Gestational Choriocarcinoma with Brain Metastases : Treatment Results and Review of Literatures

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Abstract: *Fourteen patients diagnosed as gestational choriocarcinoma with brain metastases were reviewed concerning treatment results and prognostic factors. Most patients received combination chemotherapy concomitant with whole-brain irradiation. Six of fourteen patients (42.8%) survived and were well without evidence of disease from 9 months to 18 years after the diagnosis of complete remission. Poor prognostic factors include time interval from antecedent pregnancy to start of treatment more than 1 year ($p < 0.05$), modified WHO score more than 15 ($p < 0.05$), and craniotomy performed or not ($p < 0.05$). Furthermore, survivors are also affected by neurological manifestations, failed prior chemotherapy and site of brain metastases but it is not of statistical significance. Management strategies of gestational choriocarcinoma patients at risk of developing brain metastases include initial administration of intensive combination chemotherapy in all high-risk patients and those with lung metastases to eradicate all the tumours. For those who have brain metastases, multimodality approaches including whole-brain irradiation, intensive combination chemotherapy containing high dose methotrexate, and surgical removal in selected cases are recommended. Maintenance chemotherapy of at least 3 courses should be given after achieving remission to prevent recurrence. (Thai J Obstet Gynaecoly 1991;3:103-114.)*

Key words: gestational choriocarcinoma, brain metastases

Currently, gestational choriocarcinoma has been one of the most curable malignancies with the overall cure rate approaching 90% or more[1-5]. This is primarily related to the intrinsic sensitivity of this tumour to certain chemotherapeutic agents, the effective use of sensitive human chorionic gonadotropin (hCG) assays, the identification of high-risk factors that allow for individualization of therapy, and the aggressive use of multiagent che-

motherapy, radiation therapy, and surgery[6]. However, some groups of high-risk metastatic patients still have an unfavorable outcome, 10% to 25% of them would die from this disease[7-9], in 58% of which brain metastases is responsible[10]. Despite the intensive use of multiagent chemotherapy combined with whole-brain radiotherapy and surgery in selected cases, the prognosis is still poor. The survival is no more than 50%, especially in patients who develop brain metastases during treatment or relapse after an initial complete or partial remission[11-14].

The purpose of this report is to analyze some prognostic factors and survival of 14 patients with brain metastases of choriocarcinoma who were treated at the University of Texas MD Anderson Cancer Center between February 1968 and July 1990. On the basis of results and review of the literatures, the management strategies to maximize the chance of patient survival are proposed.

Materials and Methods

A medical record search was conducted to identify all patients diagnosed as choriocarcinoma with brain metastases. Some clinical profiles were analyzed and WHO scores were subsequently assigned as described in the previous report. Prior to 1972, patients were initially treated with single agent chemotherapy either methotrexate or actinomycin-D. Since 1972, patients were treated with a five-day course of methotrexate 25 mg intravenous daily, actinomycin-D 0.5 mg intravenous daily, and cyclophosphamide 5 mg/kg to a maximum of 250 mg intravenous daily (MAC). After 1976, folinic acid was added with increased dosage of methotrexate. Courses were administered after a seven to nine days interval or as soon as recovery from toxicity permitted. Chemotherapy was changed if hCG levels reached a plateau or began to rise on two successive values. Numerous single agents or combinations, including intra-arterial actinomycin-D, intrathecal methotrexate, modified Bagshawe regimen, combination of vinblastine, bleomycin, and cis-platinum (VBP), combination of etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine (EMA-CO) and combination of bleomycin, etoposide and cis-platinum (BEP) were used in patients resistant to their first or second line treatment.

Most patients with brain metastases received 1500 to 3000 rads of megavoltage whole-brain radiotherapy over 10 days to 2 weeks (10 fractions), beginning simultaneously with the start of chemotherapy. Additionally, some patients were treated with radiotherapy for pulmonary, pelvic or hepatic metastases. Craniotomy, thoracotomy, hysterectomy and resection of their metastases were used in selected cases as indicated.

Response to therapy was monitored initially by weekly urine or serum bioassay for hCG. Since 1979, a radioimmunoassay for the beta subunit of hCG has been used. Patients were

considered to be in complete remission only after three normal weekly hCG titers. Patients who subsequently developed elevated titers were considered to have relapse. After three normal weekly titers, patients were followed with monthly titers for a period of one year; thereafter, six monthly measurement were made at least every 5 years or until the time of death. Additional follow-up included physical examination, chest x-ray, brain radionuclide or CT scan, and other indicated studies at various intervals.

Statistical analyses between groups were carried out by using log rank test and Wilcoxon rank test.

Results

All patients' treatment and outcome are summarized in Table 1.

Chemotherapy

All patients received systemic chemotherapy. One patient (LFT) received 2 courses of actinomycin-D combined with whole - brain radiotherapy and craniotomy, she survived with no evidence of disease and had 2 children later. After 1972, all patients were initially treated with multiagent chemotherapy, which was mostly the MAC regimen. Patients with progressive or drug-resistant tumours were individually considered for other regimens such as, VBP, modified Bagshawe regimen, EMA-CO, BEP and other experimental drugs. Intra-arterial actinomycin-D and cisplatin were used in two patients. Only two patients (TKT & RUN) received intrathecal methotrexate. One patient (VAP) was

Table 1 Summary of treatments and outcomes

Patients	Chemotherapy No. of courses	WBRT# (rads)	Craniotomy	Prognosis
LFT	2	2085	Yes	NED 18 yr.
CTM	7	3000	No	NED 2 yr. 4 mo.
KAD	22	2000	No	DOD 8 mo.
VAP*	60	2000	No	DOD 5 yr. 3 mo.
MJH*	14	2000	No	DOD 1 yr.
FR	20	5000	No	DOD 1 yr.
GD*	18	2000	No	DOD 1 yr. 1 mo.
PMG	21	4000	No	DOD 1 yr. 9 mo.
TKT	39	4700	No	DOD 2 yr. 1 mo
RUN	14	1200	No	NED 8 yr. 7 mo.
RDJ*	19	3000	Yes	DOD 2 yr. 1 mo.
MLS	7	3000	Yes	NED 10 yr.
KPC	17	-	Yes	NED 2 yr. 5 mo.
SKS	21	2880	Yes	NED 9 mo.

* = Developed brain metastases during treatment
\# = Whole-brain radiotherapy
DOD = Died of disease, NED = No evidence of desease

treated by immunotherapy with Bacillus Calmette Guerin (BCG) and husband's white blood cells, which resulted in a 3 fold rise of her serum hCG titer. Four patients received further maintenance chemotherapy after achieving first negative hCG titer. Recently, all patients would be treated with regimen containing higher dosage of methotrexate, in which the dosage was increased to 3.1 g/m^2 of body surface area, dividing 100 mg/m^2 given initially intravenously in 15 minutes and then followed by 3 g/m^2 intravenous infusion over 12 hours. Twenty-five milligrams of folinic acid, given every 6 hours, was also given 24 hours later. The side effects from this regimen were generally acceptable.

Radiotherapy

All but one patient (KPC) received whole - brain radiotherapy concomitant with chemotherapy as initial treatment in doses ranging from 1200 rads to 5000 rads. Additional courses of whole - brain radiotherapy were administered in 3 patients whose tumours persisted or progressed, one patient succumbed to intracranial bleeding. The other two died of extensive liver and lung involvement. Two (PMG & RUN) of four patients with liver metastases also received hepatic radiotherapy at doses of 2000 rads and 800 rads respectively, one died of massive intraabdominal hemorrhage from rupture of metastatic nodules. Furthermore, radiotherapy was also instituted to treat tumours in the lungs in 3 patients and the pelvis in 1 patient.

Surgery

During treatment, eleven of fourteen patients underwent at least one major operation. Craniotomy was performed in four patients for ventricular drainage (1)and tumour resection(3), all of them achieved complete remission. One patient's hCG (KPC) spontaneously returned to normal after undergoing tumour removal. Another patient (RDJ) who underwent suboccipital craniotomy, tumour resection could not be performed. She succumbed to brain stem herniation. Thoracotomy was performed on six patients for the purpose of removal of the resistant lung nodules in five patients, in another one, the tumours were unresectable due to extensive lung involvement and only lung biopsy was performed. Five patients underwent hysterectomy, but choriocarcinoma was identified in only one patient. D&C was performed in two patients who presented with vaginal bleeding, the results subsequently showed that the tumour still persisted in the uterus. In another patient (RUN) who received D&C, no tumour was identified but she came in with lower gastrointestinal bleeding and colonoscopy confirmed the metastatic nodules in the descending colon. One patient (MLS) underwent emergency laparotomy for small bowel perforations. The resected specimens revealed

metastatic choriocarcinoma in proximal jejunum and distal ileum.

Survival of the patients

Six of fourteen patients (42.8%) were alive and well without evidence of disease for periods ranging from 9 months to 18 years (mean 3 years) after the diagnosis of complete remission to the last follow-up. Among the surviving patients the longest duration of treatment was 18 months, utilizing a total of 17 courses of various chemotherapeutic regimens, including three major surgical procedures, and interestingly, without any radiotherapy (KPC). The shortest duration was 20 days, treatment included only 2 courses of actinomycin-D, craniotomy, and whole - brain radiotherapy (LFT). Among the dead group, the longest duration of treatment was 63 months, using a total 60 courses of various chemotherapeutic regimens, including immunotherapy, whole - brain radiotherapy, and two major operations but, without craniotomy (VAP). The shortest duration was 8 months, treatment administered including 24 courses of chemotherapy, two radiotherapies, and one major operation (KAD).

When survival by various WHO prognostic factors is separately analyzed (Table 2) to identify whether another factor had independently influenced the patients' survival, it is apparently seen that the group of patients who failed prior chemotherapy has a worse prognostic outcome. Sur-

Table 2 Survival by prognostic factors

Prognostic factors	No. of patients	Survivors		
		Number	%	
Age (years)				
≤ 39	13	6	46	
> 39	1	0	0	
Antecedent pregnancy				
Term	9	4	44	
Abortion	3	1	33	
Mole	2	1	50	
Interval				
≤ 1 year	7	5	71	
				$p < 0.05$
> 1 year	7	1	14	
Serum hCG (mIU/ml)*				
≤ 100000	5	1	20	
> 100000	7	3	43	
Prior chemotherapy				
Yes	5	0	0	
No	9	6	67	

*Two patients (LFT & CTM) were not evaluated

prisingly, only 1 of 5 patients whose serum hCG was 100000 mIU/ml or less survived, while 3 of 7 patients whose hCG titer was more than 100000 mIU/ml is still alive. However, two patients who are still alive are not included for evaluation. Type of antecedent pregnancy does not singificantly affect survival. The number of survivors in the term delivery group (44%) is nearly the same as those in combination of the other two groups (40%). Only one of seven patients attained remission when the interval was more than 1 year, compared with five of seven patients whose interval was less than 1 year survived. This difference is of statistical significance ($p < 0.05$).

Patients presenting with neurological signs or symptoms had a better prognosis, the survival rate was 57% compared with 29% in the non-neurological presenting group. With further analysis, it was discovered that four of the dead in the non-neurologic presentation group fell into the prior chemotherapy group and also developed brain metastases later. All four patients diagnosed with brain metastases during or after treatment died of the disease. Possibly, these may be the consequence of drug-resistant tumours, delay in diagnosis and treatment. Interestingly, three of these four patients had been initially treated with MAC prior to diagnosis of brain metastasis. Furthermore, three of the six survivors in the brain metastases presentation group had failed MAC chemotherapy before going into complete remission with other chemotherapeutic regimens. Only one survivor was successfully treated with MAC.

With a limited number of patients, it was found that if the size and number of brain metastases are not considered, the patients who present with brain stem seeding tend to have a worse prognosis. This is, probably, because it contains various vital centers that control circulatory and respiratory functions, even a small lesion can cause fatality. Furthermore, operation in this area is difficult and dangerous to be performed.

Further analysis was also carried out according to the modified WHO prognostic score. All those high-risk patients are, subsequently, subclassified into two groups, those with scores of 15 or less and those with scores of more than 15. The survival rate was 63% in the former and 17% in the latter groups ($p < 0.05$).

When considering survival after craniotomy was performed, it is clearly seen that the surgery group has a better prognostic outcome. The survival rate in the surgery and non-surgery groups was 80% and 22% respectively ($p < 0.05$). All five patients in the non-craniotomy group with modified WHO score of more than 15 died of the disease and also had uncontrollable brain lesion. Among the seven patients who died of diseases in the non-craniotomy group, two died from direct intracranial hemorrhage, three remained in uncontrolled brain tumours, but died from other tumour - related causes (liver and respiratory

Table 3 Causes of death

Patients	Final report
KAD	Increased hCG titer, uncontrolled brain lesion, liver failure due to extensive tumour metastases.
VAP	Progressive brain lesion, intracranial hemorrhage.
MJH	Increased hCG titer, uncontrolled brain lesion, expired at home.
JFR	Increased hCG titer, uncontrolled brain lesion, intracranial hemorrhage.
GD	Increased hCG titer, uncontrolled brain lesion, respiratory failure due to extensive lung involvement.
PMG*	Massive intraabdominal hemorrhage from rupture of metastatic tumour of the liver, diffuse metastatic tumour replacing approximately 90% of the liver; extensive lung involvement; massive infiltration of the splenic sinusoids.
TKT	Increased hCG titer, respiratory failure due to extensive and uncontrolled lung lesions.
RDJ#	Progressive brain lesions, cardiopulmonary arrest due to herniation of brain stem; choriocarcinoma in medulla oblongata.

* Autopsy performed but permission for CNS examination was not granted
\# Autopsy performed

failure) and the other two died of extensive lung and liver involvement. The only one patient who died in the craniotomy group had a lesion in the brain stem.

Table 3 lists the causes of death in eight patients. Six still had uncontrolled brain lesions documented by clinical features, elevated hCG titer, radiologic examinations and autopsy finding. Two patients died of extensive liver involvement and two died of massive lung involvement.

Discussion

Thus far, no consensus concerning proper and effective therapeutic regimens has been established for management of choriocarcinoma patients with brain metastases. In this institute, various treatment modalities have been employed according to patients' conditions, medical advancement and physician discretion.

Seven of fourteen (50%) patients presented with primary neurological signs or symptoms. Four of these patients of whom three had undergone craniotomy are alive without evidence of disease. It is probably because early diagnosis and proper treatment can be instituted in these patients when compared to the non-neurologic presentation group. Nine of fourteen (64%) patients diagnosed as choriocarcinoma with brain metastases occurred after term delivery. Antecedent term delivery is determined by some authors as an independent poor prognostic factor due to a prolonged preclinical period for tumour growth[15]. These patients, from this study, tended to have a longer interval when compared with the other types of pregnancy, but the survival does not sig-

nificantly differ. The results confirm the findings of Jones et al[12]. Interval between the end of antecedent pregnancy and the start of treatment has significant impact on the survival in this study. Those with an interval of 1 year or less had a better prognostic outcome than those with more than 1 year ($p < 0.05$). Level of serum hCG which reflects tumour burden does not affect survival among this group.

In patients whose modified WHO score is 15 or less, only one in eight (12.5%) could achieve complete remission with MAC chemotherapy. In addition, three of four patients developed brain metastases while on MAC regimen and three of the six survivors had failed this regimen before attaining complete remission with other salvage regimens. It seems questionable whether MAC regimen is virtually effective in cases of brain metastases. A report from Memorial Hospital[12] revealed that 12 of 19 patients had received MAC regimen prior to diagnosis of cerebral metastases. In contrast, a report from Charing Cross Hospital[11], utilizing EMA-CO regimen to treat patients with cerebral metastases showed satisfactory results with 72% survival rate. None of the study group with a score of more than 15 was cured by combined chemotherapy and whole - brain radiotherapy. Only one patient survived with additional tumour resection. Consequently, early neurosurgical intervention in patients with a score more than 15 is recommended if the lesions are accessible for removal without undue risks.

Since successful treatment in patients with brain metastases by 2000 rads whole - brain radiotherapy (WBRT) in addition to chemotherapy was reported at the National Cancer Institute in 1968[16], most centers have adopted this modality in their treatment schemes[10,12,17-19]. In a collected series of 228 patients with cerebral metastases, Jones[20] found that the survival in patients receiving WBRT was 37% compared with 16% for non-irradiated patients. Since choriocarcinoma is known to be both radio- and chemosensitive, intensive combined modality is definitely justified. Whether WBRT acts alone or synergistically with chemotherapy is not well documented. The only evidence that WBRT and not chemotherapy alone plays a major role in eradicating cerebral lesions derived from the autopsy findings that no tumour was identified in the brain while a tumour in other metastatic organs still persisted[16,21]. Not only does WBRT have a tumouricidal effect but also exerts a hemostatic effect on choriocarcinoma which can reduce the risk of intracerebral hemorrhage. This can allow the patients to receive further intensive chemotherapy. Due to the high incidence of multiple metastases, radiation fields usually encompass the entire intracranial contents 3000 rads WBRT over 10 fractions is recomended to be administered without delay in conjunction with simultaneous multiagent chemotherapy[10,17-18]. Since radiation only kills cells as they attempt mitosis, and normal neurons

are a nondividing tissue in adult life and therefore do not express radiation damage. Alopecia is an inevitable consequence but hair will regrow if the patient survives long enough[22]. No gross intellectual impairment was found in the series of Weed and coworkers[13].

Recently, higher dose of methotrexate (3.1 g/m^2) given by 12 hour intravenous infusion, followed subsequently by folinic acid was used to treat these patients in this center. Satisfactory results were encountered despite not having intrathecal methotrexate. Reports from Charing Cross Hospital[11] advocated intrathecal methotrexate as part of an initial combination chemotherapy with the reasons that higher drug concentration will be achieved in the CSF than by any other means, and, also the tumour will receive at least one drug both from the systemic side and from the CSF in potentially high concentration[11,14]. However, high dose systemic chemotherapy could achieve the same results[1,13]. Following conventional intravenous administration of methotrexate, the compound minimally enters the brain, with a CSF: plasma concentration ratio of 0.0006, but with high dose 24 hour methotrexate infusion the ratio has been shown to increase up to 0.03 (50 times) reaching the cytocidal concentration levels[23]. A water soluble drug could exchange readily between the blood and tumour tissue as long as a constant drug concentration was maintained in plasma, lending support to the use of prolonged intravenous infusion chemotherapy rather than bolus therapy and negating the need for intrathecal methotrexate in patients with brain metastases. No available data indicate that intrathecal methotrexate penetrates satisfactorily into tumours deep in the brain. Furthermore, ventricular methotrexate concentration administered by intralumbar route, varied considerably from patient to patient despite similar doses[24].

Despite the multimodality approach, the overall survival rate in this study is only 43%. None of the four patients who developed brain metastases during treatment survived. This may imply that the tumour is already drug-resistant. Table 4 shows the results of treatment in other series. It is clearly seen that patients who develop brain metastases during treatment or relapse after complete or partial remission have a grave prognosis. Rustin et al[14] reported 29% survival rate in this patient group with additional surgical removal of tumour combined with EMA-CO regimen. Bagshawe[25] advocated that surgical removal will offer the best chance of eradicating cerebral metastases which occur during the course of chemotherapy.

Of five patients who had undergone neurosurgical procedures, complete tumour resection could be accomplished in three. All are alive without evidence of disease. One patient (LFT) having a lesion at the brain stem received only ventricular drainage. She is still alive. Surgical removal could not be performed in

Table 4 Survival by mode of brain metastases presentation

Authors	Prior to treatment		During treatment/Relapse	
	No. Patients	Survivors (%)	No. Patients	Survivors (%)
Lurain et al[1]	16	8 (50)	13	0 (0)
Weed et al[13]	11	7 (64)	12	3 (25)
Ishizuka et al[26]	7	1 (14)	20	0 (0)
Athanassiou et al[11]	33	16 (49)	36	2 (6)
Rustin et al[14]	18	13 (72)	7	2 (29)
Jones et al[12]	4	1 (25)	15	4 (27)
Present study	10	6 (60)	4	0 (0)
Total	99	52 (52)	107	11 (10)

another patient who also had brain stem metastases. She succumbed to brain stem herniation later. Ishizuka et al[26] divided brain metastases into 4 categories; superficial, intermediate, deep and cerebellar. Deep type (basal ganglia, brain stem, etc.) occcurs in only 10% and appears to be inaccessible to surgical removal.

As generally accepted, emergency craniotomy is recommended in patients who present with acute deterioration of intracerebral hemorrhage[18,26,27]. Some authors advocated early surgical removal if the lesion appears solitary, certainly localized, and resectable without causing neurological deficit[14,28]. Since 60-80% of metastatic brain tumours are solitary and localized in the superficial layer of the cerebral cortex[10,26,28], the lesions are, possibly, accessible to successful surgical removal. Chemotherapy should also be given in conjunction with surgery to prevent further dissemination of tumour cells during manipulation. Surgical removal is also recommended in cases of drug-resistant tumours[14,26]. Early neurosurgical intervention should be considered in these very high-risk patients who fulfill the criteria for surgical removal.

In conclusion, management strategies of GTT patients at risk of developing brain metastases and those in whom brain metastases have already been diagnosed are proposed as follows. From the preventive aspect, intensive systemic chemotherapy should be initially instituted in all high-risk patients to eradicate all the tumours and minimize the chance of developing drug-resistant tumour. Regimens containing high dose methotrexate are recommended. Since brain metastases are always secondary to lung metastases, consequently, all patients with lung involvement should be administered intensive systemic chemotherapy from the start of treatment.

Should evidence of drug-resistance appear, a salvage regimen is promptly instituted. Surgical excision may be indicated in selected cases.

From the therapeutic aspect, a multimodality approach composed of WBRT in conjunction with intensive systemic chemotherapy is the treatment of choice. Early craniotomy may be considered in cases of a solitary lesion which appears resectable without causing severe neurological deficit to the patients. All patients with a history of failed prior chemotherapy or evidence of drug-resistant tumour, surgical tumour resection is recommended, especially in those whose metastatic tumours elsewhere have disappeared. Neurosurgical intervention is certainly the treatment of choice for patients developing rapid neurologic deterioration. After achieving negative hCG level, patients should receive maintenance chemotherapy at least 3 courses to prevent recurrence. Closed follow-up with sensitive hCG measurement must be employed every 1-2 weeks in the first three months, then monthly for one year and six monthly thereafter to confirm complete remission and early detection of relapse or late recurrence.

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