Management of central nervous system metastases

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Central nervous system (CNS) metastases are divided into brain metastasis and intramedullary spinal cord metastasis (ISCM). Although the blood-brain barrier (BBB) and blood-spinal barrier (BSB) protect the brain and spinal cord, metastases occur when these barriers break under abnormal conditions. Brain metastasis accounts for the largest number of brain tumors, however, ISCM rarely occurs. For brain metastasis, whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), surgery, and chemotherapy can be considered, and for ISCM, radiotherapy (RT), surgery, Cyberknife SRS, and chemotherapy can be considered. As treatment options vary depending on the patient's life expectancy, performance status (PF), extent and number of metastases, and the type of primary cancer, careful patient evaluation should be performed prior to treatment of CNS metastases.

Keywords: Brain; Central nervous system; metastases; Intramedullary spinal cord

INTRODUCTION

Among central nervous system (CNS) metastases, brain metastasis accounts majority cases compare to intramedullary spinal cord metastases (ISCM). Brain metastases remain the commonest type of brain tumor, being four times more common than primary brain tumors²³. The management of patients with multiple brain metastases remains a difficult challenge for neurosurgeons. Treatment strategies for brain metastases depend on several factors. Some patients may be candidates for whole brain radiotherapy (WBRT), while others may require surgical resection followed by WBRT or local radiation therapy. Stereotactic radiosurgery (SRS) has added another dimension to the management of these lesions. The patient with metastatic brain tumor has a poor prognosis, and historically, treatment has generally consisted of administering WBRT after the diagnosis of

multiple brain metastases is confirmed. However, nowadays, surgery has an important role in management for carefully selected cases. Surgery provides definite and accurate diagnosis, reduces intracranial mass effect, improves neurological symptoms, and may also improve overall survival (OS), all with low morbidity and mortality rates²⁹. It is generally accepted that to benefit from surgery, a patient with brain metastases must have reasonable medical fitness, with a systemic disease process amenable to benefit from local tumor control³⁰. Unlike brain metastasis, the role of surgical treatment in ISCM is controversial. Chemotherapy is usually considered by the type of primary cancer and applied for systemic control, however, the efficacy for the ISCM is unclear. The RT is generally considered as a palliative treatment for ISCM treatment^{16,20}.

EPIDEMIOLOGY

The majority of brain metastases originate from one of three primary malignancies; lung cancer (40%–50%), breast cancer (15%–25%), and melanoma (5%–20%). Among these, melanoma has the highest propensity to metastasize to the brain, with a 50% rate of brain involvement reported in patients dying of melanoma²⁾. The frequency of metastatic brain tumors appears to be rising as a result of superior imaging modalities and earlier detection as well as longer survival after a primary cancer diagnosis because of more effective treatment of systemic disease¹¹⁾. In the case of ISCM, lung cancer metastases (54%) is the most common cause, followed by breast cancer metastases (11%)¹⁹⁾. ISCM is a rare systemic cancer that autopsy studies have confirmed that ISCM is present in 0.9% to 2.1% of cancer patients. However, almost 95% of these lesions are clinically silent and remain undiagnosed before death, so they are actually less frequently encountered in practice^{7,9,10,18,31,36)}.

PATHOPHYSIOLOGY

Under physiologic condition, CNS metastases hardly occur because of the firm blood-brain barrier (BBB) and blood-spinal barrier (BSB). However, in pathologic condition, inflammatory mediators cause increased permeability of the BBB/BSB. In this environment, cancer cells can attach to microvascular endothelial cells and invade the BBB/BSB, cause CNS metastases^{1,14)}. A typical CNS metastases route is hematogenous spreading. In brain metastasis, arterial spreading is known as a major cause, and venous spreading through Batson plexus is also considered as an important route for ISCM^{10,13,17,18,31,34)}. Leptomeningeal dissemination by the cerebrospinal fluid (CSF) is also an important metastasis mechanism. In particular, it explains why the brain and ISCM often appear simultaneously^{9,31)}. Direct invasion is also known as a case of metastasis, however, this is mainly limited in the case of ISCM^{9,37)}.

CLINICAL ASSESSMENTS

The management of brain metastases can be divided into symptomatic and therapeutic strategies. Symptomatic therapy often includes corticosteroids to reduce peritumoral edema and anticonvulsants to prevent recurrent seizures. In addition, there is accumulating data to suggest that medications such as methylphenidate and donepezil can improve cognition, mood, and quality of life in patients with brain tumors^{26,35)}. Therapeutic approaches to brain metastases include surgery, WBRT, SRS, and

chemotherapy. Many patients are treated with a combination of these, and treatment decisions must take concern about factors such as patient age, functional status, primary tumor type, extent of extracranial disease, prior therapies, and number of intracranial lesions. Most ISCM patients are diagnosed with a neurological deficit. Ninety-three % of the patients showed motor dysfunction, 78% of the patients showed sensory abnormalities, and 62% of the patients showed urinogenital dysfunction¹⁶⁾. For patients who previously diagnosed with primary cancer, ISCM can be considered, but if an intramedullary spinal cord tumor is diagnosed without knowing the primary cancer, it is highly likely to be mistaken for a primary tumor. While the surgery is the treatment of choice for primary intramedullary tumor, in contrast, surgery is performed in highly selective cases for ISCM. Careful diagnosis is needed prior to the treatment.

TREATMENT MODALITIES – BRAIN METASTASIS

Systemic chemotherapy

Chemotherapy has traditionally played a limited role in the treatment of brain metastases, and has been reserved for patients who have failed other treatment modalities or for diseases known to be “chemo-sensitive,” such as lymphoma, small-cell lung cancer, germ-cell tumor and breast cancer¹¹⁾. Incredulous stance regarding the usefulness of chemotherapy for brain metastases arises from the reason that most agents cannot cross the BBB, because of their large molecular weight or hydrophilic property. The degree to which a given agent is believed to penetrate the BBB is usually based on pharmacokinetic animal and/or human studies comparing plasma with CSF drug concentrations after intravenous or oral administration. This method may underestimate the concentration of drug delivered to the tumor, however, because brain metastases are known to have local BBB breakdown (demonstrated on magnetic resonance imaging (MRI) by contrast enhancement and peritumoral edema). This is corroborated by studies showing roughly equivalent intracranial and extracranial response rates to chemotherapeutic agents assumed to have little BBB penetration, particularly when first-line agents for the systemic cancer are chosen^{4,6,33)}. The success of an agent may therefore rest more heavily upon its inherent activity against the systemic tumor than its putative ability to cross the BBB.

Radiotherapy

The mainstay of treatment for brain metastases over the past five decades has been corticosteroids and WBRT. Nonrandomized studies suggest that WBRT increases the median survival

time by 3–4 months over approximately 1 month without treatment and 2 months with corticosteroids alone. Although reports of the response rate after WBRT alone vary, complete responses (CRs) or partial responses (PRs) have been documented in approximately 60% of patients in randomized controlled studies conducted by the radiation-therapy oncology group²¹⁾. Stasis or Improvement of neurologic symptoms occurs nearly the same proportion, even though symptom response defined separately in studies⁵⁾.

SRS

Although there is controversy exists, particularly those with a limited number of brain metastases, can be treated effectively with SRS alone¹¹⁾. The assumed rationale for exclusion of WBRT is to spare patients the risk for late neurotoxicity from WBRT. Patients who were not treated upfront WBRT are typically monitored closely with serial MRI scans and treated with WBRT or additional SRS at recurrence¹¹⁾.

Surgery

Management of patients with brain metastases has been evolving over time, with a general tendency towards a more aggressive treatment approach²²⁾. Benefits of surgical resection include the provision of an accurate and definite diagnosis, immediate relief of neurological symptoms caused by extensive perilesional edema or mass effect, and local control of disease. Advances in surgical technique have led to lower rates of morbidity and mortality³⁾. Muacevic et al., demonstrate in their retrospective review of management of solitary metastasis of less than 3.5 cm of diameter concluded that result of surgery with WBRT is comparable to SRS in local tumor control rate²⁷⁾.

TREATMENT MODALITIES – ISCM

Radiotherapy

The RT is considered as standard therapy for palliative treatment for ISCM^{8,10,13,18,38)}. However, the efficacy is limited to radiosensitive tumor as small cell carcinoma, breast carcinoma, or lymphoma^{8,13,15,28,38)}. Furthermore, radiation myelitis due to radiotoxicity should be considered.

Surgery

Surgery should be performed in highly selective patients. They should have good performance status, single CNS metastasis, and long enough life expectancy. In surgical technical aspect, as the microscopic surgical skill has been advanced and neurophysiologic intraoperative monitoring (IOM) has been developed, surgical outcome gradually improved. Some groups claim that the ISCM shows fair borderline that normal neural structure is well preserved along surgery, however, some groups assert the opposite^{12,25)}. There is little evidence that surgical resection could improve OS, however, neurologic improvement has been achieved in some reports^{12,40)}.

Chemotherapy

As the BSB block the chemical, chemotherapy has little effect for ISCM treatment²⁰⁾. However, if the primary cancer is suitable for specific chemotherapy, it could be applied as adjuvant therapy for RT or surgery¹⁹⁾.

Steroid

Steroid can reduce spinal cord edema and stabilize BSB, which helps relieving pain and delay neurologic deterioration. Even

Table 1. Management recommendation for brain metastases (adopted from Lin et al.)²⁴⁾

Consider systemic therapy	Consider WBRT	Consider SRS	Consider surgical resection	No treatment is reasonable
BM from highly chemotherapy-sensitive primary tumor	CNS and systemic progression of disease, with few systemic treatment options and poor PS	OM (1-3) or multiple BMs, especially if PT is known to be radiotherapy resistant	Uncertain diagnosis of CNS lesion(s)	Systemic progression of disease, with few treatment options and poor PS
BM found on screening MRI with planned systemic treatment	Multiple (> 3-10) BMs, especially if PT known to be radiotherapy sensitive	Postsurgical resection of a single BM, especially if ≥ 3 cm and in the posterior fossa	1-2 BMs, especially when associated with extensive cerebral edema	
BM from primary tumor with identified molecular alteration amenable to targeted therapy	Postsurgical resection of a dominant BM with multiple (> 3-10) remaining BMs	Local relapse after surgical resection of a single BM	Dominant BM in a critical location	
Other therapeutic options have been exhausted and there is a reasonable drug available	Salvage therapy for recurrent BM after SRS or WBRT failure	Salvage therapy for recurrent OM (1-3) after WBRT		

BM: brain metastases; CNS: central nervous system; MRI: Magnetic-resonance imaging; OM: oligometastases; PS: performance status; SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy.

though steroid cannot prolong survival, it is commonly used with other treatment modalities^{19,20}.

Cyberknife Stereotactic Radiosurgery (SRS)

Some groups reported ISCM were treated safely with Cyberknife SRS without severe complication^{32,39}. However, the total population is too small for the conclusion. Additional studies are essential to build stronger evidence.

CONCLUSION

Recommendation of clinical decision making in treatment of brain metastasis is below (Table 1)²⁴. Many factors such as chemosensitivity of primary tumor, number and size of brain metastases (BM), clinical course such as local relapse or recurrence of BM, and patient factors such as KPS should be considered. For ISCM, golden standard is still controversial. RT is generally performed and surgery is applied in selective patients. Cyberknife SRS could be considered as well. Due to the variety of treatment options, meticulous clinical assessment of patients and disease is mandatory.

NOTES

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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