High Risk Gestational Trophoblastic Disease

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Summary: This is a study of the clinical profile of patients with high risk metastatic gestational trophoblastic disease. A proforma was used to prospectively record clinical details of patients with gestational trophoblastic disease since 1990. There were 12 cases of high risk gestational trophoblastic disease with a WHO prognostic score of 8 or more. The records of these patients were analysed using SPSS software.

The ages of patients ranged from 20 to 35 years with a mean of 25.9 (SD 6.1) years. Five patients were nulliparous while seven were parous. Five patients presented with bleeding per vaginum, three with haemoptysis, two with seizures, one with amenorrhoea and one with abnormal hCG regression after a molar pregnancy. The antecedent pregnancy was molar in 7 and an abortion in the rest. Six patients had a WHO prognostic score of 8 while four had scores above 12. All patients had lung secondaries but two had vaginal and four had brain metastases as well. All patients were initially treated with the EMA-CO regimen. Five patients had hysterectomy. Four patients required second line chemotherapy with platinum and bleomycin and one was referred for pulmonary wedge resection. Two patients had life threatening neutropenia but survived and another survived to have two babies. One patient died within two months of admission due to widespread metastases of brain, lungs, intestines and liver. Another had evacuation of an intra-cranial bleed and died of drug resistance. Follow up of patients ranged from 2 to 54 months with a mean of 23.7 (SD 18) months.

Aggressive chemotherapy offers survival rate of over 80% in patients with high risk gestational trophoblastic disease. Death is usually due to late diagnosis and inappropriate therapy.

Introduction

Gestational trophoblastic disease is a generic term that is currently used for a wide spectrum of neoplasia, from the benign hydatidiform mole at one end to highly malignant choriocarcinoma at the other extreme. Choriocarcinoma used to be considered one of worst malignancies due to its rapid proliferative and destructive course. However, with the discovery of methotrexate and the newer anti-neoplastic drugs it has become one of the most amenable to treatment. Complete cure is now possible for non-metastatic and low risk disease. The high risk metastatic disease remains a formidable challenge but in specialised centres 80% cure is possible even for these patients. This paper describes our experience with metastatic high risk gestational trophoblastic disease in the last seven years.

Methods

This is a descriptive study from a tertiary level teaching hospital. A proforma was used prospectively from 1990 onwards to document patient details at presentation as well as follow up. Once the diagnosis was made the WHO scoring system was used to categorise them as either low risk (score 4 or less), medium risk (score 5 to 7) or high risk (score 8 or more). All patients had a pre- treatment beta hCG estimation. The metastatic work up included chest x-ray, ultrasound scan of abdomen and pelvis and CT brain. Other specialised tests such as bone scan and CSF hCG level were done on an individual basis. All patients were initially given the EMA/CO regime. If CNS metastases were present, the dose of methotrexate was increased and intra-thecal methotrexate also given. Serum hCG was measured after each course of chemotherapy. If response to the first line chemotherapy was inadequate as made out from rising or plateauing hCG levels then, platinum and bleomycin based chemotherapeutic regimens were used. Toxicity was graded according to the modified GOG criteria. Chemotherapy was continued till hCG levels were normal on three consecutive occasions or the patient died. Surgery, either primary hysterectomy or excision of a resistant focus was used judiciously. Great vigilance was kept to detect toxicity and to prevent iatrogenic morbidity and mortality.

The data was entered in SPSS-PC and analysed using this software programme.

Results

There were twelve patients with high risk disease, seven of whom were parous and five nulliparous. The patient details are given in table I.

Table I
Clinical Profile of Patients With High Risk GTD

	n	range	mean	sd
Age (yrs)	12	20-35	26.9	6.1
Time to diagnosis (mths)	12	1-38	13.4	12.2
Follow up (mths)	12	2-54	23.7	18.0
Time to cure (mths)	10	2-12	5.3	3.1

The antecedent pregnancy was molar in seven and an abortion in five. Five patient presented with bleeding p/v, three with haemoptysis, two with seizures, one with abnormal hCG regression and one with amenorrhoea. Six patients had a WHO score of 8, two had a score of 9 to 12 and four had scores above 12. All twelve patients had lung metastases while, four had brain secondaries, two had vaginal deposits, one had liver metastases, one had kidney secondaries and one had bone deposits.

Five patients underwent hysterectomy while one who developed a resistant focus in the lungs benefited from pulmonary wedge resection in another hospital. Four patients required a change over to second –line platinum and bleomycin based chemotherapy. All patients had at least mild toxicity but two had severe life threatening neutropenia and had to be given wide spectrum antibiotics such as ceftazidime, metronidazole, gentamycin and fluconazole. We did not use granulocyte colony stimulating factor. There were two deaths among these twelve patients: one died three weeks after admission due to wide spread disease while another developed drug resistance and died of an intracranial bleed. The autopsy done on the patient with widespread disease showed that both lungs were almost completely replaced by tumour. The patient who developed drug resistance had multiple chemotherapeutic regimens elsewhere and presented with persistent but relatively low levels of hCG values that ranged between twenty and fifty milliunits/ml. She was given EMA/CO and EMA/POMB regimens. Her hCG levels remained normal for almost two years and she then presented with an intracranial bleed and underwent craniotomy.

Ten patients were cured while two died. One patient with brain secondaries who survived neutrophil counts of 600/ cu mm, went on to have two children and was then sterilized.

Discussion

The ratio of hydatidiform moles to deliveries was 1 in 503 and persistent trophoblastic disease to deliveries was 1 in 927 in our hospital (Peedicayil et al 1993). Although it is traditionally believed that the incidence of trophoblastic disease is more in Asia, Africa and South America most reports from developing countries are misleading. One is never sure what is included in the numerator and the denominator is virtually non- existent. Hospital studies are prone to referral bias and the true incidence may be similar to that reported in the developed countries namely, 1 in 24,096 pregnancies (Brinton et al, 1986). In the seven years reviewed in this study there were 35 cases of persistent trophoblastic disease of whom 12(34%) were high risk.

Most patients are treated as persistent trophoblastic disease on the basis of hCG regression curves rather on a histological diagnosis. Accepted criteria for diagnosis include progressively increasing hCG levels, serum hCG value >20,000 miu/ml 16 weeks after evacuation, histological diagnosis of chriocarcinoma or placental site trophoblastic tumour and metastases. Patients with non-molar gestational trophoblastic disease often present with non-gynaecological symptoms such as haemoptysis, seizures or haematuria.

All women with persistent trophoblastic disease should have computerised tomography of the thorax since 40% of patients with apparently normal chest x-rays have positive CT scans (Mutch et al 1986). Ideally the metastatic survey should include CT scans of the brain, abdomen and pelvis. Colour doppler sonography, arteriography and magnetic resonance imaging may be

useful in selected patients. However, laparoscopy, craniotomy and thoracotomy are not justified in order to make a diagnosis since elevated hCG along with radiological evidence of metastasis is sufficient to confirm the diagnosis once pregnancy is excluded.

The FIGO classification is based on anatomical site of involvement that recognises the step-wise progression of metastases in gestational trophoblastic disease but fails to take into account other prognostic factors that are important for individual patients. The National Institute of Health clinical classification used in the USA divides patients into non-metastatic, good prognosis metastatic and poor prognosis metastatic gestational trophoblastic disease (Soper et al, 1988).

The WHO prognostic scoring system is the most widely accepted and is a weighted score using the patient's age, antecedent pregnancy, time to start of chemotherapy, serum hCG level, blood group, number and sites of metastases, size of largest tumour and, prior chemotherapy. With this system all the medium risk patients can be cured by combination chemotherapy while with the American system they would be mixed in with the poor prognosis group.

Patients with a WHO score of 8 or more are at high risk of dying from their disease inspite of aggressive combination chemotherapy. Till recently most American centres have used the MAC regimen with concurrent radiation therapy for those with brain and liver metastases and reported cure rates of 60 to 80% (Gordon et al, 1989). The EMA/CO regimen is the preferred first-line treatment for high risk disease because of its high response rate with low toxicity (Newlands et al, 1986). In patients who do not respond adequately or relapse, individualised chemotherapy regimens incorporating cisplatinum, bleomycin, vinblastine and etoposide need to be used. The treatment of high risk gestational trophoblastic disease gives the best results when administered in a specialised centre. Recent developments include the use of granulocyte colony stimulating factor, total parenteral nutrition, long term intravascular access and autologous bone narrow transplantation so that higher doses of cytotoxic drugs can be given. Experience and expertise are required in the use of anti-neoplastic drugs and management of complications. In India this specialisation within a regionalised health care delivery system is sadly lacking.

Patients with brain metastases have a poor prognosis as they are at risk for cerebral oedema and intracranial haemorrhage. Early surgical resection is recommended in patients that have an isolated lesion that is anatomically accessible. The EMA/CO regimen is modified by increasing the dose of methotrexate to 1 g/m^2 and administering intrathecal methotrexate. Survival rates of 70% have been reported (Rustin et al, 1989). Liver metastases are extremely vascular and death can occur due to catastrophic intra-abdominal haemorrhage. Whole liver irradiation along with chemotherapy and selective hepatic artery embolization have been advocated (Grumbine et al, 1980,Barnard et al, 1986). Surgical extirpation of a single drug resistant focus and use of potentially active agents that have not been previously tried in the particular individual are the only hope for cure.

Patients on chemotherapy need be watched carefully for neutropenia and consequent infection. The nadir in leucocyte count occurs 10 to 14 days after chemotherapy. Broad spectrum antibiotics need to be started prophylactically if neutrophils are dangerously low. As far as possible treatment cycles should not be delayed. Disease activity needs to be monitored clinically, radiologically and by hCG estimation. After complete remission, patients should have at least three treatment cycles and continue to have monthly hCG estimations for two years and then every six months for the rest of their lives. Almost 80% of relapses occur within the first twelve months after completion of chemotherapy.

With first-line EMA/CO therapy for previously untreated patients, the complete response rate is 80% and the partial response is 18% (Newlands et al, 1991). Surgery and second-line chemotherapy achieves cure in the majority of partial responders. Even after complete response there is a 5 to 6% relapse rate. Patients who relapse respond to salvage therapy with individualised treatment protocols. The cumulative survival rates according to life-table

analysis is 85 to 90%. Patients that die do so either early in the treatment due to extensive disease or, late in the course of treatment due to drug resistant tumour. Early diagnosis is thus crucial, especially when the disease develops after a normal pregnancy (Tidy et al, 1995).

Pregnancy should be deferred for one year after completing treatment so that disease surveillance is not interrupted. However, if the patient does get pregnant it can be allowed to continue if the ultrasound scan is normal. After delivery, the placenta should be examined histologically to exclude choriocarcinoma and the serum hCG checked at 8 weeks. The risk of retained placenta and molar pregnancy are increased but abortions, malformations, twins and perinatal mortality rate are no different from the general population(Song et al, 1988).

Conclusion

Patients with gestational choriocarcinoma need to be systematically evaluated and appropriately staged and treated. These patients need to be referred to specialised centres that offer an aggressive and multimodal approach. Current clinical research should be directed toward making the treatment less toxic, less expensive and more convenient. Death from high risk gestational trophoblastic disease is usually due to late diagnosis and inappropriate treatment and rarely due to development of drug resistance.

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