LOW RISK GROUP GESTATIONAL TROPHOBLASTIC DISEASES - A STUDY OF 40 CASES

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Abstract:

This prospective study was done over 40 patients suffering from low risk gestational trophoblastic diseases(GTD) from January 2002 to December 2008 in the department of Radiotherapy , Dhaka Medical College Hospital and Mitford Hospital. They aged between 18 and 45 years, mean age 26.72 years with peak occurrence(70%) in the 3rd decade(21-30Years). Among the 40 cases, one belonged to FIGO score-1, eight to FIGO score-2, twenty to score-3 and 11 to score-4. Only eight patient presented with beta-hCG above 100000u/ml.

All the patients were planned for two weekly chemotherapy with methotrexate and leucovorin (methotrexate – 1mg/kg IV/IM on day 1,3,5,7 and oral leucovorin -0.1mg/kg on day 2,4,6,8) and were continued until beta-hCG level comes down to normal range. Then another three cycles of same chemotherapy were given. Two patients dropped during the course of chemotherapy.

Chemotherapy schedule was changed to five drug regimen, EMA-CO schedule (etoposide-100mg/m^2 on day1&2, methotrexate-100mg/m^2 IV bolus and 200mg/m^2 IV drip day-1, actinomycin-D- 0.5mg/m^2 IV day-1&2, cyclophosphamide-600mg/m^2 day-8 and vincristine-1mg/m^2 IV day-8) due to increase in beta-hCG titre during chemotherapy with methotrexate and leucovorin. Another patient became pregnant after completion of methotrexate plus leucovorin, delivered a healthy male baby and came to us with recurrence. He was also treated with EMA-CO schedule.

After completion of treatment, they were evaluated monthly for three months, three monthly for two years and then six monthly. Follow up period ranged between two to six years (median –four years).

Among the 40 cases included in this study, two patients(5%) dropped during therapy, one(2.5%) expired due to post pregnancy recurrence and remaining 37(92.5%) are yet in disease free state.

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Introduction:

Gestational trophoblastic disease encompasses a spectrum of inter related conditions spanning proliferative changes resulting from an abnormal fertilization to highly malignant lesions such as choriocarcinoma[1]. Though they constitute fewer than 1% of gynaecological malignancies, they are highly important to recognize because of their life-threatening potential and at the same time their high curability if treated early and by experienced center[1].

It's incidence varies widely among the various populations, with figure as high as 1 in 120 pregnancies in some ares of Asia and South America, compared to 1 in 1200 in United States[2]. The risk is five fold higher in women older than 40 years and is also increased in those younger than 20 years[3].

Chemotherapy is highly effective for all forms of gestational trophoblastic disease. Forty years ago, women with gestational trophoblastic disease had 95% mortality rate. But today, with the advent of effective chemotherapy and the development of a reliable tumor marker beta-hCG, the cure rate is now 90%-95%[4].

Scoring of the patients suffering from gestational trophoblastic disease by separate individual points e.g. age, antecedent pregnancy, interval from pregnancy, serum beta- hCG, blood group(OAB grouping), tumor size, metastasis, prior chemotherapy is very very important on the basis of which risk group(low, intermediate and high) classification is done. Chemotherapy is planned according to risk group the patient belonging to. This practice has been started in our country in limited sphere and the result is quite satisfactory. This study is one of them showing encouraging response in our limited sphere.

Materials and Methods:

The study was done in the Department of Radiotherapy, Dhaka Medical College Hospital

and Mitford Hospital from January 2000 to December 2008. The patients suffering from low risk gestational trophoblastic disease referred from Gynae Department of those Hospital and other Clinics and Hospital of the country were the materials of this study.

Details history was taken individually for each case. Thorough physical examination was done. Routine blood counts, kidney and liver functions were done. Ultrasonogram of the whole abdomen, chest X-ray were done in all the cases. CT scan of the brain was done in one case for cerebral metastasis. Beta-hCG was done before starting treatment in all the cases & repeated before each cycle.

Scoring was done according to FIGO guide lines e.g. age, beta-hCG, antecedent pregnancy/ abortion/molar pregnancy, tumor size, metastases etc. All the patients included in this study belonged to FIGO score 1-4 (patients with score-0 were excluded from the study). On Bagshaw's risk group classification, they belonged to low risk group.

After correction of deficiencies(eg transfusion if anaenic), they all were planned chemotherapy as per schedule: a) Inj. Methotrexate 1mg/kg IV/IM Day1,3,5,7 and b) Folinic Acid(leucovorin) 0.1mg/kg IV/orally on Day 2,4,6,8. The cycles were two weekly and continued till beta-hCG comes down to normal range and then another three cycles were given.

Chemotherapy schedule was changed to five drug regimen, EMA-CO schedule as per: Inj Etoposide-100mg/m^2 IV drip on day 1&2, Inj. Methotrexate-100mg/m^2 IV bolus and 200mg/ m^2 IV drip day-1 with leucovorin resque Inj. Actinoycin-D- 0.5mg IV day-1&2, Inj. Cyclophosphamide-600mg/,^{2} IV day-8 and Inj. Vincristine-1mg/m 2 IV day-8 due to increase in beta-hCG titre during chemotherapy with methotrexate and leucovorin in six cases. Another patient became pregnant after completion of methotrexate plus leucovorin, delivered a healthy male baby and came to us with recurrence & was treated with EMA-CO schedule. This schedule was also two weekly and continued upto 3rd additional cycles after declining the beta-hCG to normal level.

After completion of treatment all the patients were evaluated monthly for three months, three monthly for two years and then every six monthly. During evaluation thorough physical examination, routine bood count, beta-hCG, ultrasonogram of whole abdomen, chest X-ray were done. All the documents were recorded in individual file/sheet.

Results:

In this series 40 patients suffering from gestational trophoblastic diseases were studied. Among them 26 were primi and 14 multipara. Majority of them(82.5%) gave the history of antecedent molar pregnancy, abortion in six(15%) cases and full term pregnancy in one(2.5%) cases.

Table-I

Classification of the patients according to age (n=40)

Age in years	No. of patients	Percentage
Up to 20 years	5	12.5%
21-30 years	28	70%
31-40 years	2	5%
41-50 years	5	12.5%

Age range : 18-45 years
Mean age : 26.72 years.

Table-II

Distribution of the patients according to ß-hCG level (n-40)

Beta-hCG Level in IU/L	No. of Patients	Percentage
Up to 1000 IU/L	5	12.5%
1001-10000 IU/L	14	35%
10001-100000 IU/L	13	32.5%
>100000IU/L	8	20%

Table-III

Distribution of the patients according to FIGO score (n-40)

FIGO Score	No. of Patients	Percentage
FIGO Score - 1	1	2.5%
FIGO Score - 2	8	20%
FIGO Score - 3	20	50%
FIGO Score - 4	11	27.5%

Table-IV

Results on the basis of FIGO-Score (n-40)

FIGO-Score	No. of Patients	Dropped	Expired	Remission	Percentage
1	1	0	0	1	100%
2	8	0	0	8	100%
3	20	2(10%)	1(5%)	17	85%
4	11	0	0	11	100%

All the patient were planned for chemotherapy with methotrexate and folinic acid. Among them chemothetrapy schedule was changed to five drugs regimen (EMA-CO) in six cases due to progression of beta-hCG during the course of chemotherapy. Another one cases who became pregnant just after completion of treatment, came with recurrence and was treated with EMA-CO schedule and cranial irradiation for cerebral metastasis and expired during the course of radiotherapy.

Among the 40 cases 38 achieved complete remission of the disease and two absconded during treatment by chemotherapy. Number of cycles of chemotherapy required to bring the beta-hCG within normal range varied from three to 12 cycles. Then another three cycles of same chemotherapy were given in every case.

After completion of treatment, they have been evaluated up to six years(median follow up four years). Two patients were dropped during the course of chemotherapy. Another one patient, who became pregnant within four months after completion of treatment delivered a healthy male baby and presented to us with recurrent growth with generalized metastases and expired. All the remaining 37 patients(92.5%) are yet in state of complete remission. Among them, two ladies gave issue of two healthy baby three years after completion of treatment.

Discussion:

Gestational trophoblastic disease, a spectrum of neoplastic disorders arising from the human placenta, is highly curable, even when advanced. Four distinct clinicopathological entities have been described: molar pregnancy, invasive mole, placental-site trophoblastic tumors and choriocarcinoma[1].

Gestational trophoblastic disease most commonly follows molar pregnancy but may also occur after normal or ectopic pregnancy and spontaneous or therapeutic abortions[1]. Prior molar pregnancy, lower socioeconomic status and women of blood group A and married with men of blood group O are at increased risk[5]. Parity, ethnicity, nutritional factors and cigarette smoking have been blamed as risk factors, but no clear association have been found. However, oral contraceptives and number of sexual partners before the index pregnancy appear to double the risk of Gestational trophoblastic tumors[6].

Majority (82.5%) of the patients included in this study gave the history of antecedent molar pregnancy, abortion in six (15%) cases and full term pregnancy in one(2.5%) cases.

The risk is five fold higher in women older than 40 years and is also increased in those younger than 20 years[3]. In this series patients aged between 18 and 45 years, mean age 26.72 years and 70 belonging to 3rd decade (21-30 years).

Stratification of patients in to low, intermediate and high risk group is done on scoring system based on prognostic factors that was developed at Charing Cross Hospital by Bagshawe[7]. Low risk group includes FIGO score up to 4, intermediate risk group includes score 5-7 and high risk group score more than 7. In this study, only low risk group of patients who showed persistent or increased levels of beta-hCG were included (patients with FIGO score-0 were excluded). Among them, one belonged to FIGO score-1, eight to score-2, 17 to score-3 and eight to score-4.

Prognostic Scoring of the patients suffering from gestational trophoblastic disease is done

by separate individual points e.g. age, antecedent pregnancy, interval from pregnancy, serum beta- hCG, blood group(OAB grouping), tumor size, metastasis, prior chemotherapy[7].

Among them the level of beta-hCG is crucial in helping to establish the diagnosis , providing prognostic information that will help in adopting therapeutic strategy, observing response of therapy and finally in evaluation during follow up. Only eight patients in this series had initial beta-hCG >100000IU/L, others <100000IU/L.

For low risk group Gestational trophoblastic disease, methotrexate by itself or with leucovorin rescue has most commonly been used[8]. Etoposide is also effective, but it's leukaemogenic effect is a concern in low risk patients[8]. Other drugs used in the past for low risk group are; cyclophosphamide, vincristine, doxorubicin, hydroxyurea and 5-flurouracil[1]. Current Gynaecologic Oncology Group studies for low-risk disease begun in 1999 are comparing methotrexate with dactinomycin and also assessing dactinomycin in patients not responding to methotrexate[1].

In our series 33 patients were treated with two weekly methotrexate and leucovorin rescue schedule & two of them absconded during therapy. On average 6.43 such cycles(Range 3 -12 cycles) were needed to bring the beta-hCG value within normal range and then another three additional cycles of same chemotherapy were given. Two patients absconded during therapy. Six patients were also planned for methotrexate and leucovorin rescue and then shifted to five drugs (EMA-CO) schedule. One unfortunate young lady achieved complete remission by methotexate and leucovorin rescue and became pregnant immediate after completion of treatment. She gave birth to a healthy male baby and presented with recurrence having generalized metastases. She received two cycles of chemotherapy with EMA-CO schedule and then showed features of cerebral metastasis, confirmed by CT-scan. Urgent concomitant cranial irradiation was started along with chemotherapy and she expired during the course of chemo-radiotherapy.

Chemotherapy is highly effective for all forms of gestational trophoblastic disease. Bagshawe reported 83% survival in patients with risk group of gestational trophoblastic disease[9]. Brewer Trophoblastic Disease Center showed 100% cure rate[10]. Ilancheran showed 100% cure rate in low risk group gestational trophoblastic disease[11].

In this series result of treatment of low risk gestational trophoblastic disease is also satisfactory. Among the 33 patients of low risk group trophoblastic disease who were treated by methotrexate and folinic acid rescue, 31 have become disease free and other two were absconded during therapy. Another six patients of low risk group who did not respond to initial methotrexate and folinic acid rescue were treated by EMA-CO schedule and al of them became cured. Only one patient who achieved complete remission by methotrexate and folinic acid rescue, but became pregnant immediately after completion of treatment and expired due to recurrence of the disease at both primary and metastatic sites including brain.

So, among the 40 cases low risk group gestational trophoblastic disease included in this study, 37(92.5%) patients have become cured, two(5%) absconded and one(2.5%) expired. Three mothers have been blessed with healthy baby.

In conclusion, we want to give more emphasis on proper assessment of the patients, proper FIGO scoring, then Bagshawe's risk group classification and then treatment planning accordingly. Finally follow up to be ensured and pregnancy should not be advised within one year(preferably two years) after completion of treatment.

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