Recent Advances in the Biology and Management of Lung Cancer Brain Metastase

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Introduction

- Brain metastase are common complication in a wide range of cancer
- Particularly common among patient with lung cancer (40-50%)
- ± 10% of newly diagnosed patients NSCLC
- 10-20% with advaced NSCLC → 40-50% with stage III lung adenocarcinoma, 20-40% with ALK-rearranged tumour

Loeffler JS. Brain Metastase in Non Small Cell Lung. UpTodate 2019

Introduction....

- Incidence is higher in patients → EGFR mutation or anaplastic lymphoma kinase (ALK) rerrangement

- Often present as multiple lession, although 1/3 of patients are singular

Preusser M. et al Recent Advanced in the biology and treatment of NSCLC: Summary of mutidisiplinary roudtable discussion . ESMO Open 2018;3:e000262

Biology and molecular alterations of NSCLC Brain Metastase

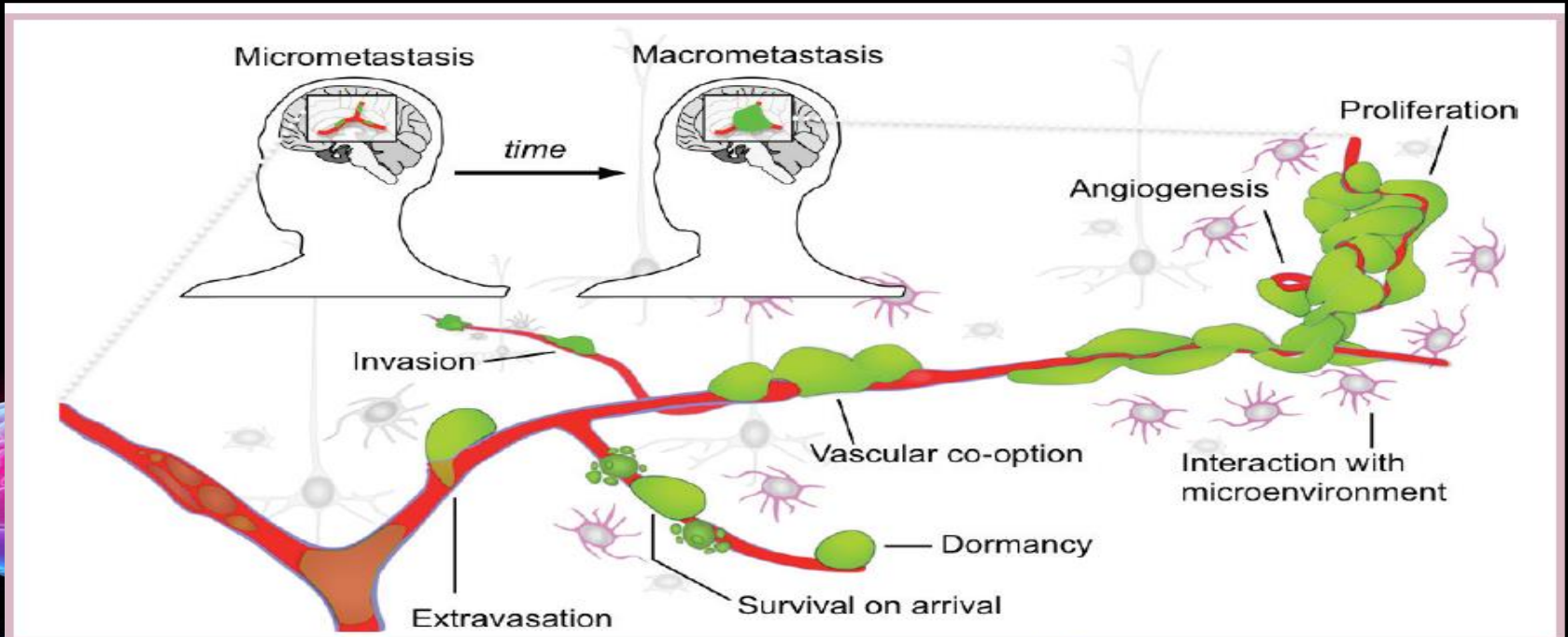

Figure 1 Key mechanisms of a metastatic cell developing in the brain (see reference[22]).

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Management of Lung Cancer Brain Metastase

- For a long time, brain metastases in lung cancer have been considered a final event and were treated by either by whole brain radiation therapy (WBRT) or palliative care

- Current treatment algorithms of NSCLC brain metastases:
  - surgical resection
  - radiotherapy
  - chemotherapy
  - targeted drugs
  - multi-modality approaches

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Management of .....

Surgical resection

- Limited metastatic lession (1-3 metastases) → neurosurgical resection is one of the main therapeutic option

- Can be combined with radiotherapy such as
  - ✓ Stereotatic radiosurgery (SRS): increase in local control
  - ✓ Whole Brain Radiation Therapy (WBRT): neurocognitive deterioration ↑

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Management of .....

Surgical resection

- Multiple metastatic lessions (> 3 lessions)

→ WBRT is still an option alone or combination with SRS, a radiosensitiser or chemoteraphy

→ erlotinib (radiosensitiser) + WBRT: failed to show benefit in local controls or overall survival but has increased toxicity

→ Chemotherapeutic agent: temozolomide to radiation: failed to improve survival, increases toxicity

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Management of .....

Chemotherapy

- Standard cytotoxic chemoterapy (platinum based) is limited with respect to the treatment of brain metastases → poor penetration of the blood brain barrier

Morin S. et al Brain metastases in NSCLC: are TKI and checkpoint inhibitors now viable options. Current Oncology 2018(S1): S103-S114

Management of .....

Targeted drugs: ***EGFR TKI therapy***

- NSCLC with EGFR mutations→ TKIs seem more efective

- EGFR TKIs: low molecular weight organic compounds with low – moderate CSF penetration
  - 1st generation (gefitinib & erlotinib) and 2nd generation (afatinib) , integrated in the treatment algorithm of advanced metastatic mutated NSCLC (first line)
  - 3rd generation (AZD 3759 & osimertinib): recently accelerated the debate

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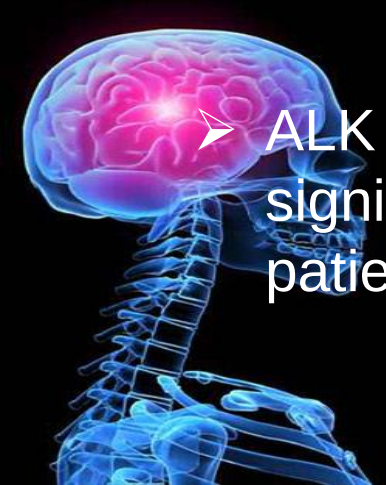
Management of .....

Targeted drugs: ***TKI for patients with ALK –rearranged NSCLC***

- NSCLC wtith ALK rearrangement → 5 compound registered with US FDA (crizotinib, certinib, alectinib, lorlatinib and brigatinib. EMA: pending for brigatinib



- ALK directed TKI crizotinib took a rather short time and a significant improvement compared with chemotherapy in patient with ALK rerrangement.

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Radiotherapy

- Especially radiosurgery or hypo-fractionated stereotatic radiotherapy (HFSRT) → the main weapon to increase local control, and possible survival, without affecting neurocognition

- WBRT + SRS or surgery → not increase overall survival (OS) but less neurocognitive deficit

- SRS alone compared with SRS + WBRT: same OS and less neurocognitive deficit, shorter time to intracranial failure → SRS considered a standard treatment for patiens brain metastase

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Prospective Randomized Trial of Post-operative Stereotactic Radiosurgery versus Observation for Completely Resected Brain Metastases

Anita Mahajan, M.D., Salmaan Ahmed, M.D., Mary Frances McAleer, M.D., Ph.D., Jeffrey S. Weinberg, M.D., Jing Li, M.D., Paul Brown, M.D., Stephen Settle, M.D., Sujit S. Prabhu, M.D., Frederick F. Lang, M.D., Nicholas Levine, M.D., Susan McGovern, M.D., Ph.D., Erik Sulman, M.D., Ph.D., Ian E. McCutcheon, M.D., Syed Azeem, M.D., Daniel Cahill, M.D., Ph.D., Claudio Tatsui, M.D., Amy B. Heimberger, M.D., Sherise Ferguson, M.D., Amol Ghia, M.D., Franco Demonte, M.D., Shaan Raza, M.D., Nandita Guha-Thakurta, M.D., James Yang, Ph.D., Raymond Sawaya, M.D., Kenneth R. Hess, Ph.D., and Ganesh Rao, M.D.

Interpretation—Decline in cognitive function was more frequent with WBRT than with SRS and there was no difference in overall survival between the treatment groups. After resection of a brain metastasis, SRS radiosurgery should be considered one of the standards of care as a less toxic alternative to WBRT for this patient population.

Management of .....

Combination & sequencing of medical therapies with radiotherapy for NSCLC Brain Metastases

- Irradiation can induce tumor cell death as mitotic cell death, apopotosis but also autophagy and senescence

- SRS or HFSRT: induction of apoptosis of endothelial cells, → tumor radio-sensitisation
- I

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Management of .....

Combination & sequencing of medical therapies with radiotherapy for NSCLC Brain Metastases

- Irradiation can induce an imune cell death (CD8 T-Cell) and stimulation of tumour antigen presetation

- SRS could induce the expression of programmed death ligand 1 (PDL1) and programmed cell death protein 1 (PD1) → radiosensitisation

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Management of .....

Radiotherapy and TKI

- Promising treatment: SRS/ HFSRT + targeted drugs + irradiation

- EGFR mutation: ALK-positive NSCLC → higher risk of brain metastases
- EGFR/ALK inhibitor + radiotherapy → radiosensitisation

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Evaluation on efficacy and safety of tyrosine kinase inhibitors plus radiotherapy in NSCLC patients with brain metastases

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[*] These authors have contributed equally to this work

Results: Eight controlled trials (980 participants) were included in the study. Compared with radiotherapy without TKIs (non-TKI-group), TKIs plus radiotherapy (TKI-group) had a significant benefit on objective response rate (ORR) (RR = 1.56, 95%CI [1.25,2.03]; *P* =0.0008), significantly prolonged the time to central nerves system progression (CNS-TTP) (HR =0.58, 95% CI [0.35, 0.96]; *P* =0.03) and median overall survival (MOS) (HR =0.68, 95% CI [0.47, 0.98]; *P* =0.04) of NSCLC patients with BM. There was no significant difference in overall severe adverse events (Grade≥3) (RR = 1.49, 95% CI [0.88,2.54]; *P* = 0.14) between two groups.

Conclusion: This meta-analysis showed TKI-group produced superior response rate when compared with non-TKI-group. TKIs plus radiotherapy significantly prolong the CNS-TTP and MOS of patients without enhancing overall severe adverse events.

Management of .....

Radiotherapy and immunotherapy

- SRS with checkpoint inhibitors (SRS + ipilimumab) atau SRS + anti PD1

- SRS performed before and concurrently to immunotherapy would have better results than SRS performed after

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Systematic Review

Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data

Eric J. Lehrer [a], Jennifer Peterson [b,c], Paul D. Brown [d], Jason P. Sheehan [e], Alfredo Quiñones-Hinojosa [c], Nicholas G. Zaorsky [f,1], Daniel M. Trifiletti [b,c,*,1]

[a] Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, USA; [b] Department of Radiation Oncology; [c] Department of Neurological Surgery, Mayo Clinic, Jacksonville, USA; [d] Department of Radiation Oncology, Mayo Clinic, Rochester; [e] Department of Neurological Surgery, University of Virginia, Charlottesville; and [f] Department of Radiation Oncology, Penn State Cancer Institute, Hershey, USA

Conclusions: Concurrent administration of SRS/ICI may be associated with improved safety and efficacy versus sequential therapy. These findings, however, are hypothesis-generating and require further validation by ongoing and planned prospective trials.

Management of .....

Neurosurgical resection of NSCLC Brain Metastases

- Subsequent initiation of postoperative radiotherapy has demonstrated → positive impact on Overall survivall

- complete “macroscopic” removal of surgically treated → significantly better prognosis than incomplete resection

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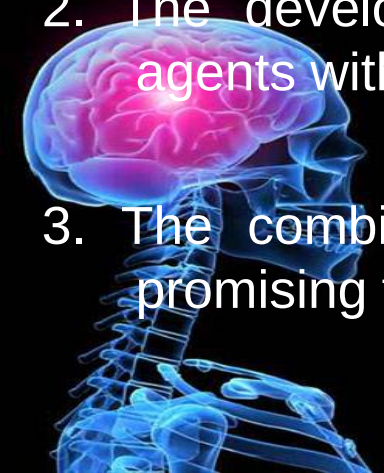
Summary

1. The naive brain microenvironment can eliminate multiple brain metastasis (BM) cells by activating innate immunity mechanisms. However, successful BM cells have developed ways to avoid them and progress in the metastatic cascade by colonising the crucial perivascular niche in the brain.

2. The development of EGFR TKIs has now reached third-generation agents with promising early results.

3. The combination of radiotherapy and TKIs or immunotherapy is a promising treatment for NSCLC BMs



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Terima Kasih