



National Comprehensive
Cancer Network®

**2019美国NCCN非小细胞肺癌指南
(奥西替尼进展后的脑/脑膜转部分)**
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 5.2019 — June 7, 2019

NCCN.org

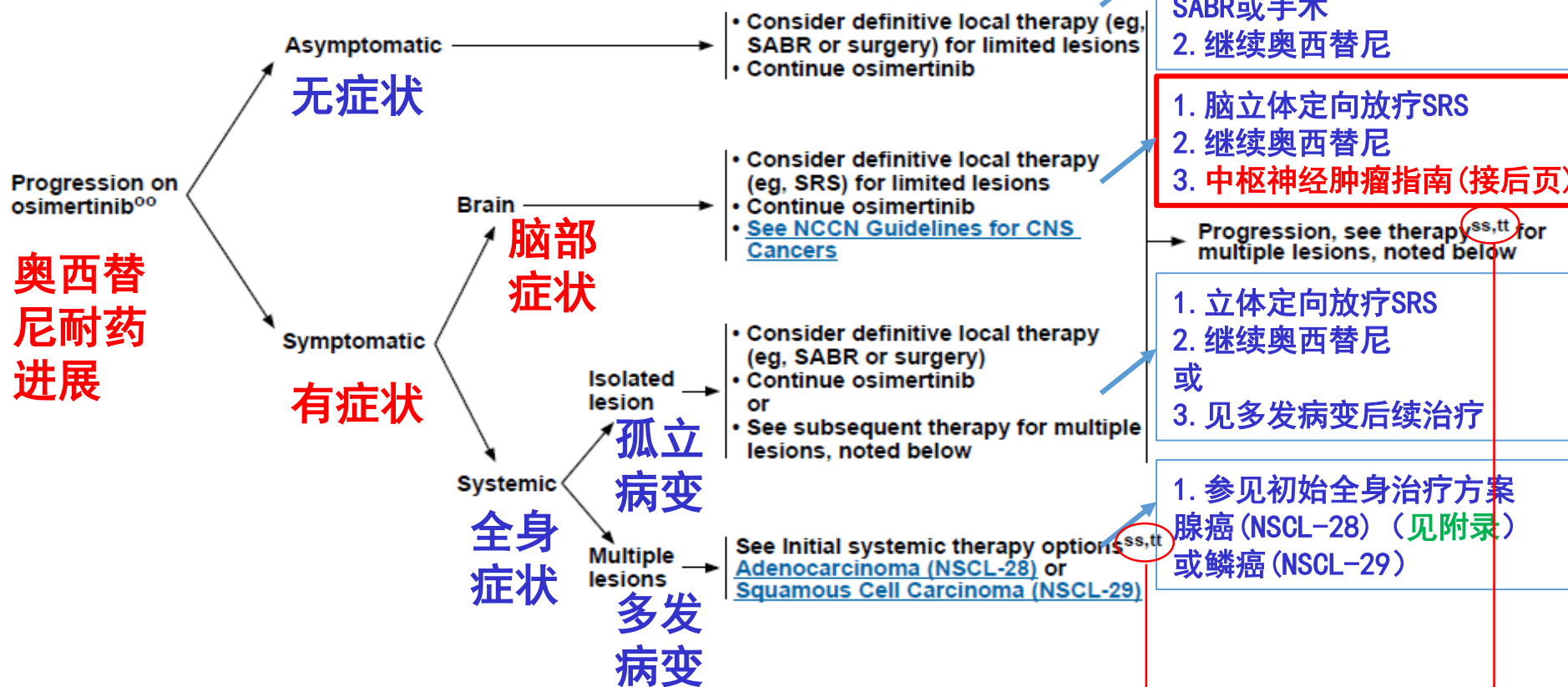
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SENSITIZING EGFR MUTATION POSITIVE^{hh}

SUBSEQUENT THERAPY^{mm}



^{hh}See [Principles of Molecular and Biomarker Analysis \(NSCL-G\)](#).

^{mm}See [Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\)](#).

^{oo}Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

^{ss}Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

^{tt}The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in EGFR+/ALK+ NSCLC.

脚注：oo. 注意区分某些病人因中断靶向而导致的获得性耐药

ss. EGFR靶向治疗进展，可考虑阿法替尼 + 西妥昔 (E靶点单抗) (见讨论)

tt. 对于EGFR/ALK突变非小细胞肺癌，无论PD-L1表达如何，PD-1/PD-L1单药治疗效果均较差



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2019美国NCCN中枢神经肿瘤指南（接上页）

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Central Nervous System Cancers

Version 1.2019 — March 5, 2019

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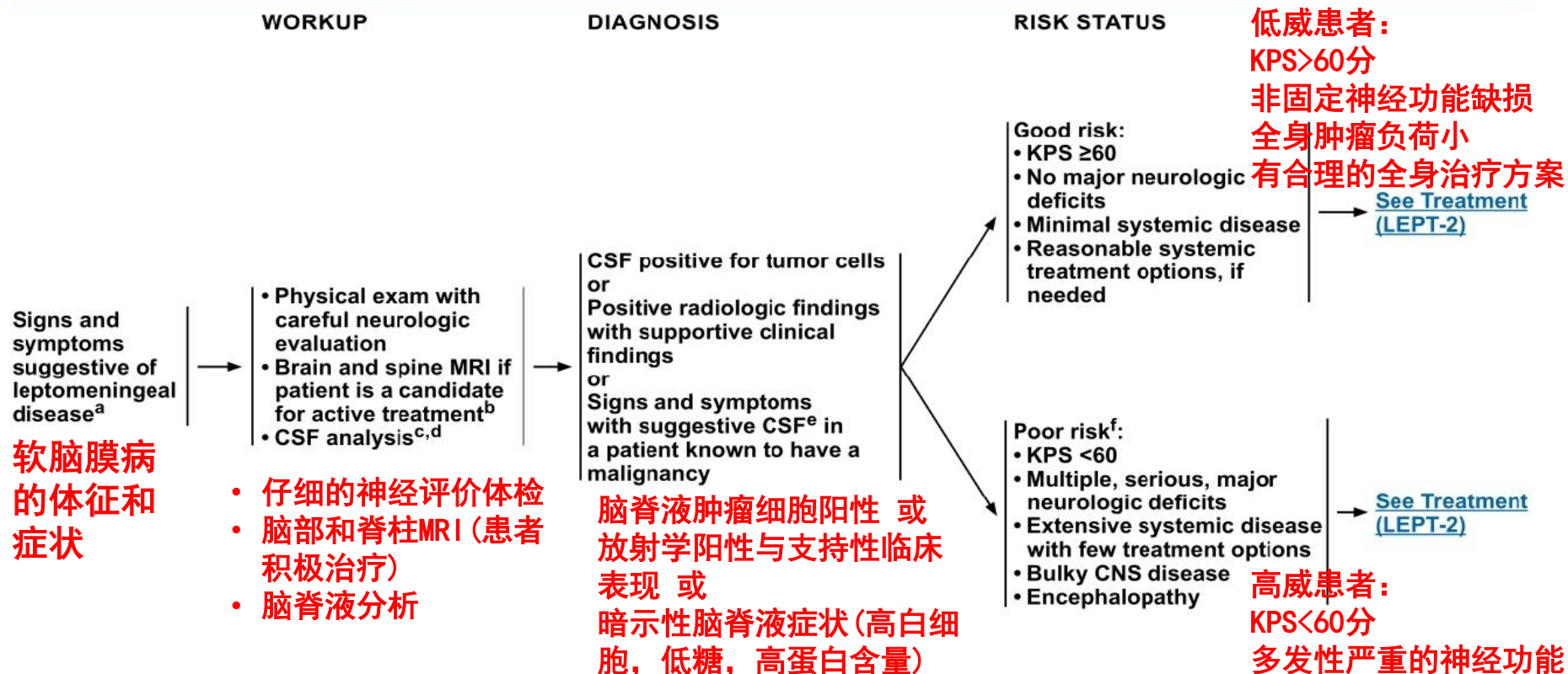
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NCCN Guidelines Version 1.2019

Leptomeningeal Metastases

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2019软脑膜转移指南



^aConsider a multidisciplinary review in treatment planning, especially once pathology is available. [See Principles of Brain and Spine Tumor Management \(BRAIN-E\)](#)

^b[See Principles of Brain and Spine Tumor Imaging \(BRAIN-A\)](#).

^cCaution is indicated in patients who are anticoagulated, thrombocytopenic, or who have a bulky intra-cranial mass.

^dCSF analysis should include: a cell count, differential, glucose, and protein. For solid malignancies, order cytopathology. When available, assessment of circulating tumor cells (CTC) increases sensitivity of tumor cell detection and assessment of response to treatment. For hematologic malignancies, use flow cytometry.

^eSuggestive CSF includes high WBC, low glucose, and high protein. If CSF is not positive for tumor cells, a second lumbar puncture is sometimes helpful. This is a volume-dependent test, and ideally ≥10 mL should be sent for cytologic analysis.

^fPatients with exceptionally chemosensitive tumors (eg, small cell lung cancer, lymphoma) may be treated. Patients with a good risk status who do not desire further therapy may also be treated with palliative and/or best supportive care.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

2019软脑膜转移指南

RISK STATUS

TREATMENT

低危患者:
KPS>60分
非固定神经功能缺损
全身肿瘤负荷小
有合理的全身治疗方案

Good risk:^f
• KPS ≥60
• No major neurologic deficits
• Minimal systemic disease
• Reasonable systemic treatment options, if needed

- Systemic chemotherapy^g
- Intra-CSF chemotherapy^{g,h}
 - ▶ If symptoms or imaging suggest CSF flow blockage, perform a CSF flow scan prior to starting intra-CSF chemotherapy.
 - If flow abnormalities confirmed:
 - ◊ Fractionated external beam RTⁱ to painful metastatic sites of obstruction and repeat CSF flow scan to see if flow abnormalities have resolved.
 - or
 - ◊ High-dose methotrexate if breast cancer or lymphoma
- WBRT and/or involved-field RT^{i,j} to bulky disease and neurologically symptomatic (such as cranial neuropathies) or painful sites.

[See Assessment of response \(LEPT-3\)](#)

若症状或影像提示脑脊液流动受阻, 则开始鞘注前行脑脊液流动扫描。

如果确认流动异常:

- 分次外部照射阻塞流动的疼痛转移灶, 重新流动扫描检查流动异常是否消除
- 对乳腺癌或淋巴瘤, 注射高剂量甲氨喋呤

高危患者:
KPS<60分
多发性严重的神经功能缺陷
广泛性系统性疾病, 治疗方案有限

Poor risk:^f
• KPS <60
• Multiple, serious, major neurologic deficits
• Extensive systemic disease with few treatment options
• Bulky CNS disease
• Encephalopathy

- Palliative/best supportive care and Consider involved-field RTⁱ to neurologically symptomatic or painful sites for palliation (including spine and intracranial disease)

3. 全脑放或累及野照射

弥漫性病灶和神经症状 (如颅神经性病变) 或疼痛部位的全脑放 和/或 累及野照射

^fPatients with exceptionally chemosensitive tumors (eg, small cell lung cancer, lymphoma) may be treated. Patients with a good risk status who do not desire further therapy may also be treated with palliative and/or best supportive care.

^gSee Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

^hStrongly consider Ommaya reservoir/intraventricular catheter.

ⁱSee Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

^jDue to substantial toxicity, craniospinal RT should only be considered in highly select patients (eg, leukemia, lymphoma).

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

LEPTOMENINGEAL AND SPINE METASTASES

脑膜和脊柱转移

• **Treatment**

▶ **Systemic therapy specific to primary cancer type; emphasizing drugs with good CNS penetration**

▶ **Intra-CSF chemotherapy¹⁵⁶**

- ◊ Thiotepa¹⁵⁷
- ◊ Topotecan¹⁵⁸
- ◊ Etoposide¹⁵⁹
- ◊ Interferon alfa (category 2B)¹⁶⁰

治疗:

➤ 针对原发性癌症类型的全身性治疗；强调入脑强的药物

➤ 鞘内化疗

▶ **Lymphoma/leukemias**

- ◊ Intra-CSF chemotherapy
 - Cytarabine¹⁶¹⁻¹⁶⁴
 - Methotrexate^{163,165}
 - Rituximab (lymphoma only)¹⁶²
- ◊ High-dose methotrexate^m (lymphoma only)¹⁴¹

▶ **Breast Cancer**

- ◊ Intra-CSF chemotherapy
 - Methotrexate^{166,167}
 - Trastuzumab¹⁶⁸
- ◊ High-dose methotrexate^m,¹⁴⁰

▶ **Non-Small Cell Lung Cancer**

- ◊ Osimertinib (EGFR mutation positive)¹⁶⁹
- ◊ Weekly pulse erlotinib for (EGFR exon 19 deletion or exon 21 L858R mutation) (category 2B)¹⁴⁸

Metastatic Spine Tumors

• Use regimen for disease-specific site

• 按周脉冲厄洛替尼(EGFR19, 21, L858R突变)

注意：2019年指南中，对于脑膜与脊柱转移，鞘注一线药物为噻替派，而不再是甲氨蝶呤

^mConsider glucarpidase (carboxypeptidase G2) for prolonged methotrexate clearance due to methotrexate-induced renal toxicity. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. Oncologist 2018;23:52-61.

Note: All recommendations are category 2A unless otherwise indicated.

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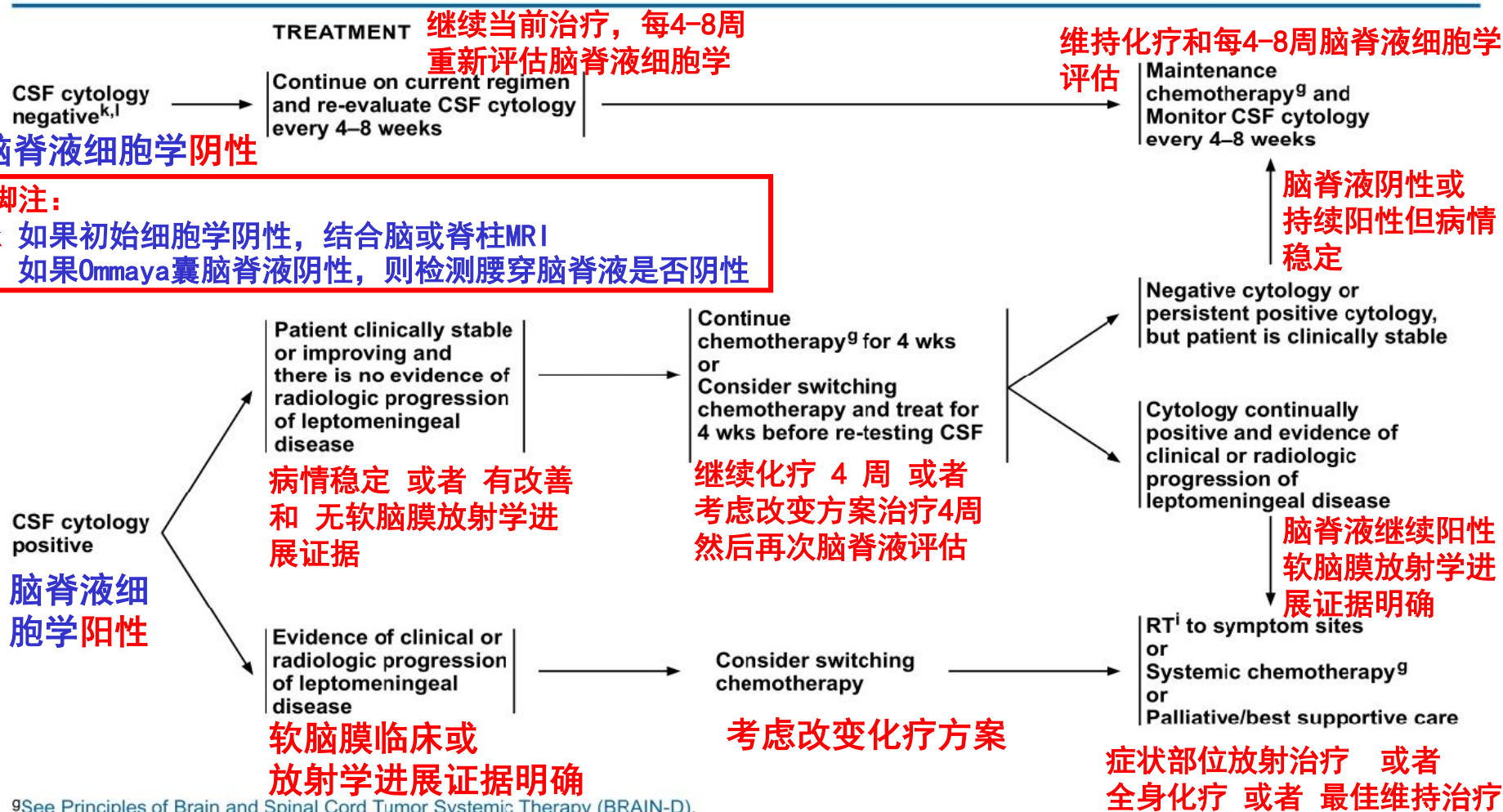
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2019软脑膜转移指南



脚注：

k 如果初始细胞学阴性，结合脑或脊柱MRI

l 如果Ommaya囊脑脊液阴性，则检测腰穿脑脊液是否阴性

⁹See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

ⁱSee Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

^kIf CSF cytology was initially negative, then assess response with MRI of spine/brain.

^lIf cytologic analysis is negative from CSF obtained from an Ommaya reservoir, then assess CSF obtained via a lumbar puncture to confirm CSF cytology is negative.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

非小细胞肺癌脑与脊柱转移 指南治疗原则

➤ 针对原发性癌症类型的全身性治疗；强调入脑/CNS强的药物

➤ 鞘内化疗

- Thiotepa/噻替派
- Topotecan/托泊替康
- Etoposide/依托泊苷
- 干扰素阿尔法 (2b类)

理解：

- ① 脑膜转一线治疗为鞘内化疗。
- ② 2019年指南中，对于脑与脊柱转移，一线药物为噻替派，不再是甲氨蝶呤。

➤ 非小细胞肺癌

- 奥西替尼（EGFR突变阳性）
- 按周脉冲厄洛替尼 (EGFR19, 21, L858R突变)

关于最终进展后指南脚注

- 肺癌脑部（含脑膜）进展后，“EGFR靶向治疗进展，可考虑阿法替尼(2992) + 西妥昔单抗”。
- 问题1：这两种药均不入脑，指南为何如此建议？
问题2：对于EGFR突变患者，有没有可能鞘注西妥昔单抗这一类E靶点药物？
- 附：E靶点单抗：西妥昔（注射用）；V靶点单抗：雷莫芦、贝伐（注射用）

指南中“鞘注”相关条目

□若症状或影像提示脑脊液流动受阻，则开始鞘注前，行脑脊液流动扫描。

□如果确认流动异常：

- ① 分次外部照射阻塞流动的疼痛转移灶，重新进行脑脊液流动扫描，检查流动异常是否消除
- ② 对乳腺癌或淋巴瘤，注射高剂量甲氨喋呤

关于脑脊液阴性的指南脚注

- “如果初始细胞学阴性，结合脑或脊柱MRI”。
- “如果Ommaya囊脑脊液阴性，则检测腰穿脑脊液是否阴性。”
- 问题：Ommaya囊与腰穿脑脊液检测结果不同的临床意义？是否与脑脊液流动受阻相关，是否可结合体感判断脑脊液流动性？



ADENOCARCINOMA, LARGE CELL, NSCLC NOS

INITIAL SYSTEMIC THERAPY

腺，大细胞，病理不确定型非小细胞肺癌
初始全身治疗 (NSCL-28)

身体
状态
0-2级
(生活自理等)

全身
治疗

效果
评估

PS 0-2 → Systemic therapy^{hhh} → Tumor response evaluation^{hhh}

PS 3-4 → Best supportive care
[See NCCN Guidelines for Palliative Care](#)

进展
Progression

响应
或稳定
Response
or stable
disease

4-6
周期
4-6
cycles
(total)

效果
评估
Tumor
response
evaluation^{hhh}

身体
状态
良好
PS 0-2

PS 3-4

SUBSEQUENT THERAPY^{hhh}

Systemic immune checkpoint inhibitors (preferred)^{c,tt,iii}
Nivolumab (category 1)
or pembrolizumab (category 1)^{jjj}
or atezolizumab (category 1)
or
Other systemic therapy:^{xx}
Docetaxel or pemetrexed or
gemcitabine or
ramucirumab + docetaxel

Best supportive care
[See NCCN Guidelines for Palliative Care](#)

Progression → See Subsequent Therapy, above

进展
同上

Continuation maintenance^{hhh}
• Bevacizumab (category 1)
• Pemetrexed (category 1)
• Bevacizumab + pemetrexed^{kkk}
• Pembrolizumab + pemetrexed (category 1)^{ddd}
• Atezolizumab and/or bevacizumab (category 1)^{eee}
• Gemcitabine (category 2B)
or
Switch maintenance^{hhh}
• Pemetrexed
or
Close observation

响应
或稳定

0, K, T药免疫治疗
或其他全身治疗：
紫杉醇、培美、吉
西他滨或

雷莫芦单抗 (V靶点
单抗) 联紫杉醇

1. 贝伐
2. 培美
3. 贝伐+培美
4. K药+培美
5. T药和或贝伐
6. 吉西他滨

Progression,
see
Subsequent
Therapy,
above
进展，同上

^cTemel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small cell lung cancer. *N Engl J Med* 2010;363:733-742.
^{tt}The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in EGFR+/ALK+ NSCLC.
^{xx}If not previously given.
^{ooo}If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
^{eee}If atezolizumab/carboplatin/paclitaxel/bevacizumab given.
^{hhh}[See Systemic Therapy for Advanced or Metastatic Disease \(NSCL-J\)](#).
^{jjj}If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not routinely recommended.
^{jjj}Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.

^{kkk}If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.
^{lll}If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

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