一线含纳武利尤单抗联合治疗脑膜转移癌的真实世界随访观察

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【摘要】 目的 观察一线使用含纳武利尤单抗的方案联合治疗脑膜转移癌(meningeal carcinomatosis,MC)的临床效果。**方法** 收集2019年4月1日至10月1日在复旦大学附属华山医院肿瘤科经脑脊液(cerebrospinal fluid,CSF)细胞学确诊的4例MC患者,一线给予含纳武利尤单抗的联合治疗方案,总结CSF肿瘤负荷(tumor burden,TB)、软脑膜强化、脑积水和中枢神经系统(central nervous system,CNS)症状等临床特征,分析其与近期疗效和远期疗效的相关性。**结果** 原发灶包括2例多线靶向治疗后失败的肺癌、1例胆管细胞癌和1例原发灶不明。2例患者CSF TB低,2例CSF TB高且合并脑积水行CSF分流术挽救治疗。纳武利尤单抗联合化疗和/或抗血管生成药物治疗中位疗程5.5(5~33)个,截至2022年5月1日末次随访,4位患者中位随访610(153~947)天,1例无进展,2例仍存活,所有患者均未观察到CNS毒性。治疗后首次评估中位时间为46(37~65)天,4位患者CNS症状均缓解,3例CSF TB下降,CNS无进展生存期(progression free survival,PFS)分别为108天、134天和>944天;1例CSF TB无变化,PFS仅76天。CSF TB低相较于高的患者总生存期(overall survival,OS)更长(>947天和>944天 *vs.* 153天和275天)。**结论** 一线含纳武利尤单抗联合治疗MC患者,CSF TB短期内下降可能预示CNS PFS更长,CSF TB低可能预示OS更长,其疗效值得进一步验证。

【关键词】 脑膜转移癌(MC); 纳武利尤单抗; 脑脊液肿瘤负荷

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First line nivolumab combined regimen for meningeal carcinomatosis: a real-world follow-up observation

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【Abstract】 Objective To observe the efficacy of first line regimen containing nivolumab in the treatment of meningeal carcinomatosis (MC). **Methods** Four patients diagnosed by cerebrospinal fluid (CSF) cytology in the Department of Oncology, Huashan Hospital, Fudan University from Apr 1 to Oct 1 2019 were enrolled. They all received nivolumab combined regimen in the first line. The clinical characteristics of CSF tumor burden (TB), meningeal enhancement, hydrocephalus, and central nervous system (CNS) symptoms were summarized, and their relevance with short-term and long-term efficacy was analyzed. **Results** The primary tumor included two cases of lung cancer treated by multi-line targeted treatment, one case of cholangiocarcinoma, and one case of unknown primary tumor. Two patients had low CSF TB. The other two patients with high CSF TB complicated with hydrocephalus were treated with CSF shunt first. The median course of treatment with nivolumab combined with chemotherapy and/or antiangiogenic drugs was 5.5 (5-33). Until the final follow-up on May 1, 2022, the median follow-up was

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610 (153-947) days, one patient had no progression, two were still alive, all patients had no CNS side effect. The CNS symptoms of all patients were relieved on the first assessment after treatment, and the median follow-up was 46 (37-65) days. Three patients had decreased CSF TB, and their CNS progression free survival (PFS) were 108, 134 and >944 days, respectively. One patient had no change in CSF TB, and his PFS was only 76 days. Patients with low CSF TB had longer overall survival (OS) than those with high CSF TB (>947 days and >944 days *vs.* 153 days and 275 days). **Conclusion** In the first line treatment of MC patients with nivolumab, the decrease of CSF TB in the short term may indicate a longer CNS PFS, and the low CSF TB may indicate a longer OS. The efficacy is worthy of further verification.

【Key words】 meningeal carcinomatosis (MC); nivolumab; cerebrospinal fluid tumor burden

脑膜转移癌又名脑膜癌病(meningeal carcinomatosis，MC)，定义为肿瘤细胞转移至软脑膜并随着脑脊液(cerebrospinal fluid，CSF)在蛛网膜腔播散。8%的实体瘤患者通过尸检发现，MC有时可成为肿瘤首发转移部位[1]，预后极差，既往中位总生存期(overall survival，OS)仅约3个月[2]。随着多学科治疗对颅外转移肿瘤的有效控制及OS的延长，MC越来越多地被发现，需要引起关注。

免疫检查点抑制剂中的纳武利尤单抗最早在国内获批，近年来先后用于实体肿瘤颅外复发转移，例如肺癌和胃癌等[3-4]，初步发现非小细胞肺癌脑转移患者可从中获益[5]。但是MC患者既往被大多数临床试验严格限定甚至排除入组[6]，因此该方面的数据需要真实世界研究来补充。我们回顾性分析了纳武利尤单抗治疗MC患者的治疗效果，从真实世界长期随访观察中找出共性，分享经验。

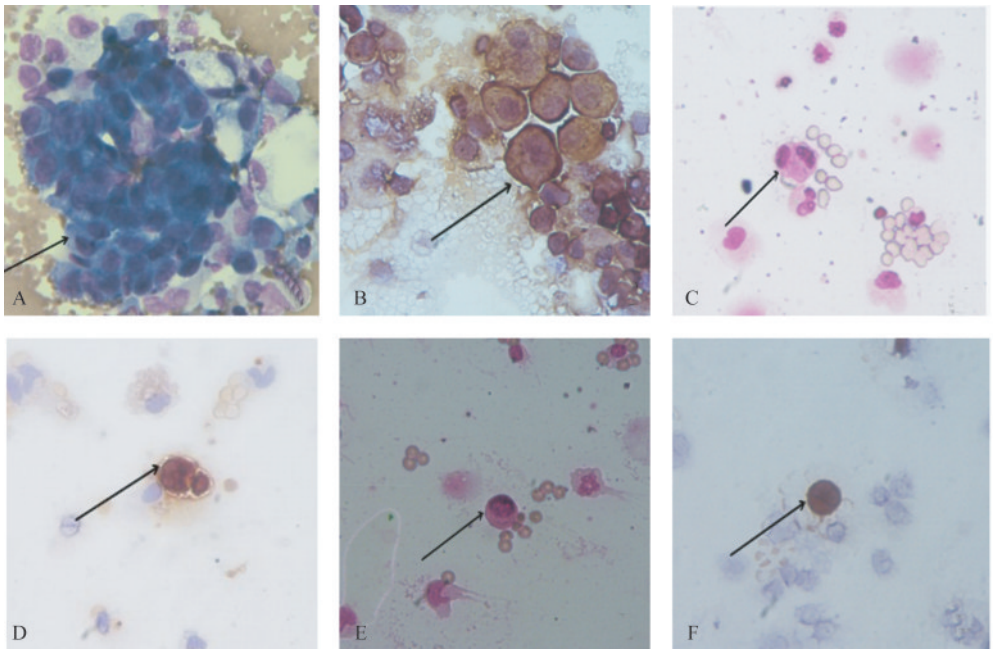
资料和方法

资料来源 收集2019年4月1日至10月1日复旦大学附属华山医院肿瘤科连续接受纳武利尤单抗治疗的4例MC患者，MC确诊定义为CSF中找到肿瘤细胞。所有患者均签署了诊疗知情同意书，回顾性收集临床资料经过我院伦理委员会批准(批准号：KY2019-366)。CSF经腰穿获取，离心涂片，用Wright染色和CK7免疫组化标记后于显微镜下找到典型的肿瘤细胞，根据所有有核细胞中肿瘤细胞的百分比评估CSF肿瘤负荷(tumor burden，TB)(图1)：≥10%表示大量，被认为CSF TB高；1%～10%代表少量；<1%被描述为偶见，被认为CSF TB低。脑3.0磁共振(magnetic resonance，MR)增强≤5 mm扫描检查有无软脑膜强化、脑室扩大和脑实质转移。纳武利尤单抗(美国百时美施贵宝公司)每2周静脉滴注3 mg/kg，联合化疗和/或抗血管生成治疗等。

分析参数 软脑膜转移为不可测量病灶，目前无专门的疗效评估标准，因此我们评估治疗反应采用以下方法和指标：CSF细胞学评估TB变化、脑MR增强观察软脑膜强化是否加重和中枢神经系统(central nervous system，CNS)症状是否缓解[7-9]。随访截止日期为2022年5月1日，随访时间、CNS无进展生存期(progression free survival，PFS)和OS分别定义为首次纳武利尤单抗治疗至随访截止、至CNS症状明显进展和至死亡的间隔时间。

结　　果

患者的一般情况和临床特征 4例患者的临床特征、治疗方案及对治疗的反应见表1。患者男性和女性各2例，平均55(48～62)岁，原发肿瘤包括肺腺癌2例、胆管癌和原发灶不明(胃癌可能大)各1例。肺腺癌患者均为EGFR突变但是多线靶向药物治疗失败。所有患者CSF均找到肿瘤细胞并确诊为MC，脑MR增强显示仅患者2存在软脑膜强化同时CSF发现少量肿瘤细胞，患者3和患者4无软脑膜强化而是存在脑室扩大同时CSF均发现大量肿瘤细胞，接受脑室-腹腔CSF分流术挽救治疗了脑积水，为后续纳武利尤单抗等药物治疗赢得了机会。所有患者均存在明显的头痛、头晕或呕吐症状，美国东部肿瘤协作组体力状况评分(Eastern Cooperative Oncology Group performance status，ECOG PS)都很差(≥3分)，接受了纳武利尤单抗治疗的中位疗程为5.5 (5～33)个，联合药物包括化疗和(或)抗血管生成药物：顺铂、白蛋白紫杉醇、卡



A and B: A large number of tumor cells are found in cerebrospinal fluid(black arrow), accounting for about 90% of all nucleated cells (×400). A: Wright staining;B:CK7(+)by immuno-histochemical staining. C and D: A few of tumor cells are found in cerebrospinal fluid(black arrow), accounting for about 6% of all nucleated cells (×400). C: Wright staining; D:CK7(+)by immuno-histochemical staining.E and F: Tumor cells are occasionally visible in cerebrospinal fluid(black arrow), accounting for <1% of all nucleated cells (×400). E: Wright staining; F:CK7(+) by immuno-histochemical staining.

图1 脑脊液细胞学检查显示脑脊液中肿瘤细胞大量、少量和偶见图

Fig 1 Cytological examination of cerebrospinal fluid showed the images of a large number of tumor cells, a few tumor cells and occasionally visible tumor cells in cerebrospinal fluid

培他滨、贝伐珠单抗以及安罗替尼。

治疗后首次评估 首次评估的中位时间为46(37~65)天,4例患者CNS症状全部得到缓解。患者2脑MR增强提示软脑膜强化未缓解,并且CSF的肿瘤细胞数量级别也无明显变化,CNS PFS最短仅76天;其余3例患者初次评估CSF肿瘤细胞均下降:患者4和患者3由大量减为少量,患者1由偶见变为阴性至末次随访仍未进展,CNS PFS分别为108、134和>944天,均超过3个月。

长期随访结果 末次随访至2022年5月1日,4例患者中位随访610(153~947)天,随访过程中均未观察到CNS不良反应,无明显骨髓抑制和肝肾功能损害,仅1例患者有轻度皮疹,对症治疗后完全缓解。患者4和患者3最终因脑膜转移病情进展而死亡,OS分别为153和275天。患者2的CSF肿瘤细胞为少量,接受纳武利尤单抗治疗后76天进展为梗阻性脑积水,接受脑室-腹腔CSF分流术后仍存活,OS>947天。患者1的CSF肿瘤细胞为偶见,接受纳武利尤单抗1年后逐渐延长治疗间期为每4周直至每8周1次,随访截止时脑膜转移仍未进展,OS>944天。

讨 论

CSF见到肿瘤细胞是MC诊断的金标准[10],CSF TB高低与脑MR增强是否发现软脑膜强化似乎无相关性,CSF中存在大量肿瘤细胞时并不一定会在脑MR增强图像中表现出脑膜异常强化,但是却容易发生脑膜粘连,导致交通性脑积水,表现为脑室扩大。因此,对于有肿瘤病史并且存在明显CNS症状的患者,尽管脑MR增强无明显脑膜强化,仍需积极行腰穿检查,即使肿瘤细胞暂时未找到也应密切随访,当发现脑室扩大时CSF涂片更容易找到肿瘤细胞。

本研究中纳武利尤单抗初始治疗时患者一般情况均较差,ECOG PS≥3分,但是与化疗药物和(或)抗血管生成药物联合治疗时并没有发现明显的不良反应,安全性良好,ECOG PS评分差系MC所致而并非受颅外肿瘤导致,故对于MC患者不要轻易放弃系统性药物治疗。本研究中4例患者纳武利尤单抗治疗后均未出现CNS不良反应,其中1例

表1 患者的临床特征、治疗方案及对治疗的反应

Tab 1 The clinical characteristics, treatment regimen and responses to treatment of patients

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Female	Male	Female	Male
Age (y)	62	48	53	47
Primary tumor	Cholangiocarcinoma	Unknown	Lung adenocarcinoma	Lung adenocarcinoma
Brain parenchymal metastasis before MC	No	No	Yes	No
Extracranial metastatic sites concurrent with MC	Cervical and abdominal LN	–	Lung, bone and neck LN	Lung, adrenal gland and axillary LN
ECOG PS	3	4	4	4
Before nivolumab treatment				
CNS Symptoms	Dizziness, unstable walking	Headache, vomiting	Headache, vomiting	Headache, dizziness, vomiting
Tumor cells in CSF	Occasionally visible	A few	A large number	A large number
Meningeal enhancement	No	Yes	No	No
Obstructive hydrocephalus	No	No	Yes	Yes
CSF shunt	NA	NA	+	+
The cycles of nivolumab	33	5	5	6
Combined drugs × cycles	Anlotinib × 2 after sequential Capecitabine × 2	Capecitabine + Cisplatin × 3	Paclitaxel-albumin + Cisplatin× 4	Paclitaxel-albumin + Cisplatin + Bevacizumab× 4
Time point of first evaluation (d)	37	46	46	65
After nivolumab treatment				
CNS symptoms remission	Yes	Yes	Yes	Yes
Tumor cells in CSF	Negative	A few	A few	A few
Meningeal enhancement	No	Yes	No	No
Side effect of CNS	No	No	No	No
Follow-up time (d)	944	947	275	153
CNS PFS (d)	＞944	76	134	108
Local therapy after CNS PD	No	CSF shunt	No	No
OS (d)	＞944	＞947	275	153

MC: Meningeal carcinomatosis; LN: Lymph node; CSF: Cerebrospinal fluid; ECOG PS: Eastern Cooperative Oncology Group performance status; CNS: Central nervous system; PFS: Progression free survival; PD: Progressive disease; OS: Overall survival. Anlotinib: 10 mg d1-14 q3w; Capecitabine: 1 g/m^2 d1-14 q3w; Cisplatin: 75 mg/m^2 d1 q3w; Paclitaxel-albumin 260 mg/m^2 d1 q3w; Bevacizumab: 7.5 mg/kg d1 q3w.

患者治疗长达33个疗程，耐受性良好，因此本研究从真实世界角度分享了安全性数据供临床参考。

在治疗后近期疗效评估方面，我们发现除了观察CNS症状是否缓解外，还要关注CSF TB是否下降。本研究中2个月内下降患者的CNS PFS超过3个月，而未下降的患者PFS相对较短，因此，患者CSF TB的下降与CNS PFS的关联值得进一步被关注。

对于远期疗效而言，本研究中CSF TB低相较于高的患者OS更长（＞947天和＞944天 *vs*. 153天和275天），似乎治疗前的TB越低预后越好。这与文献报道[11]CSF肿瘤细胞数量与死亡风险呈正相关相符。对于治疗前的TB高合并脑积水的患者或治疗后进展为脑积水的患者，脑室-腹腔CSF分流术对含纳武利尤单抗系统药物治疗的保驾护航非常重要，回顾性病例分析报道CSF分流术可以使90.3%患者的CNS症状得到快速缓解[12]，与未行CSF分流术的患者相比中位OS可延长（5.7个月 *vs*. 1.7个月）[13]。鉴于免疫检测点抑制剂对生存的改善更多体现在OS方面，因此，CSF分流术与纳武利尤单抗等药物的联合治疗对延长患者生存有重要的积极作用。前瞻性Ⅱ期临床研究报道[14]帕博利珠单抗单药治疗20例MC患者（17例乳腺癌、2例肺癌和1例卵巢癌），最长随访时间12.5个月，60%患者OS大于3个月。在既往以系统化疗药物和（或）放疗和（或）鞘注化疗的三板斧时代[10]，若原发肿瘤无有效的靶向药物，MC患者的OS通常不超过6个月[15]。本研究中所有患者OS均大于3个月，最长超过30个月，因此，我们认为一线含纳武利尤单抗的联合治疗可能改善MC患者的OS，需要随机对照研究的进一步证实。

通过本研究对真实世界数据的回顾性分析,我们总结出以下经验:CSF的TB初始评估和随访、脑积水的及时发现和含纳武利尤单抗的联合治疗可能是MC诊疗的关键要素。我们建议,确诊MC时需要对CSF的TB进行评估,明确有无合并脑积水,若有脑积水则需要积极行CSF分流术挽救治疗,若无脑积水可首选纳武利尤单抗联合化疗和或抗血管生成治疗;当出现CSF TB下降可能提示对治疗敏感,即使近期疗效不理想,CNS进展后若并发脑积水,仍可行CSF分流术挽救治疗。以上经验可能有助于MC患者尽可能延长生存期。

由于MC治疗非常棘手,治疗机会稍纵即逝,我们的回顾性分析病例数较少且存在异质性,希望来自真实世界的长期随访数据能为未来开展前瞻性临床研究提供借鉴,从而能进一步验证含纳武利尤单抗的联合治疗对MC患者的疗效。

作者贡献声明 初钊辉 数据采集,论文构思、撰写和修订。刘涛 数据采集,患者随访和图表修订。陈锟 脑脊液肿瘤细胞检验,数据量化和图片提供。詹琼,王玉 数据采集和患者随访。

利益冲突声明 所有作者均声明不存在利益冲突。

参 考 文 献

[1] ENTING RH. Leptomeningeal neoplasia: epidemiology, clinical presentation, CSF analysis and diagnostic imaging [J]. *Cancer Treat Res*, 2005, 125: 17-30.

[2] HYUN JW, JEONG IH, JOUNG A, *et al*. Leptomeningeal metastasis: clinical experience of 519 cases [J]. *Eur J Cancer*, 2016, 56: 107-114.

[3] VOKES EE, READY N, FELIP E, *et al*. Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases [J]. *Ann Oncol*, 2018, 29(4): 959-965.

[4] KANG YK, BOKU N, SATOH T, *et al*. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial [J]. *Lancet*, 2017, 390(10111): 2461-2471.

[5] GROSSI F, GENOVA C, CRINO L, *et al*. Real-life results from the overall population and key subgroups within the Italian cohort of nivolumab expanded access program in non-squamous non-small cell lung cancer [J]. *Eur J Cancer*, 2019, 123(12): 72-80.

[6] MCCOACH CE, BERGE EM, LU X, *et al*. A brief report of the status of central nervous system metastasis enrollment criteria for advanced non-small cell lung cancer clinical trials: a review of the clinical trials.gov trial registry [J]. *J Thorac Oncol*, 2016, 11(3): 407-413.

[7] CHAMBERLAIN M, JUNCK L, BRANDSMA D, *et al*. Leptomeningeal metastases: a RANO proposal for response criteria [J]. *Neuro Oncol*, 2017, 19(4): 484-492.

[8] LE RHUN E, DEVOS P, WELLER J, *et al*. Prognostic validation and clinical implications of the EANO ESMO classification of leptomeningeal metastasis from solid tumors [J]. *Neuro Oncol*, 2021, 23(7): 1100-1112.

[9] XU Y, HU M, ZHANG M, *et al*. Prospective study revealed prognostic significance of responses in leptomeningeal metastasis and clinical value of cerebrospinal fluid-based liquid biopsy [J]. *Lung Cancer*, 2018, 125(11): 142-149.

[10] LE RHUN E, WELLER M, BRANDSMA D, *et al*. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours [J]. *Ann Oncol*, 2017, 28 (suppl_4): iv84-iv99.

[11] NEVEL KS, DISTEFANO N, LIN X, *et al*. A retrospective, quantitative assessment of disease burden in patients with leptomeningeal metastases from non-small-cell lung cancer [J]. *Neuro Oncol*, 2020, 22(5): 675-683.

[12] MITSUYA K, NAKASU Y, HAYASHI N, *et al*. Palliative cerebrospinal fluid shunting for leptomeningeal metastasis-related hydrocephalus in patients with lung adenocarcinoma: a single-center retrospective study [J]. *PLoS One*, 2019, 14(1): e0210074.

[13] JUNG TY, CHUNG WK, OH IJ. The prognostic significance of surgically treated hydrocephalus in leptomeningeal metastases [J]. *Clin Neurol Neurosurg*, 2014, 119: 80-83.

[14] BRASTIANOS PK, LEE EQ, COHEN JV, *et al*. Single-arm, open-label phase 2 trial of pembrolizumab in patients with leptomeningeal carcinomatosis [J]. *Nat Med*, 2020, 26 (8): 1280-1284.

[15] 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 [J]. *Int J Cancer*, 2016, 139(8): 1864-1872.

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