OBJECTIVES: This phase I/II study was to evaluate maximum tolerated dose (MTD) of intrathecal pemetrexed (IP) with vitamin supplementation and antitumor activity for leptomeningeal metastases (LM) from solid tumors. METHODS: Phase I study followed the classic 3 + 3 design, with dose escalated from 15 mg. Phase II followed Simon 2-stage design with recommended dose determined in phase I. IP was administered twice per week for 2 weeks (induction therapy), followed by once per week for 4 weeks (consolidation therapy). Vitamin B12 (1000 µg) and folic acid (400 µg, q.d.) were given at the beginning of treatment. Primary end points were MTD in phase I and clinical response rate (CRR) in phase I/II. RESULTS: Between Feb 2022 and Jan 2023, 34 patients were enrolled, including non-small cell lung cancer (20), small-cell lung cancer (3), breast cancer (8), others (3). Ten patients were enrolled in phase I. Three of 4 patients receiving IP at 15 mg completed induction and consolidation treatment without dose limiting toxicity (DLT). Two DLT (1 grade 4 hematologic toxicity and 1 grade 5 arachnoiditis) occurred in 6 patients at 20 mg. MTD was determined to be 15 mg. Then 24 patients were enrolled in phase II and given 15 mg of IP. 82.4% (28/34) and 38.8% (20/51) patients completed induction and consolidation therapy, respectively. Adverse events (AEs) rate was 73.5% (25/34), 50% (17/34) patients showed grade ≥ 3 AEs. Overall CRR was 41.2% (14/34), including 10 (29.4%) with improved neurological dysfunction, 11 (32.4%) with CSF cytological response and 4 (11.8%) with neuroimaging improvement. Median survival was 7.6 (range 0.3–13.7) months in phase I, while has not yet been achieved in phase II. CONCLUSION: MTD of IP was 15 mg with folic acid and vitamin B12 supplementation. IP is an optimal therapeutic option for LM from solid tumors.