



· 论 著 ·

鞘内注射培美曲塞联合程序性死亡蛋白-1 抑制剂治疗实体瘤脑膜转移的 I 期临床研究

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[摘要] 背景与目的: 鞘内化疗是治疗实体瘤脑膜转移 (leptomeningeal metastases, LM) 的主要方法之一。既往的 I 期临床研究证实了鞘内程序性死亡蛋白-1 (programmed death-1, PD-1) 抑制剂治疗黑色素瘤 LM 的安全性和潜在疗效。系统化疗联合 PD-1 抑制剂的协同抗肿瘤作用已被广泛认可。本研究旨在探索鞘内注射培美曲塞联合 PD-1 抑制剂治疗实体瘤 LM 的安全性及可行性。方法: 以广州医科大学附属惠州医院/惠州市第三人民医院收治的实体瘤 LM 患者为研究对象, 采用“3+3”剂量递减策略, 寻找推荐的安全给药剂量。培美曲塞给药方案为初始诱导治疗 2 次/周, 连续 2 周; 随后巩固治疗 1 次/周, 连续 4 周; 治疗有效的患者给予每个月 1 次维持治疗。PD-1 抑制剂给药从第 4 次培美曲塞给药开始, 每 2 周 1 次, 连续 6 周; 随后对治疗有效的患者, 与培美曲塞同时给予每个月 1 次维持治疗。单次给药起始剂量为 PD-1 抑制剂 (特瑞普利单抗) 40 mg、培美曲塞 15 mg。主要研究终点为安全性及推荐给药剂量, 安全性基于不良反应进行评估。同时观察临床有效率 (clinical response rate, CRR)、疾病控制率 (disease control rate, DCR) 和总生存期 (overall survival, OS)。本研究经广州医科大学附属惠州医院/惠州市第三人民医院伦理委员会审批通过 (伦理编号: 2024-KY-029-01)。结果: 2024 年 6—9 月共入组 7 例患者 (男性 3 例, 女性 4 例, 中位年龄 57 岁), 包括非小细胞肺癌 6 例和乳腺癌 1 例。所有患者的脑脊液 (cerebrospinal fluid, CSF) 细胞学检查结果均为阳性。6 例存在 LM 相关神经功能障碍。5 例存在 LM 相关影像学异常。6 例完成诱导及巩固治疗并接受维持治疗。1 例因细菌性脑膜炎未完成巩固期最后 1 次 PD-1 抑制剂鞘内给药, 感染控制后接受维持治疗。总不良反应发生率为 100% (7/7), 包括骨髓抑制 7 例 (100.00%)、转氨酶升高 3 例 (42.86%)、乏力 2 例 (28.57%) 和甲状腺功能减退 1 例 (14.29%)。其中 3 级不良反应发生率为 42.86% (3/7), 全部为骨髓抑制。免疫相关不良反应 (immune-related adverse event, irAE) 发生率为 14.29% (1/7), 为 II 级甲状腺功能减退。未见剂量限制毒性 (dose-limiting toxicity, DLT) 发生, 推荐剂量为 PD-1 抑制剂 40 mg 联合培美曲塞 15 mg。3 例患者神经功能改善, 1 例 CSF 细胞学检查结果转阴, 2 例影像学缓解。根据神经肿瘤疗效评估 (response assessment in neuro-oncology, RANO) 标准, CRR 为 57.14% (4/7), DCR 为 100% (7/7)。3 例出现远隔效应, 分别表现为脑转移灶、原发肺病灶及纵隔淋巴结退缩。截至 2025 年 4 月 10 日, 1 例死亡, 中位随访时间为 7.7 (5.9~9.3) 个月。中位 OS 未达到。6 个月 OS 率为 85.71%。结论: 鞘内注射培美曲塞联合 PD-1 抑制剂治疗非小细胞肺癌等实体瘤 LM 患者显示出良好的安全性和可行性, 并且具有潜在的临床疗效。

[关键词] 实体瘤; 脑膜转移; 鞘内注射; 抗程序性死亡蛋白-1; 培美曲塞; I 期临床研究

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[**Abstract**] **Background and purpose:** Intrathecal chemotherapy is one of the mainstay treatment options for leptomeningeal metastases (LM) from solid tumors. A previous phase I study demonstrated the safety and potential efficacy of intrathecal anti-programmed death receptor 1 (anti-PD-1) for LM from melanoma. The synergistic efficacy of systemic chemotherapy combined with anti-PD-1 has been widely known. This study aimed to evaluate the safety and feasibility of intrathecal chemotherapy (pemetrexed) and anti-PD-1 (toripalimab) for LM patients from solid tumors. **Methods:** The subjects were patients with LM from solid tumors who were treated at Affiliated Huizhou Hospital of Guangzhou Medical University/Third People's Hospital of Huizhou City. A 3+3 dose de-escalation strategy was implemented to determine the recommended dose with an initial dose of PD-1 inhibitor (toripalimab) 40 mg and pemetrexed 15 mg. Pemetrexed was administered twice weekly for the initial 2 weeks of induction therapy, once weekly for the subsequent 4 weeks of consolidation therapy, and once monthly during maintenance therapy. PD-1 inhibitor was initiated at the 4th administration of pemetrexed, administered every 2 weeks for 6 weeks; subsequently, responders continued monthly maintenance therapy alongside pemetrexed. The primary objective was to assess safety based on adverse events and the recommended dose. All participants were observed to investigate the clinical response rate (CRR), disease control rate (DCR) and overall survival (OS). This study was approved by the ethics committee of Affiliated Huizhou Hospital of Guangzhou Medical University/Third People's Hospital of Huizhou City (ethics number: 2024-KY-029-01). **Results:** Seven patients (male: 3, female: 4, median age: 57 years) were enrolled between June and September 2024, including non-small cell lung cancer (6) and breast cancer (1). All patients presented with positive cerebrospinal fluid (CSF) cytology. Six patients presented LM-related neurological dysfunction. Five patients showed LM-related neuroimaging findings. Six patients completed the induction and consolidation therapy, and subsequently received maintenance therapy. One patient, due to bacterial meningitis, did not complete the final administration of toripalimab during consolidation therapy, and maintenance therapy was administered after infection control. Adverse events rate was 100% (7/7), including myelosuppression (100.00%, $n=7$), elevation of hepatic aminotransferases (42.86%, $n=3$), fatigue (28.57%, $n=2$) and hypothyroidism (14.29%, $n=1$). Three (42.86%) patients had grade 3 adverse events (myelosuppression). The immune-related adverse event (irAE) rate was 14.29%, manifested as hypothyroidism (Grade 2). No dose-limiting toxicity (DLT) was observed. Thus, no de-escalation was applied. The recommended dose was determined to be PD-1 inhibitor 40 mg in combination with pemetrexed 15 mg. Three patients showed improved neurological dysfunction, 1 with CSF cytological response, and 2 with neuroimaging improvement. CRR was 57.14% (4/7) by response assessment in neuro-oncology (RANO) proposal criteria. DCR was 100% (7/7). Three patients exhibited abscopal effects with regression of brain metastasis lesions, primary lung lesion and mediastinal lymph nodes, respectively. As of April 10, 2025, 1 patient died. The median follow-up time was 7.7 (5.9-9.3) months. The median OS was not reached with a 6-month OS rate of 85.71%. **Conclusion:** The combination therapy of intrathecal pemetrexed and a PD-1 inhibitor was well-tolerated and feasible, while also exhibiting potential clinical efficacy in treating LM from solid tumors including non-small cell lung cancer.

[**Key words**] Solid tumors; Leptomeningeal metastases; Intrathecal therapy; Anti-programmed death-1; Pemetrexed; Phase I study

实体瘤脑膜转移 (leptomeningeal metastases, LM) 是指肿瘤细胞通过侵入蛛网膜下腔并播散增殖, 造成中枢神经系统弥漫受累。5%~10%的肿瘤患者会发生LM^[1]。鞘内化疗是LM的主要治疗手段之一。培美曲塞是新型鞘内注射化疗药物, 被证实用于鞘内注射化疗安全有效^[2]。

近年来, 包括程序性死亡蛋白-1 (programmed death-1, PD-1) 抑制剂在内的免疫治疗在全身各种实体瘤中发挥出显著的抗肿瘤作用^[3-5]。有临床研究^[6]探索了静脉注射免疫药物治疗实体瘤LM的疗效及安全性, 采用帕博利珠单抗系统治疗的研究结果显示, 最佳疗效仅为维持疾病稳定, 未见明确有效的病例, 3

个月总生存 (overall survival, OS) 率为60%, 中位OS仅3.6个月。另一项相似的研究^[7]同样采用帕博利珠单抗, 结果显示, 颅内客观缓解率 (objective response rate, ORR) 为15.6%, 中位OS为4.9个月。伊匹木联合纳武单抗治疗LM的研究^[8]结果显示, 颅内ORR为5.6%, 3个月OS率为44%, 中位OS为2.9个月。总的来说, 全身免疫治疗实体瘤LM效果不理想, 颅内ORR仅有0.0%~15.6%, 中位OS仅为2.9~4.9个月。造成疗效不佳的主要因素考虑为PD-1抑制剂是大分子蛋白质, 静脉给药时难以穿过血-脑屏障进入中枢神经系统发挥抗肿瘤作用^[9]。直接将PD-1抑制剂药物注入脑脊液 (cerebrospinal fluid,

CSF)中,可能获得更好的疗效。有I期临床研究^[10]纳入25例黑色素瘤LM患者,给予鞘内及静脉PD-1抑制剂(纳武利尤单抗)治疗,结果显示,单独鞘内注射PD-1抑制剂仅40%的患者出现1级不良反应,包括恶心、头晕及呕吐,鞘内及静脉联合的给药方式,主要不良反应为1/2级,鞘内PD-1抑制剂具有良好的安全性和耐受性,全部患者的中位OS为4.9个月,4例患者生存期达到1.4~2.7年,显示出显著生存获益。该研究提示鞘内PD-1抑制剂治疗LM安全可行,并具有潜在疗效。鞘内PD-1抑制剂治疗推荐剂量方案为50 mg,每2周1次。

肺癌、乳腺癌等实体瘤不同于黑色素瘤,多属于“冷肿瘤”,单纯免疫治疗有效率较低。因此,参考实体瘤临床普遍采用的化疗联合免疫治疗设计本研究,探索鞘内注射培美曲塞化疗联合PD-1抑制剂治疗实体瘤LM的安全性及可行性。

1 资料和方法

1.1 患者资料

自2024年6月开始从广州医科大学附属惠州医院/惠州市第三人民医院收治的患者中招募研究对象,纳入标准:①具有明确的CSF细胞学诊断为LM;同时,具有明确的组织病理学诊断的实体瘤,除外颅内生殖细胞瘤。②年龄21~75岁,性别不限;肝肾功能正常;血常规检查白细胞不低于 $4.0 \times 10^9/L$,血小板不低于 $100 \times 10^9/L$ 。③既往无严重神经系统疾病或病史,无严重恶病质状态。排除标准:①明显的神经系统衰竭的表现,包括严重脑病,影像学检查显示3度脑白质病变;昏迷及明显意识障碍。②严重且致命性中枢神经系统外肿瘤进展,且缺少有效治疗方案,预期生存期不足3个月;③具有艾滋病病史;急性或慢性乙肝病毒或丙肝病毒感染史;既往接受抗PD-1治疗时发生3级或3级以上免疫相关不良反应(immune-related adverse event, irAE);过去2年内患有严重的需要系统治疗的自身免疫性疾病。本研究经广州医科大学附属惠州医院/惠州市第三人民医院伦理委员会审批通过(伦理编号:2024-KY-029-01),所有患者在筛选前均签署知情同意书。本研究在clinicaltrials.gov(<https://register.clinicaltrials.gov>)中注册,注册号为NCT06462222。

1.2 试验设计

本研究为开放性、前瞻性、单臂、I期临床研究。研究药物为PD-1抑制剂(特瑞普利单抗,

上海君实生物医药科技股份有限公司)和培美曲塞二钠(美国Eli Lilly公司)。采用经Ommaya囊脑室内给药或经腰穿给药。初始给药剂量为PD-1抑制剂单抗40 mg及培美曲塞二钠15 mg。培美曲塞诱导期给药为2次/周,连续2周;巩固治疗为1次/周,连续4周;治疗有效的患者接受每个月1次维持治疗。PD-1抑制剂给药从第4次培美曲塞给药开始,每2周1次,连续6周;随后对治疗有效的患者,与培美曲塞同时给予每个月1次维持治疗。患者持续治疗直至出现疾病进展或死亡。治疗期间补充维生素B12(1 mg肌肉注射,每周1次)及叶酸(0.4 mg口服,每天1次)。随访时间不少于6个月。剂量限制毒性(dose-limiting toxicity, DLT)规定为:①3级或3级以上中枢神经系统不良反应;②4级irAE或3级irAE经治疗后未缓解至 ≤ 2 级;③血液学毒性包括4级中性粒细胞减少持续 ≥ 7 d或3级伴发热,4级血小板减少或3级伴出血,因血液学毒性导致下1个周期延迟 > 14 d;④其他任何4级或4级以上不良反应。评估DLT的时间为第1次治疗开始后的6个月内。采用剂量递减策,首先纳入6例患者,如发生 $DLT \leq 1$ 例,则为推荐给药剂量。如 $DLT > 1$ 例,根据不良反应情况,调整培美曲塞为10 mg,或PD-1抑制剂降低为30 mg,如果再次发生DLT,再次降低给药剂量。

1.3 研究终点

主要研究终点是PD-1单抗联合培美曲塞二钠的安全性,根据不良事件通用术语标准(Common Terminology Criteria for Adverse Events, CTCAE)5.0版进行分级。次要研究终点包括临床有效率(clinical response rate, CRR)、疾病控制率(disease control rate, DCR)和OS,治疗反应评价采用神经肿瘤疗效评估(response assessment in neuro-oncology, RANO)标准。神经功能改善参照RANO标准,定义为体征评分改善2~3分。CRR为有效人数占总人数的比例,DCR为有效及稳定人数占总人数的比例,OS定义为从第1次鞘内注射开始直至患者死亡或最后1次随访的时间。以院内复诊及电话的方式随访,随访内容包括患者的症状、体征、影像学检查结果、CSF结果及其他一般情况等。末次随访时间为2025年4月10日。

1.4 统计学处理

研究采用意向性治疗分析,所有指标均纳入分析。在所有至少接受过1次PD-1单抗联合培美曲塞治疗的患者中评估安全性。在诱导及巩固期

完成后进行第1次疗效评估, 后续每2个月1次评估, 基于最佳疗效计算CRR和DCR。

2 结 果

2.1 基本特征

2024年6—9月共入组7例患者(图1), 其中男性3例, 女性4例, 中位年龄57岁, 包括6例非小细胞肺癌和1例乳腺癌。所有患者CSF细胞学检查结果均为阳性, 6例存在LM相关神经功能障碍, 5例显示LM相关影像学异常。患者的症状多表现为头晕、头痛、恶心或呕吐。患者特征见表1。

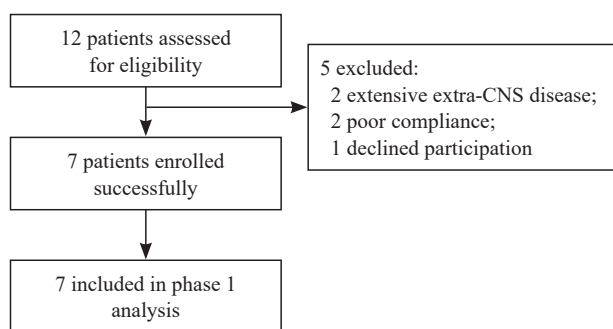


图1 患者纳入和排除标准流程图

Fig. 1 Flowchart of patients inclusion and exclusion criteria

表1 患者基本特征及治疗情况

Tab. 1 Basic characteristics of patients and treatment details

No.	Gender	Age/year	Primary tumor type	Molecular Characteristic	CPS/TPS	Prior systematic treatment	Extraneural lesions at enrollment
P1	Female	41	Breast cancer	HER2 3+	NA	Chemotherapy, targeted therapy	Stable
P2	Female	53	Lung adenocarcinoma	21L858R	NA	Gefitinib, almonertinib, chemotherapy	Stable
P3	Male	59	Lung adenocarcinoma	KRAS Exon-2G12C	3%	Sotorasib	Stable
P4	Male	58	Lung adenocarcinoma	21 L858R	0%	Chemotherapy, icotinib, osimertinib (80, 160 mg), furmonertinib (160 mg)	Stable
P5	Female	60	Lung adenocarcinoma	21L858R	0%	Icotinib, erlotinib, osimertinib (80 mg), chemotherapy	Stable
P6	Male	62	Lung adenocarcinoma	21L858R	98%	Chemotherapy, gefitinib, almonertinib (110 mg), furmonertinib (80 mg)	Stable
P7	Female	54	Lung adenocarcinoma	21L858R	0%	Furmonertinib (80, 160 mg), chemotherapy, osimertinib (160 mg)	Stable

No.	KPS	Symptom	Sign	Imaging	Cytology	Previous treatment related to LM
P1	70	Headache	Hypoesthesia, abnormal gait	Linear and nodular enhancement	Positive	none
P2	50	Dizziness, headache, vomiting	Bilateral blindness	Linear and nodular enhancement	Positive	none
P3	70	Dizziness, headache	Decreased hearing, decreased vision	Linear enhancement	Positive	none
P4	70	Dizziness	Hypoesthesia, decreased hearing, decreased muscle strength	Linear enhancement	Positive	none
P5	70	Headache, nausea, vomiting	none	none	Positive	none
P6	60	Dizziness, headache	Hypoesthesia, abnormal gait, decreased muscle strength	Linear and nodular enhancement	Positive	Intrathecal methotrexate 10 times
P7	60	Dizziness, headache, nausea, vomiting	Blurred vision, decreased muscle strength	none	Positive	none

KPS: Karnofsky performance status; CPS: Combined positive score; TPS: Tumor proportion score; NA: Not available.

所有患者入组前均接受过全身系统治疗，其中全身化疗5例，靶向治疗7例。5例表皮生长因子受体（epidermal growth factor receptor, *EGFR*）突变患者接受了酪氨酸激酶抑制剂（tyrosine kinase inhibitor, TKI）治疗，4例患者口服过一代TKI治疗，5例患者接受了三代TKI治疗。1例*KRAS*突变患者接受了索脱拉西布治疗。1例人表皮生长因子受体2（human epidermal growth factor receptor 2, *HER2*）阳性乳腺癌患者接受了化疗、抗体药物偶联物（antibody drug conjugate, ADC）及*HER2*靶向药物治疗。其中6例患者初始诊断LM，1例患者入组前接受鞘内氨甲蝶呤化疗。所有患者纳入时，中枢神经系统外肿瘤病灶稳定。

2.2 治疗情况

全部患者完成诱导治疗，1例因细菌性脑膜炎未完成巩固期最后1次鞘内给药治疗（P6），因此额外纳入1例患者。6例患者完成诱导及巩固治疗。全部7例患者进入维持治疗。截至2025年4月10日，全部患者接受培美曲塞鞘内化疗12~15次，中位化疗次数13次，共92次。接受鞘内PD-1抑制剂治疗4~10次，中位免疫治疗7次，共51次。仅1例患者（P6）因诱导治疗后发生3级血小板下降，治疗延后13 d。P1患者接受同步小脑脑膜病灶及部分脑转移灶放疗；P3、P5及P6患者接受局部椎管放疗。所有患者在研究过程中，继续应用原有全身系统治疗方案。P1继续口服拉帕替尼治疗。P2、P4、P5、P6、P7患者应用双倍剂量的三代TKI，包括奥西替尼、阿美替尼或伏美替尼。P3患者继续口服索脱拉西布。

2.3 不良反应发生情况

未观察到DLT。推荐安全剂量为PD-1单抗40 mg联合培美曲塞15 mg。不良反应发生率为100%（7/7），包括骨髓抑制7例（100.00%）、转氨酶升高3例（42.86%）、乏力2例（28.57%）和甲状腺功能减退1例（14.29%）。3例出现3级不良反应，均为骨髓抑制，2例为白细胞下降，1例为血小板下降。化疗相关不良反应（chemotherapy-related adverse event, crAE）集中于诱导及巩固期，主要为骨髓抑制及转氨酶升高，经过对症治疗后1~2周内恢复。仅1例患者出现irAE，为2级甲状腺功能减退，发生在维持期。经过左甲状腺素片替代治疗后甲状腺功能恢复正常。治疗相关不良反应详见表2。

2.4 疗效评价

根据RANO标准，4例患者评估有效，CRR达57.14%，DCR为100%（7/7）。4例患者神经功能改善（P1、P4、P6、P7），1例CSF细胞学转阴（P1），2例影像学缓解（P1、P6），P1放疗区域及非放疗区域的病灶均缩小，P6仅放疗区域病灶缩小。6例患者症状缓解（P1、P2、P4、P5、P6、P7）。

P1患者治疗后可见病灶明显缩小，大部分消失，并且在照射野外的病灶也明显缩小甚至消失（图2），考虑发生了远隔效应。P3入组后继续应用原系统治疗方案，在诱导及巩固期治疗完成后复查，可见纵隔淋巴结较前明显缩小，部分消失（图3）。P5接受鞘内化疗联合免疫治疗后肺原发病灶缩小（图4）。所有患者诱导及巩固治疗后疗效评价见表3。

表2 治疗相关不良反应

Tab. 2 Treatment-related adverse events during therapy

No.	Timepoint of adverse events occurrence	Adverse events and grading	Treatment
P1	After the 3rd IP; After the 6th IP; After the 11th IP	Grade 3 hematologic toxicity; Grade 1 EHA; Grade 2 hypothyroidism	Leukocyte and platelet elevation therapy; Hepatoprotective therapy; Levothyroxine tablet replacement therapy
P2	After the 3rd IP; After the 3rd IP	Grade 1 hematologic toxicity; Grade 1 EHA	Leukocyte elevation therapy; Hepatoprotective therapy
P3	After the 6th IP	Grade 1 hematologic toxicity	Iron supplementation
P4	After the 6th IP	Grade 1 hematologic toxicity	Leukocyte elevation therapy
P5	After the 4th IP; After the 4th IP; After the 7th IP	Grade 3 hematologic toxicity; Grade 2 fatigue; Grade 1 EHA	Leukocyte and platelet elevation therapy; None; Hepatoprotective therapy
P6	After the 4th IP; After the 7th IP	Grade 3 hematologic toxicity; Bacterial meningitis	Leukocyte and platelet elevation therapy; Suspend intrathecal injection, initiate antibacterial therapy
P7	After the 4th IP; After the 6th IP	Grade 2 fatigue; Grade 1 hematologic toxicity	None; Iron supplementation

EHA: Elevation of hepatic aminotransferase.

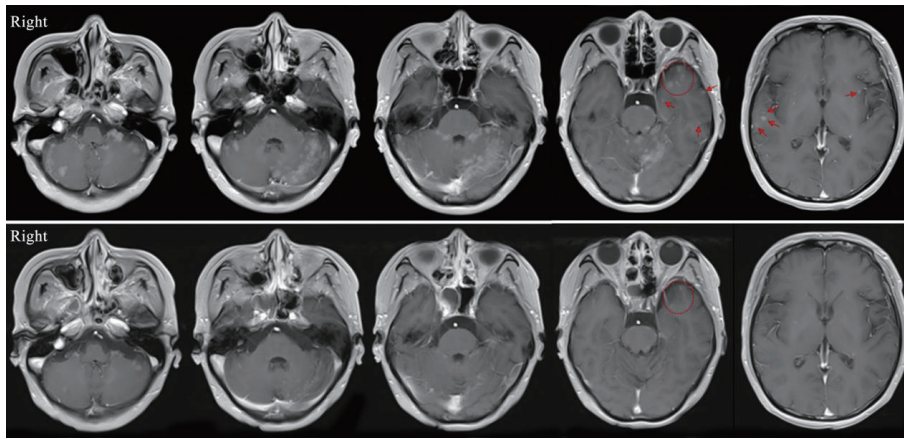


图2 第1例患者治疗前后脑磁共振成像对比

Fig. 2 Comparison of brain magnetic resonance imaging before and after treatment in the first patient

Red markings indicate lesions that have regressed or disappeared outside the irradiation field.

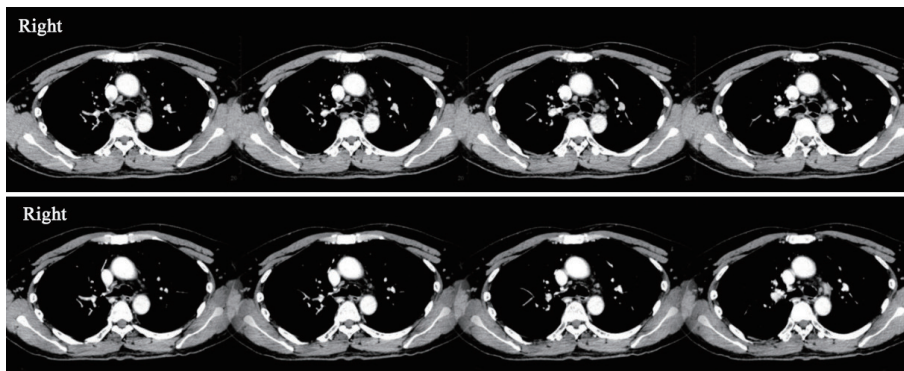


图3 第3例患者治疗前后纵隔淋巴结对比

Fig. 3 Comparison of mediastinal lymph nodes before and after treatment in the third patient

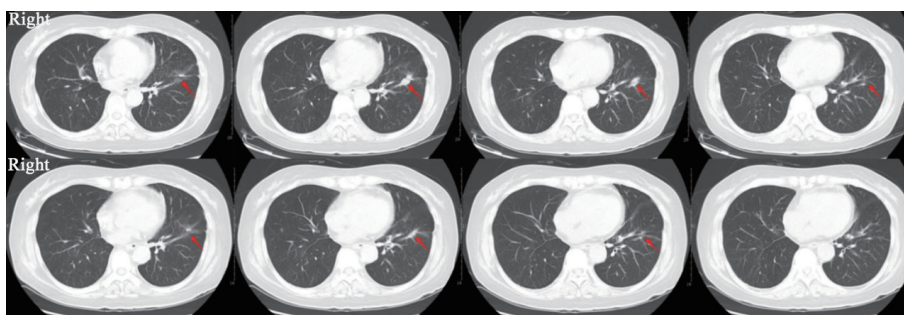


图4 第5例患者治疗前后肺部原发灶对比

Fig. 4 Comparison of primary lung lesions before and after treatment in the fifth patient

The red arrow indicates the regressed primary lung lesion.

2.5 随访及后续治疗

7例患者继续接受维持期鞘内注射, P6中枢感染控制后在维持期第4次恢复鞘内免疫治疗。1例患者LM进展, 接受挽救性全脑放疗。2例更换系统治疗方案, 5例继续应用原治疗方案。1例患者死于肿瘤并发症。截至2025年4月10日, 中位随访时间为7.7 (5.9~9.3) 个月, 中位OS未达到, 6个月OS率为85.71%, 1例死亡。

3 讨论

本研究的给药方案参考了培美曲塞鞘内化疗, 以及PD-1抑制剂鞘内给药的相关研究。既

往研究^[11]显示, 在补充叶酸及维生素B12条件下, 推荐培美曲塞单次给药剂量为15 mg。PD-1抑制剂鞘内给药的临床前研究^[10]发现, 小鼠体内鞘内注射PD-1抑制剂剂量为13 μg时具备安全性, 根据CSF体积的差异, 该剂量相当于人体的50 mg。临床爬坡研究^[10]推荐, 鞘内PD-1抑制剂给药方案为每次50 mg, 每2周1次。本研究同时应用鞘内化疗及鞘内PD-1抑制剂治疗, 考虑到化疗联合免疫治疗的潜在不良反应, 我们将PD-1抑制剂减量至单次40 mg。

鞘内注射PD-1抑制剂单抗联合培美曲塞具有较好的耐受性及安全性。主要不良反应与鞘内

表3 诱导及巩固治疗后疗效评价

Tab. 3 Efficacy evaluation after induction and consolidation therapy

No.	Number of intrathecal injections		Concurrent treatment during trial participation	CSF cytological		Symptom	Imaging		Signs	Outcome	Survival time/month	Follow-up status
	IT-P	IT-PD-1		Before treatment	after treatment		NRT	RT				
P1	15	10	Local LM and BM RT	+	-	Improved	Improved	Improved	Improved	Response	9.3	Under follow-up
P2	12	7	none	+	+	Improved	Stable	NA	Stable	Stable	5.9	Died
P3	14	9	Partial spine RT	+	+	Stable	Stable	Stable	Stable	Stable	8.1	Under follow-up
P4	12	7	None	+	+	Improved	Stable	NA	Improved	Response	7.7	Under follow-up
P5	13	7	Partial spine RT	+	+	Improved	Stable	Stable	Stable	Stable	7.3	Under follow-up
P6	12	4	Partial spine RT	+	+	Improved	Stable	Improved	Stable	Response*	8.3	Under follow-up
P7	14	7	None	+	+	Improved	Stable	NA	Improved	Response	6.3	Under follow-up

IT-P: Intrathecal pemetrexed; IT-PD-1: Intrathecal PD-1 inhibitor; BM: Brain metastasis; RT: Assessment of effects in the irradiated area; NRT: Assessment of effects in the non-irradiated area. *: The response is only due to the effect of radiotherapy; NA: Not applicable.

化疗相关，主要为骨髓抑制及转氨酶升高，这与既往研究^[2, 12-13]结果一致。3级不良反应为骨髓抑制，且经过对症治疗后不良反应恢复。本研究中，仅1例患者发生轻度irAE，低于PD-1抑制剂全身给药治疗LM的相关临床研究^[6-8]结果。此外，既往I期研究^[10]显示，单独鞘内注射PD-1（纳武利尤单抗）抑制剂未出现3级及3级以上不良反应，与本研究结果一致，说明鞘内化疗联合免疫治疗不会提高治疗相关不良反应的发生率。既往研究鞘内注射纳武利尤单抗的常见不良反应包括恶心、头晕和呕吐。而本研究鞘内注射特瑞普利单抗的irAE为甲减。甲减是PD-1抑制剂单抗静脉给药常见的不良反应，在纳武利尤单抗中的发生率为1%~10%，在特瑞普利单抗中的发生率大于10%。这可能与不同PD-1抑制剂药物特点相关。本研究中，患者甲减发生在维持治疗期间，提示irAE具有迟发性，值得临床关注。

既往单独鞘内注射培美曲塞15 mg治疗实体瘤LM的CRR为40%^[14]。本研究CRR为57.14%，高于单纯鞘内注射培美曲塞治疗，提示鞘内化疗联合免疫治疗可能具有治疗优势。此外，多例患者出现远隔效应，提示鞘内化疗联合免疫治疗的潜在优势。另一个值得注意的现象是1例患者CSF细胞学检查结果持续转阴，截至末次随访仍持续阴性。这不同于既往单纯鞘内化疗，CSF细胞学检查结果转阴常发生在密集鞘内注射后，随

后进入每个月1次的维持治疗后，往往很快转为阳性，可见免疫治疗可能出现持续的抗肿瘤拖尾效应。

本研究中有5例（71.43%）患者具有EGFR突变，对于这部分患者，三代EGFR-TKI药物是重要的治疗手段^[15-18]，本研究中所有EGFR突变患者均为应用三代EGFR-TKI治疗后发生LM。经过鞘内化疗联合免疫治疗，3例患者评估有效，提示鞘内化疗联合免疫治疗是三代EGFR-TKI治疗后LM患者潜在的有效治疗方法。

本研究中，有3例患者发生了远隔效应。P1治疗后在照射野外的脑转移灶明显缩小甚至消失，P3及P5鞘内化疗联合免疫治疗后出现了系统病灶缩小。远隔效应最初发现于应用放疗的患者中，是指接受局部抗肿瘤治疗后，未接受治疗的肿瘤病灶也出现退缩的现象。研究^[19-22]表明，远隔效应的发生是由免疫介导的，且免疫治疗可以使这种效应更加显著。放疗导致细胞死亡后释放肿瘤相关抗原，进一步活化适应性免疫，从而特异性识别并杀伤射野外肿瘤细胞，免疫治疗可以协同增效。鞘内化疗联合免疫治疗，具有增强远隔效应发生的理论基础。

然而本研究为I期临床研究，存在一定局限性，入组病例数有限，仅纳入了非小细胞肺癌及乳腺癌患者，更多的相关不良反应需要在更广泛的人群中进一步临床观察。在后续的II期研究

中, 我们将扩大样本量, 进一步探索在广泛实体瘤患者中给药的安全性及有效性。

综上所述, 鞘内注射培美曲塞联合PD-1抑制剂治疗显示出良好的安全性和可行性, 并且具有潜在的临床疗效。

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