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CLINICAL MANAGEMENT OF GTN WITH BRAIN METASTASIS: A 20-YEAR EXPERIENCE IN PEKING UNION MEDICAL COLLEGE HOSPITAL, CHINA

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19.1. INTRODUCTION

Gestational trophoblastic neoplasia (GTN) is remarkably sensitive to chemotherapy. Indeed,with current chemotherapy regimens, the cure rates are almost 100% in the low-risk group and nearly 90% in the high-risk group[1]. Brain metastasis from GTN is rare with an incidence of 3% to 21.4% and about only 222 cases documented in the literature[2]. In our hospital, from January 1994 to December 2013, 97 GTN patients were identified as having brain metastasis, representing 3.4% of all patients treated with this cancer at our hospital during the same period. Metastatic disease to the brain from GTN was regarded as a poor prognostic indicator in previous reports, with survival rates significantly reduced as low as 35-60%[3]. However, more recent reports suggest improved survival rates (e.g. Newlands et al J Reprod Med. 2002 Jun;47(6):465-71) and during the past 20 years we have achieved an overall five-year survival (OS) rate of 83.5% for patients receiving primary chemotherapy in our hospital. In addition, where we have given secondary salvage therapy to patients who have failed chemotherapy elsewhere, our 5 yr OS has been 53.3% (excluding 6 early deaths).

In this chapter, we will describe our large experience and great success in the management of GTN patients with brain metastases over the past 20 years at the Peking Union Medical College (PUMC) Hospital.

19.2. CLINICAL PRESENTATION

Almost all patients with brain metastases from GTN either have already had or present with co-existing pulmonary metastasis, and about 30% of cases had a preceding or concurrent diagnosis of disease involvement in other organs, such as the liver, spleen, kidney, gastrointestinal tract, skin, and bone.

19.2.1 Symptoms

In studying the clinical records, it was found that about 60% of cases had prodromal symptoms of brain metastases, such as severe headache usually accompanied by nausea and vomiting, visual and mental disturbances, and sensory and motor disturbances. These neurologic symptoms could occur singly but more often several of them appeared simultaneously. Symptoms were commonly mild and transient in nature, and may have been present for several weeks before the onset of the classical neurological symptoms. Apart from the headaches, which may persist longer in some patients, most of the symptoms improved or disappeared within a few minutes to several hours. Therefore, they were likely to be overlooked or considered as occasional events, owing to lack of knowledge. The patients appeared normal after subsidence of the prodromal symptoms[4].

After an average interval of one month (range from several days to more than 2 months), the prodromal neurologic symptoms would reappear. However, unlike the initial symptoms, these were then persistent and progressive in nature and we have termed this as 'classical symptoms'. Moreover, with the increase in severity of the headaches if the patients did not receive proper treatment immediately, they typically succumbed from sudden respiratory arrest associated with raised intracranial pressure. Exceptionally, some rare cases with progressive deterioration and early death did not have these classical symptoms. With the innovation of computed tomography (CT) and magnetic resonance imaging (MRI) scans, some patients were diagnosed at an early stage before the appearance of classical symptoms. In our current 97 case series, there were 86

patients presented with classical symptoms at diagnosis, which are summarized in Table 19.1.

Table 19.1. Classical neurological symptoms in brain metastasis (86 cases)

Symptoms	No. of cases	Symptoms	No. of cases
Headache	55	Motor disturbance	29
Vomiting	39	Convulsion	23
Mental cloudiness	31	Coma	21
Visual disturbances	32	Aphasia	22
Hemiplegia	29	Others	12

19.2.2 Physical Signs

At the prodromal stage with the first appearance of symptoms, if the patients were examined in time, some positive neurologic signs could be found. In some cases, signs of facial paralysis such as unilateral shallowing of the naso-labial groove, deviation of tongue on protrusion and pathologic reflexes such as exaggeration of knee jerk, positive Babinski's signs or Hoffmann's signs were also observed or elicited. These signs like the prodromal symptoms were also transient in nature and likely to be ignored.

The physical signs did not reappear until the classical symptoms developed. At this point, all of the pathologic reflexes became markedly exaggerated but then totally disappeared if a deep coma occurred. If the patients had intracranial hemorrhage, meningeal irritation signs such as neck stiffness, could be observed. Also, in advanced cases, opthalmoscopy revealed signs of raised intracranial pressure with blurred optic discs and sometimes retinal hemorrhagic changes.

It is noteworthy that all of these symptoms and signs were closely related to the location, size and number of metastatic lesions as well as the co-existing pathologic changes in the brain such as edema and hemorrhage. Brain metastases from GTN showed a greater tendency to be hemorrhagic compared to brain metastases from other primary tumors.

19.3. PROCESS OF DEVELOPMENT OF BRAIN METASTASIS

According to pathological and clinical findings, the process of brain metastases development from GTN may be divided into three stages[4]:

(1) Initial stage or stage of tumor embolism. As the tumor cells gain access into the cerebral arteries through the internal carotid or vertebral artery and lodge in the arteries or their branches, a tumor embolism is formed. The mechanical obstruction of the vessels as well as the reflexive vascular spasm of adjacent arteries induced by the mechanical stimulation of the embolus will result in ischemia of those parts of the brain. A series of neurologic symptoms (prodromal symptoms), such as headache, collapse, motor disturbance of the limbs, blindness, etc. will appear. The duration of the symptoms is very short, lasting from a few minutes to several hours, depending on the location of the vessels affected. As the vascular spasm is relieved, the tumor embolus is usually driven distally to much smaller arterial branches by the blood pressure. At this time, the impairment of cerebral function may be reduced to a minimum and the symptoms disappear spontaneously. This accounts for the transient nature of the symptoms at this stage. Consequently, the appearance of the prodromal symptoms are apparently due to tumor embolism and should be considered as the beginning of brain metastasis.

(2) Progressive stage or stage of tumor formation. If the patient is not promptly and properly treated, continuous growth of the tumor cells in the vessels will rupture the vascular wall with invasion of tumor cells into the surrounding brain tissues, resulting

in hemorrhage and tumor formation. This can explain the appearance of the classical neurologic symptoms. As the tumor mass grows in size and the subsequent brain edema and hemorrhage become more pronounced, the intracranial pressure rises quickly. This accounts for the rapid progression of symptoms, repeated convulsions and coma of patients at this stage.

(3) Terminal stage or stage of brain herniation. If the patient still does not receive effective management, the rapidly increased cerebral edema and intracranial pressure will lead to herniation of some part of the brain, resulting in sudden respiration arrest and death.

However, the three stages may not be clearly seen in every patient with brain metastasis. If the tumor embolism affects only a minor vessel which supplies blood to a small part of the brain with little function, the prodromal or initial symptoms may not be very conspicuous and may be easily ignored. Moreover, the transient nature of the prodromal symptoms may lead to diagnostic difficult in the first stage. On the other hand, if the tumor cells in the embolus invade and rupture an important artery resulting in massive hemorrhage, sudden death may occur in the absence of a prodromal phase, so the stages can be indistinguishable clinically.

19.4. DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

19.4.1 Diagnosis

The diagnosis of late stage cases of brain metastasis with classical symptoms and signs can be quite easily made, especially with help of laboratory tests. However, it is much more difficult to diagnose a patient in the early or prodromal stage. In our experience, the key to early diagnosis is dependent on prompt recognition of the prodromal symptoms. Any patient with pulmonary metastasis once observed to have prodromal neurological symptoms, should be taken seriously and put under close observation. If

correlative positive signs can be seen or elicited at this moment, the diagnosis of brain metastasis should be highly suspected and the patient should undergo further investigations, such as contrast enhanced CT or preferably MRI scan of the brain and cerebrospinal fluid (CSF) examination. If the serum human chorionic gonadotropin (hCG), especially β-hCG, shows a raising titer or the patient has evidence of other metastases, such as liver, spleen, kidney, intestines, etc. indicating dissemination of tumor cells by the general circulation, the diagnosis of GTN is highly likely. However, definitive diagnosis of brain metastasis should rely on the laboratory tests, the brain CT or MRI scan and pathological findings.

19.4.1.1 Laboratory tests

(1) hCG determinations

In all of the 97 cases, the serum hCG levels were elevated but the titers varied greatly. Therefore, a single hCG determination had a limited role in making a diagnosis of brain metastasis due to GTN. However, if the tests were repeated after the appearance of neurologic symptoms, a steadily raising titer could also be observed. This is very useful in diagnosis.

The measurement of a CSF/serum β-HCG ratio is a quite traditional diagnostic test for detecting brain metastasis due to GTN. Athanassiou et al[5] pointed out that a CSF/serum β-HCG ratio over 1/60 is a valuable and sensitive indicator of metastasis to the brain. However, Shi et al[6] in PUMCH had evaluated the effect of CSF/serum β-hCG ratio in 44 patients with brain metastases and 29 patients with lung metastases. Their results demonstrated: ① the CSF/serum β-hCG ratio was over 1/60 in the stage of tumor formation in 94% cases; ② but the ratio was less than 1/60 in the stage of tumor embolism; ③ the CSF/serum β-hCG ratio was more than 1/60 in 5.5% cases who did

not have brain metastases; ④ because of the blood brain barrier, the serum β -hCG level declined more quickly than CSF level after effective treatment, so the ratio was over 1/60 in some cases at this time. Therefore, the CSF/serum β -hCG ratio in the diagnosis of brain metastasis is not accurate enough and more sensitive methods are needed such as contrast enhanced CT or MRI scans.

(2) CSF examinations

The appearance of CSF was clear in most cases. Nevertheless, it also could be bloody if the patients had intracranial hemorrhage. The intracranial pressure and CSF protein were often within normal range in the prodromal stage, but could be mildly elevated in the advanced stages. According to the clinical records of the 82 patients with brain metastasis in PUMCH, the intracranial pressure was elevated (above 180mm H_2O) in 38 cases (46.7%). A value of more than 200mm H_2O was observed in 18 cases, the highest being 380 mm H_2O. Since mannitol was administered routinely before lumbar puncture as a dehydration therapy, the true incidence of elevated intracranial pressure might be much higher. Elevated protein content was noted in 42 cases (51.3%) but the glucose levels were always within the normal range. As patients condition improved, both intracranial pressure and protein content reduced to normal.

19.4.1.2 CT and MRI scanning

Since the 1990s, various new diagnostic strategies were utilized to identify brain metastasis from GTN, including the latest generation of CT and more recently MRI scan. These methods may be more sensitive in detecting disease compared to traditional diagnostic tests, such as CSF/serum β -hCG ratio. Since about 50% of brain metastases from GTN patients showed a tendency to be hemorrhagic, the lesions showed hyperdense (bright) centres surrounded by hypodense areas (dark) which indicated edema on CT scans. MRI scanning is more sensitive than CT imaging, especially in

detecting the edema. However, it typically costs more and may take more time to perform than CT scans. Now, both these two strategies play an important role in detecting the early stage brain metastases.

19.4.2 Differential diagnosis

There are some diseases that clinically present in a similar fashion to the brain metastasis from GTN. These conditions should be differentiated carefully.

(1) Subarachnoid hemorrhage. This may occur in some cases of GTN for example as a consequence of chemotherapy-induced thrombocytopenia. Symptoms and signs of subarachnoid hemorrhage include a sudden-onset severe headache, vomiting, confusion / lowered level of consciousness, seizures, and some pathologic reflexes. At lumbar puncture the intracranial pressure may be elevated and the cerebrospinal fluid is bloody. Whilst many of these features overlap with brain metastasis from GTN, there are still some clues to help the clinician differentiate between this and subarachnoid hemorrhage: the latter often occurs 7~10 days after chemotherapy; the platelet count is low; there may be hemorrhage in other parts of the body such as the subcutaneous tissues.

(2) Convulsions induced by hypocalcaemia. We have seen the latter occurring as a consequence of metabolic alkalosis caused by severe vomiting. The patients presented with seizures. The characteristics of the convulsions induced by hypocalcaemia are carpopedal and generalized tetany with opisthotonos; the patient remains sane during the whole process and after the convulsion; symptoms are relieved immediately after intravenous administration of 10% calcium gluconate. In contrast, the convulsion caused by brain metastasis is often accompanied by unconsciousness.

(3) Cryptococcal meningitis. Cryptococcal meningitis is believed to result from dissemination of this fungus by the general circulation. Symptoms include fatigue, headache, blurred vision, and confusion are easily misdiagnosed as brain metastases. But

the patients often has associated fever and dry cough. Cryptococcal antigen can be detected by culture of CSF, sputum and urine.

19.5. MANAGEMENT

Patients with cerebral metastasis from GTN require intensive multimodal therapy to obtain remission. In our hospital the treatment of the patients with GTN metastatic to the brain is consistently a combination of systemic and intrathecal chemotherapy with additional other emergency therapy in some cases. Sometimes craniotomy is also a necessary life saving strategy for these patients. With the multimodality therapy，the death rate declined rapidly from 100% to about 20~30% in past 20 years in our hospital.

19.5.1 Systemic and intrathecal chemotherapy

Nowadays, multiagent systemic chemotherapy combined with intrathecal injection of methotrexate remains the main method in patients with the brain metastasis from GTN.

19.5.1.1 Systemic chemotherapy

The systemic chemotherapy is mainly used to control the extracranial disease. According to the previous protocol of chemotherapy, several different chemotherapy regimens were used. Fuorouracil (5-FU) or floxuridine (FUDR)-based combination chemotherapy was favorable in the magement of GTN in our hospital for half of a century[7-9]. Furthermore, the 5-FU- or FUDR-based combination chemotherapy (floxuridine, dactinomycin, etoposide, and vincristine, FAEV) is also an effective regimen with manageable toxicity for patients with relapsed/chemoresistant GTN[9]. Therefore, FAEV is the first-line chemotherapy for the patients with brain metastasis from GTN in our hospital. The doses and detailed usage of this regimen is summarized in Table 19.2. There were 50 patients (54.9%, excluding 6 early death patients) with brain metastasis from GTN who received primary treatment with FAEV in our hospital, of whom, 86% (43/50) achieved a complete remission (CR).

Table 19.2. The dose and detailed usage of FAEV regimen

Drug	Dose	Administration	Time
VCR	2 mg/d	Diluted in 30ml normal saline, 3 hours before other agents administered	day 1
VP-16	100 mg/m^2/d	Diluted in 300ml normal saline and infused in 1 hour	days 1-5
FUDR/5-FU	800-900 mg/m^2/d	Diluted in 500ml glucose 10% and infused in 1 hour intravenously	days 1-5
Act-D	200 μg/m^2/d	Diluted in 200ml glucose 10% and infused in 1 hour	days 1-5

Treatments are given in 3-week cycles

VCR: vincristine; FUDR/5-FU: floxuridine/ fuorouracil, Act-D: dactinomycin, VP-16: etoposide.

If drug resistance had developed or the reduction of the serum β-hCG level was unsatisfactory[9], a replacement regimen of alternating etoposide, methotrexate, dactinomycin (EMA) with cyclophosphamide and vincristine (CO), or alternating EMA with etoposide and cisplatin (EP) was used. If patients remained refractory, almost all salvage regimens were platinum-based.

19.5.1.2 Intrathecal injection

Methotrexate (MTX) is the the most widely used drug for intrathecal injection to control the intracrainial disease of patients with brain metastases from GTN. In our centre we give 10mg ~15mg every 1-3 days so that patients receive 3~4 intrathecal injections with a total dose of 45mg ~50mg during each systemic chemotherapy cycle. To prevent brain herniation due to raised intracranial pressure during each lumbar puncture, the following

points are important: ① Mannitol should be administered routinely before lumbar puncture as a dehydration therapy and if necessary can be repeated 4 hours later. ② The procedure should use thin needles to reduce the risk of spinal fluid leakage. ③ Only small amounts of CSF should be withdrawn for routine testing of hCG and protein content and unless meningitis is suspected samples for glucose and bacteriology may be avoided.

In our series, once the serum β-hCG level was normal, intrathecal injections were stopped, but patients still received an additional 2 to 4 courses of consolidation systemic chemotherapy. The majority of patients required granulocyte colony-stimulating factor because of blood toxicity of chemotherapy.

19.5.2 Emergency（Supportive）therapy

Emergency treatment is of the essence in the management of GTN patient as an early life-saving therapy. There are several important supportive treatment strategies for patients with brain metastases.

(1) Strategies to decrease raised intracranial pressure. In order to decrease intracranial pressure to prevent brain herniation, osmotherapy may be carried out by administering IV mannitol to create a hypertonic solution within the blood to draw water out of the neurons. This helps to reduce fluid within the intracranial space and decrease the pressure in the brain. Because the half life of mannitol is 2–4 hours, we use intravenous 20% mannitol solution (1-1.5 g/kg), followed by 0.25-1g/kg doses as needed every 4 to 6 hours. Sometimes dexamethasone is another good choice to decrease intracranial pressure. It is used to counteract the development of edema of the brain. When dexamethasone is used, the dosage is 10mg intravenously followed by 4mg every 6 hours.

(2) Analgesics. Seizures can increase metabolic demands and oxygen consumption, thereby exacerbating the brain oedema. Furthermore, the problem can be exacerbated by

severe headache making the patient restless. Analgesia and sedation are used to reduce agitation and metabolic needs of the brain.

(3) Management of intravenous fluids. Intravenous fluid is a fundamental component of treatment for patient with brain metastases, because most drugs should be administer by intravenous drips. But excessive fluid administration may increase brain swelling and intracranial pressure. To balance the fluid, the total amount of intravenous liquid the patient receives should be limited in 2500ml~3000ml per day. And these liquids should be hypertonic. The key of management of intravenous fluids is to maintain homeostasis of the patient, and to avoid electrolyte disturbances and acid-base imbalance.

(4)

The nursing care of these patients is also very important. Prevention of the complications associated with coma, convulsions, and hemiplegia is necessary for these patients.

19.5.3 Surgery

Hemorrhage from cerebral metastases is a common cause of death in patients with GTN. Sometimes, the rapidly growing metastasis and surrounding brain edema may have a significant mass effect. The mass effect and the intracranial hemorrhage result in raised intracranial pressure and the development of progressive neurological deficits that require emergent craniotomy and decompression of the tumor. Yang et al.[10] reported 63 patients with cerebral metastases from 1985 to 2004 who received combination chemotherapy in PUMCH. Emergency craniotomy was performed on 13 of these patients in our or the referring hospital to relieve intracranial hemorrhage, hypertension / cerebral hernia development. Of the thirteen patients, 7 achieved CR, 5 a partial remission (PR), and only one died of disease progression. Salvage craniotomy was sometimes required for the removal of therapy-resistant cranial metastases. In our current

series of 97 cases(excluding 6 early death patients), there were 24 patients who received 25 craniotomies (one patient had two operations). Most of them (83.3%) received emergency craniotomy to remove intracranial hematomas and/or to relieve pressure. Of the 24 patients, 18 (75%) achieved a CR.

19.5.4 Irradiation

We seldom used cranial radiation in the patients with brain metastases from GTN in our patients since it can induce long-term intellectual impairment in patients who are cured. We do not think that the use of routine cranial radiation to reduce the chance of brain hemorrhage is appropriate since the effect on tumor vasculature from radiotherapy is a late phenomenon. In fact, the cerebral hemorrhage of these patients is often an early stage event. Some of them even firstly present with intracranial hemorrhage and high intracranial pressure. In this time, emergency craniotomy plays a key role in saving the patient's life. Our results clearly demostrate that it is possible to have a good outcome with chemotherapy and in selected cases craniotomy.

19.6. PROGNOSIS

Our results showed that GTN metastastic to brain was curable if the patients did not have an early death. In the past 20 years our centre's overall 5-year survival rate for patients who received their primary treatment in our hospital was 83.5%. This fell to 53.3% (excluding 6 early-deaths) in patients transferred to us from other centres with multidrug resistant disease.

Univariate analysis showed that age over 40 years, interval from antecedent pregnancy more than 13 months, number of distant metastatic sites more than 1 (lung metastases excluded), failure of previous multidrug chemotherapy, concurrent liver or kidney metastases, and FIGO score over 12 were poor prognostic factors. Craniotomy in

selected cases can improve the prognosis. While multivariate analysis demonstrated that FIGO score over 12, previous multidrug chemotherapy failure history, and concurrence with renal metastasis were independently significant for poor survival.

19.7. CONCLUSION

In conclusion, we have shown that the outcome of patients with brain metastasis from GTN is most favorable with early diagnosis and the use of combined systemic combination agent chemotherapy plus intrathecal methotrexate with or without additional craniotomy in selected cases. Following the innovation and use of CT or MRI scans, diagnosis of patients with early stage brain metastases is no longer a difficult problem. Nevertheless, the presence of symptoms and signs especially the prodromal symptoms and signs are simple but effective clues of early diagnosis. 5-FU or FUDR-based multidrug chemotherapy plus intrathecal MTX injection can produce favorable outcomes for patients with brain metastases from GTN who were treated primarily. The prognosis for patients with age over 40 years, presence of kidney metastasis, previous multidrug chemotherapy failure history, multiple-site distant metastasis, and FIGO scores over 12 was poor. Further work needs to be done to improve the prognosis of the patients with these poor prognostic factors.

For women of childbearing age presenting with unexplainable lung or brain metastases, a diagnosis of GTN should be considered and serum hCG measured as part of the initial work-up. The best outcomes are achieved when such patients are transferred to major GTN centers for specialised management delivered by experts.

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