

Management of high risk gestational trophoblastic disease with brain metastases – A single institution experience from 1996 to 2010

Abstract

Objective: Gestational trophoblastic disease (GTD) is a peculiar disease in females of reproductive age group because of their natural history, management, high potential for bleeding and excellent response to chemotherapy. Although the incidence of brain metastases is only 10%, propensity for uncontrollable hemorrhage in brain parenchyma makes this situation, a medical emergency. We discuss case series of 7 patients with high risk GTD with brain metastases and their management. **Study Design:** A retrospective analysis of 15 years from January 1996 to December 2010 was done to study all cases of GTD treated in this institution. Patients who presented with brain metastases on initial diagnosis (early group) and who had metachronous disease (late group) during the course of treatment or follow-up were summarized in this study. **Materials and Methods:** Of 1208 cases of hydatidiform mole treated in this institution, 325 cases had low risk (WHO score 6 or less), and 38 patients had metastatic disease (score 7 and more). Seven cases were diagnosed to have a high risk GTD with brain metastases, 5 (71.43%) presented initially and 2 (28.57%) developed late brain metastases. **Results:** In our analysis, patients who had brain metastases on presentation had better survival (median = 52 months, range = 18-61) compared with patients who developed brain disease later in the course (median = 5.5 months, range = 3-8). **Conclusion:** Gestational trophoblastic disease with early brain metastases presentation showed better response and survival compared with late presentation group.

Key words: Brain metastasis, gestational trophoblastic disease, high risk gestational trophoblastic disease

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Access this article online

Website: www.oghr.org

DOI: 10.4103/2348-3113.139620

Quick response code:



INTRODUCTION

Survival of patients with gestational trophoblastic disease (GTD) is now improved with appropriate risk stratification according to the WHO prognostic scoring index and institution of multiagent chemotherapy in high risk group. Most common sites of metastases are lungs (80%), vagina (30%), pelvis (20%), brain (10%), and liver (10%).^[1] Brain metastases pose a serious threat with a high incidence of death due to edema, hemorrhage and herniation.^[2,3] Sustained remission/cure were attained in patients with central nervous system (CNS) metastases by the use of multiagent chemotherapy with whole brain radiation therapy (WBRT). Here, we present the outcome of patients who had brain metastases at presentation and those who subsequently developed metastases.

MATERIALS AND METHODS

Between January 1996 and December 2010, 1208 cases of hydatidiform mole were registered and treated in this institution, Institute of Obstetrics and Gynecology/Madras Medical College, Chennai, India. 38 patients were diagnosed with metastatic GTD. 7 patients were diagnosed as high risk GTD with brain metastases of which 5 (71.43%) had initial presentation, 2 (28.57%) developed late brain metastases and their outcome is discussed here. Most common presenting symptoms were seizures, headache, hemiparesis, vomiting, and altered sensorium. All patients were evaluated with computerized tomography of the brain [Table 1]. Consent was obtained from all patients before starting therapy.

Table 1: Incidence of gestational trophoblastic neoplasia in this institution

Study period	January 1996- December 2010
Number of GTD registered	1208
Number of low risk GTD	325
Number of high risk GTD	38
Number of patients with brain metastases	7
Early brain metastases	5
Late brain metastases	2

GTD: Gestational trophoblastic disease

Institutional Review Board clearance was obtained before preparing this manuscript.

Chemotherapy

All 5 (71.43%) patients in the early group were started on EMA-CO regimen when diagnosed with brain metastases. One patient in the late group had initially received EMA-CO and was started on etoposide, methotrexate, actinomycin-D, etoposide, cisplatin (EMA-EP) regimen. Another patient in the late group completed etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine (EMA-CO), EMA-EP priorly and was started on bleomycin, etoposide, cisplatin (BEP) when diagnosed with brain metastases. All patients in the early group had received –intrathecal methotrexate (12.5 mg) every month after whole brain radio therapy.

Radiation therapy

Whole brain radiation therapy was delivered to all patients with brain metastases up to a total dose on 30 Gy in 15 fractions. They received dexamethasone and ondansetron concurrently with WBRT. Radiation was started on day 8 (median), range (0-13 days) from the date of diagnosis.

RESULTS

The median age at diagnosis of all patients with brain metastases was 24 (range: 20-37). Four had a molar pregnancy and three had term pregnancy as antecedent event. The early group had favorable scores in the WHO/FIGO prognostic scoring system compared with the late group (range: 8-14 in early vs. 15-16 in late).

Response to chemotherapy

Early group

All patients responded (100%) to chemotherapy. However the rate of complete response (CR) was more in the early group 4/5 (80%). One patient in the early group progressed to develop spinal metastases and uncontrolled lung metastases after 16 months of completion of treatment. She developed bed sores and died of septicemia.

Late group

Both patients received chemotherapy earlier and the systemic disease was not controlled with chemotherapy. Both patients in the late group developed metastatic disease at 8 months and 11 months respectively after the initial diagnosis. The survival was 3 and 8 months in the

late group after development of brain metastases. Both patients had partial response (PR) to radiation and chemotherapy.

Toxicity

No serious treatment related toxicity was encountered in all patients. Whole brain radiation and all cycles of chemotherapy were completed without any undue delay.

DISCUSSION

Gestational trophoblastic disease with brain metastases is an emergency due to its accompanying complications. Brain metastases can occur in 3-28% of patients.^[4] We found it in 18.57% (7/38) in our study. Multiagent chemotherapy and WBRT can induce remission in about 80-90% of the cases in GTD. In our series all patients in the early group responded well (CR - 80%, PR - 20%). Patients who achieved CR had a good survival with a median of 52 months (range: 28-61 months). However, one patient developed uncontrolled disease and spinal metastases at died 16 months. This data is comparable to the literature evidence.^[5,6] We observed the survival was greatly influenced by the presence of extra-cranial disease. Patients who were chemo-naïve responded well to chemotherapy and had better survival. They were found to have minimal values of β human chorionic gonadotropin (β HCG) on follow-up. Patients in the late group had poor response to chemotherapy and β HCG levels did not levels. This clearly correlated with the extra-cranial disease control status. All patients in the late group developed uncontrolled extra-cranial disease and had poor survival. Schechter *et al.* had demonstrated the need for disease control at the extra-cranial site for achieving better survival.^[6] In this study, 2 years and 5 years survival rate were 100% and 83% in whom disease was controlled at extra-cranial sites. On the contrary, it was 8% and 0% for patients who did not have extra-cranial disease control. The 2 year and 4 year survival in our early group was 100% and 60%. Comparable with literature the survival in our late group was 0% at 1 year denoting the poor prognosis of patients with metachronous CNS lesions depicting an aggressive disease behaviour.

Our observation is that patients with early presentation have a good response to chemotherapy and radiation. Athanassiou *et al.* had published similar results in his study.^[4] However Ayhan *et al.* had reported contrary results.^[7]

All patients in our study received intrathecal methotrexate. Only 3 (60%) patients had prolonged survival >24 months in the early group compared to 0% in late group. We cannot attribute it to intrathecal methotrexate efficacy although Athanassiou *et al.* had proved benefits combining intrathecal methotrexate with systemic chemotherapy. At this point of time, it is not clear if intrathecal methotrexate really adds to decreasing further CNS metastases or accelerating the response of intracranial disease to systemic chemotherapy/radiation. We could probably conclude that combining intrathecal methotrexate may be beneficial to be added to patients with high risk of developing CNS metastases (e.g. uncontrolled systemic disease)

and chemo-naïve patients along with WBRT. However, this approach needs to be further evaluated in clinical trials.

Altıntaş and Vardar had reported overall survival of 66.6% for patients with brain metastases.^[8] We did not encounter any treatment related complications due to combination of chemotherapy and WBRT. None of our patients developed late effects of radiation.

CONCLUSION

Brain metastases pose a serious risk to patients due to high failure rates to therapy. Our study proved better survival for patients who present early and are chemo-naïve treated by combination of systemic chemotherapy and WBRT. The prognosis for late presentation group with uncontrolled systemic disease is dismal due to aggressive disease behavior.

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How to cite this article: Kannan K, Eswaran P, Ismail S. Management of high risk gestational trophoblastic disease with brain metastases - A single institution experience from 1996 to 2010. *Onc Gas Hep Rep* 2015;4:1-3.

Source of Support: Nil, **Conflict of Interest:** None declared.