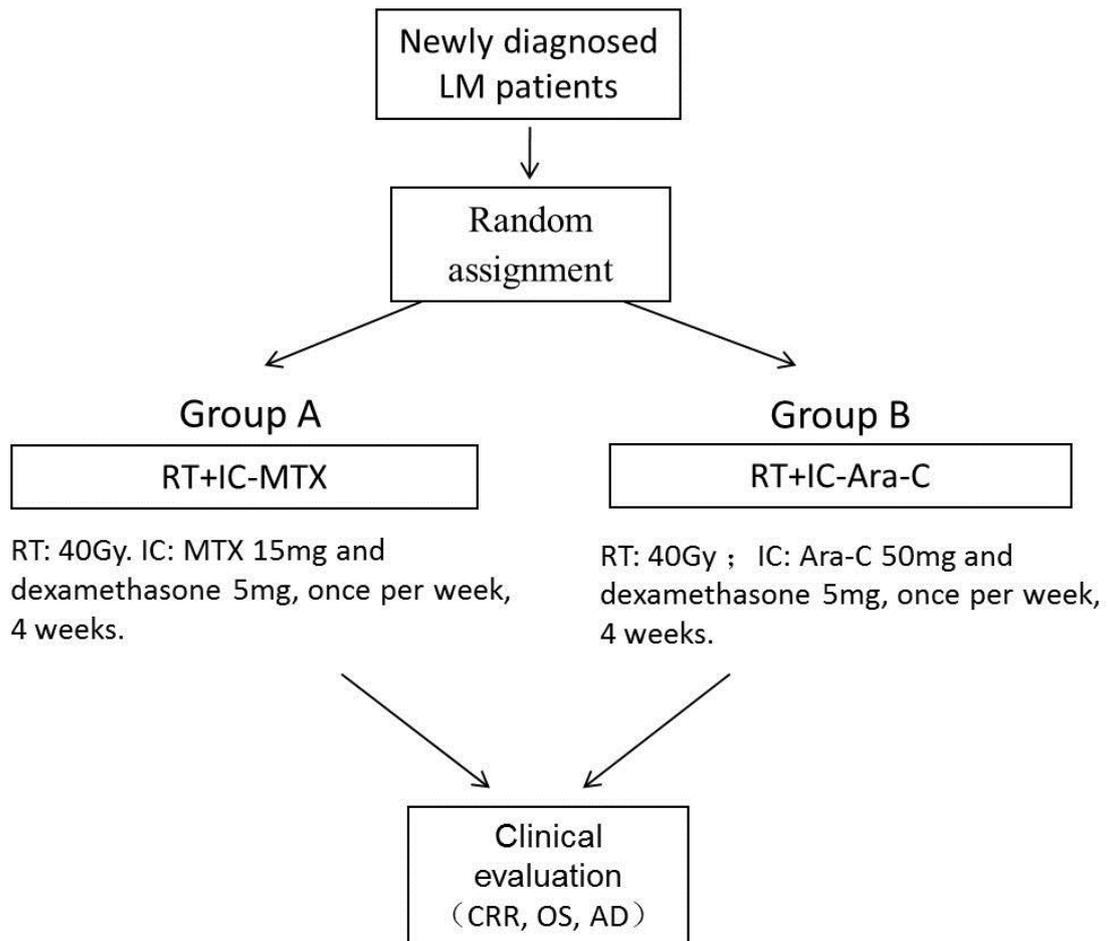
Statistical Analysis Plan

SPSS 17.0 software was used for data analysis. Survival analysis was performed using the Kaplan-Meier method. Log-Rank test was used to compare the survival time of patients. Univariate and multivariate Cox regression analysis were carried out to determine the risk factors of OS. Chi square test and Fisher exact test were used to evaluate the difference of clinical response rate and OS between patients with various features. $P < 0.05$ demonstrated significant difference.

References:

- [1] Pan Z, Yang G, He H, et al. Concurrent radiotherapy and intrathecal methotrexate for treating leptomeningeal metastasis from solid tumors with adverse prognostic factors: A prospective and single-arm study. *Int J Cancer*. 2016;139(8):1864-72.

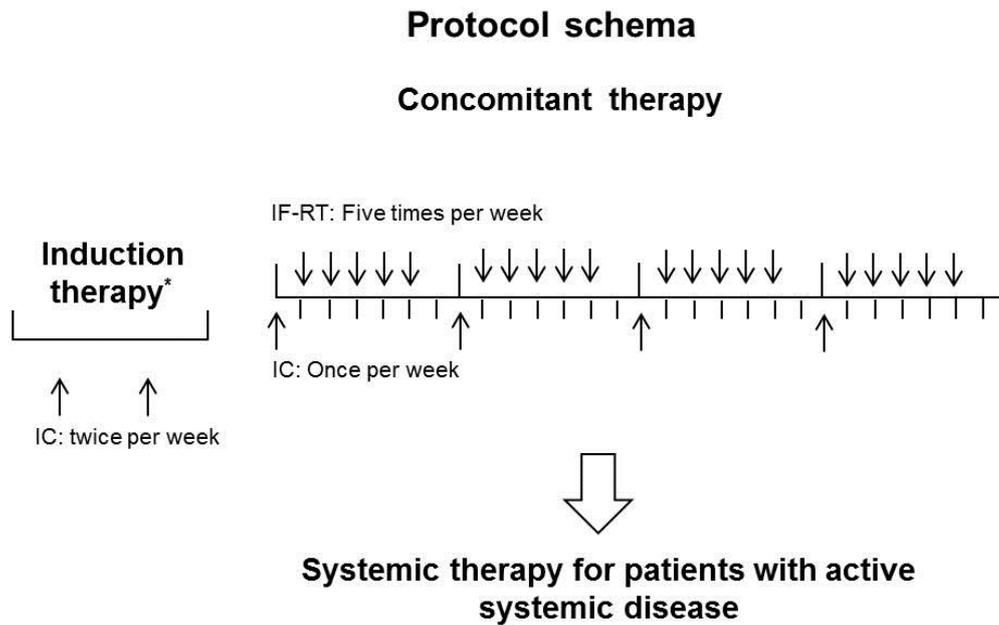
Figure 1



LM: Leptomeningeal metastasis;
IC: intrathecal chemotherapy;
Ara-C: Cytarabine ;
OS: overall survival;

RT: involved-field radiotherapy;
MTX: Methotrexate ;
CRR: clinical response rate;
AD: adverse events.

Figure 2



IF-RT: involved-field radiotherapy; IC: intrathecal chemotherapy.

↓ Involved-field radiotherapy: daily: 20×200 cGy, total dose: 40 Gy.

↑ Intrathecal chemotherapy: Methotrexate 10 mg/ Cytarabine 50mg+dexamethasone 5 mg.

* Induction therapy were those with a Karnofsky performance status score of ≤ 40 and with no tolerance to radiotherapy.

Table 1 **Criteria of clinical response evaluation**

	Neurological symptoms and signs	KPS score
Complete response	Almost normal neurological examination. Mild cranial nerve symptoms including tinnitus or blurred vision may exist. GCS score of 15.	≥90
Obvious response	Significant neurologic improvement. No severe symptoms/signs, such as severe headache, somnolence, mental status. Dizziness, confusion, mild headache, cranial nerve paralysis, or radiculitis may exist. GCS≥12.	≥ 70, or elevation of ≥ 30 compared with the baseline level.
Partial response	Partial neurological improvement. Still with headache, or other mild/moderate symptoms/signs. GCS≥9.	50-70, or elevation of 10-20 compared with the baseline level.
Stable disease	No visible neurological improvement.	Elevation of ≤ 10 compared with the baseline level.
Progressive disease	Deteriorative neurological symptoms and signs.	Decrease of KPS compared to the baseline level.

Two conditions both of neurological symptoms/signs and KPS must be satisfied synchronously.

KPS, Karnofsky performance status score; GCS, Glasgow Coma Scale.

The clinical response was evaluated by at least two experienced neuro-oncologists. Clinical evaluation was performed twice per week from the beginning of LM-related therapy, till 2 weeks later after salvage therapy. Clinical response was defined as continuous presence of complete response (CR), obvious response (OR), partial response (PR) within an interval of at least 1 week. Stable disease (SD) and progressive disease (PD) were defined as ineffective.