Management of “Ultra-High Risk” Gestational Trophoblastic Neoplasia at a Tertiary Center in India

Abstract

Aims: The aim of this study is to identify clinicopathological features associated with increased morbidity and mortality in cases of “ultra-high risk” gestational trophoblastic neoplasia (GTN) and to compare initial low-dose etoposide-cisplatin (EP) induction chemotherapy with respect to etoposide methotrexate adriamycin cyclophosphamide vincristine (EMACO) regimen. Settings and Design: This was a retrospective study of patients of high-risk GTN from January 2012 to December 2016 with criteria mentioned as “ultra-high-risk group;” pathological or suspected diagnosis of choriocarcinoma, multiple (>20) pulmonary metastases or associated with hemoptysis, brain metastases, large-volume liver metastases, profuse vaginal bleeding, human chorionic gonadotropin >1000,000 IU/L, interval since the last antecedent pregnancy of >2.8 years. Subjects and Methods: Comparison between the two groups of chemotherapy regimens and the median number of chemotherapy courses required to achieve complete remission was done. Statistical Analysis Used: Data were analyzed using the SPSS software version 18 and Fisher’s exact test with P value statistically significant at the level of 0.05. Results: Thirty-seven cases were high-risk GTN and 24 were “ultra-high risk.” The higher percentage of patients underwent remission of disease following low-dose induction chemotherapy as compared to primary EMACO therapy, 71.4% versus 58.8%. No resistance to second-line chemotherapy was noted, and no surgical intervention was required in the patients receiving low-dose induction chemotherapy before EMACO. Conclusions: We noted a decrease in the proportion of patients developing resistance to primary chemotherapy and lesser adverse effects in those receiving initial low-dose induction EP chemotherapy.

Keywords: Choriocarcinoma, EMACO regimen, gestational trophoblastic neoplasia, high risk gestational trophoblastic neoplasia, low dose etoposide-cisplatin

Introduction

Gestational trophoblastic neoplasia (GTN) comprises malignant trophoblastic disorders, namely invasive mole, choriocarcinoma (CC), placental site trophoblastic tumor, and the extremely rare epithelioid trophoblastic tumor.[1-3] GTN has been divided into “low risk” and “high risk” tumors based on the FIGO prognostic score.[4] Low-risk GTN has excellent remission rates with cure rates noted to be approaching 100%. Cases of high-risk GTN are also responsive to chemotherapy; however, cure rates decline to approximately 85% with overall 5-year survival being 75%–90%.[1] They tend to have increased resistance to single-agent chemotherapy, increased risk of recurrence, and require combination chemotherapy to achieve remission.[3]

This subgroup of ultra-high risk GTN required salvage chemotherapy in the form of low-dose induction chemotherapy consisting of etoposide-cisplatin (EP) as they were associated with increased risk of early death either due to the tumor pathology itself or respiratory compromise and hemorrhage secondary to a heavy burden of disease or rapid tumor destruction with full-dose chemotherapy.[6] However, there is very limited information about ultra-high risk subgroup so far due to its rarity.
Aims

We have undertaken this study at our institution to determine clinico-pathological features in this subgroup, comparison of initial low-dose EP induction chemotherapy with respect to combination multidrug chemotherapy EMACO regimen in terms of patient morbidity, requirement of subsequent additional treatment, and patient mortality.

We tried to identify clinico-pathological features associated with increased morbidity and mortality in cases of “ultra-high risk” GTN. Clinical conditions included in the subgroup of “ultra-high risk” GTN are:[7]

• Pathological or suspected diagnosis of CC
• Multiple (>20) pulmonary metastases or associated with hemoptysis
• Brain metastases
• Large volume liver metastases
• Profuse vaginal bleeding
• Human chorionic gonadotropin (hCG) >1000,000 IU/L
• Interval since the last antecedent pregnancy of > 2.8 years
• Comparison of initial low-dose EP induction chemotherapy with respect to combination multidrug chemotherapy EMACO regimen in terms of patient morbidity, requirement of subsequent additional treatment, and patient mortality.

Subjects and Methods

This was a retrospective study conducted at a tertiary care Regional Cancer Center in India. This regional center caters to majority of oncology patients in Western and Central India. Data were obtained from medical case files and electronic database of all the patients of high-risk GTN who underwent treatment at the hospital from January 2012 to December 2016. All patients underwent an initial assessment before treatment, including medical history, physical examination, transvaginal or transabdominal sonography, chest X-ray or computed tomography (CT), blood routine test, serum biochemistry, and serum b-hCG levels. Brain magnetic resonance imaging and CT were also performed.

Information regarding staging, prognostic scoring, treatment, resistance, relapse, and survival information was extracted. Patients with placental site trophoblastic tumor and epithelioid trophoblastic tumor or those who defaulted on treatment were excluded from the study. Patients with the following criteria-pathological or suspected diagnosis of CC, multiple (>20) pulmonary metastases or associated with hemoptysis, brain metastases, large-volume liver metastases, profuse vaginal bleeding, b-hCG >1000,000 IU/L, interval since the last antecedent pregnancy of >2.8 years were included in the “ultra-high risk” study group.

A total of 37 high-risk GTN patients were identified, of which 24 were found to fulfill the criteria of ultra-high risk.

Of these, 17 patients received primary therapy as multidrug combination chemotherapy (EMACO), whereas seven patients received low-dose induction EP chemotherapy followed by definitive EMACO combination chemotherapy. Low-dose induction EP chemotherapy consists of etoposide 100 mg/m² and cisplatin 20 mg/m² on days 1 and 2 repeating weekly for one to two cycles before commencing EMACO.[4,7] Patient selection for low-dose induction chemotherapy was dependent on the clinical judgment of disease volume, particularly within the thorax, presence of brain and/or liver metastases, and an overall assessment of the risk of organ failure and early death.

The outcome measure was the comparison between two groups of chemotherapy regimens to achieve complete remission, (defined as a normal b-hCG value after the completion of treatment), and the median number of chemotherapy courses required to achieve complete remission in two groups. Data regarding salvage chemotherapy, adjuvant treatment modalities were also noted. Short-term toxicities and mortality were registered.

Data were analyzed using IBM SPSS software 18.0 (IBM, United States) Windows and Fisher’s exact test with P value statistically significant at 0.05.

Results

A total of 72 patients of GTN were treated at The Gujarat Cancer and Research Institute, Ahmedabad during a period of 5 years. Of these, 37 were high-risk GTN patients and 35 belonged to the low-risk group. Of the 37 patients, 24 patients were classified in the “ultra-high risk” GTN cohorts as per the criteria. The demographic and clinical characteristics of these are summarized in Table 1.

The mean age of the patients categorized as ultra-high risk was 26.9 years (21–40 years). Mean beta hCG was found to be 745,845.5 IU in “ultra-high risk” as compared to 177,680 IU in patients who were high-risk GTN.

Of the 24 patients, 12 cases had a term pregnancy as the antecedent pregnancy and 12 had an abortion as the antecedent pregnancy. The mean duration of interval from the antecedent pregnancy in the “ultra-high risk” group was found to be 17.5 months, significantly higher than patients of high-risk GTN that was 12 months. Mean duration of interval from antecedent pregnancy for those patients receiving primary EMACO combination therapy and those receiving initial low-dose induction EP was comparable. In the cohort studied, 21 patients (87.5%) had lung metastasis, eight patients (33.3%) had vaginal metastasis, of which three had profuse vaginal bleeding, three (12.5%) had brain metastasis, and four (16.6%) had liver metastasis. The mean prognostic score was found to be 12.7.

As described earlier, patients with high-risk GTN were termed to be at risk for adverse morbidity and mortality outcomes in the presence of high-risk features.[8] Table 2 enumerates these features and the distribution of cases in
In the current cohort. It is important to note that multiple high risk features present in some patients. Patient selection for low-dose induction chemotherapy was dependent on the clinical judgment of disease volume, particularly within the thorax, presence of brain and/or liver metastases, and an overall assessment of the risk of organ failure and early death. Consistent with this, patients who received EP induction chemotherapy had a higher number of lung metastases (more than twenty metastases), brain metastases, large-volume liver metastases and/or higher total FIGO score.

Table 3 shows a comparison of treatment modalities employed in the two groups; receiving primary EMACO combination therapy and those receiving initial low-dose induction EP followed by EMACO chemotherapy. Out of the seven patients receiving low-dose induction EP, five received two cycles of low-dose EP before combination EMACO therapy and one patient received only one cycle of low-dose EP. In this group, one patient succumbed following administration of low-dose EP.

The average number of doses of EMACO administered in patients receiving primary combination EMACO regimen was 5.7 as compared to those receiving low-dose induction EP that was 6. Remission rates were noted in both groups.

The higher percentage of patients underwent remission of disease following low-dose induction chemotherapy as compared to primary EMACO therapy, 71.4% versus 58.8% (P = 0.66). Brown et al. have previously described persistence rates of disease in 20%–25% of the patients when treated with combination EMACO regimen. Lesser percentage of remission may be noted in our study as the cohort consists of those patients with increased burden of disease, predisposed to increased resistance to treatment. Resistance to EMACO was noted in 7 (41%) of the patients. In patients receiving low-dose induction EP, resistance to chemotherapy was noted in two (28%) of the patients. Two patients who received primary EMACO therapy developed resistance to second-line chemotherapy. Furthermore, two patients required surgical intervention. One patient underwent hysterectomy due to refractory disease following five cycles of combination EMACO therapy, and the other underwent bilateral internal iliac artery ligation to limit hemorrhage. Both the procedures were carried out in the cohort receiving primary EMACO combination chemotherapy. No resistance to second-line chemotherapy or surgical intervention was required in the group of patients receiving low-dose induction chemotherapy before EMACO.
As noted in Table 4 out of the 24 patients, nine developed resistance to first-line chemotherapy. Factors associated with patients developing resistance to combination EMACO therapy are mentioned in Table 4.

Table 5 summarizes the adjuvant therapy required in addition to combination chemotherapy administered to the patients in view of distant metastasis in patients within the study group. Brain metastasis was noted in three patients, of which all received intrathecal methotrexate. In addition to chemotherapy, one of the patients received cranial external beam radiation therapy. Eight patients were seen to have vaginal metastasis, of which one had to undergo emergency internal iliac artery ligation in view of significant hemorrhage. Patients with lung metastasis and liver metastasis had a good response to combination chemotherapy, and no further additional therapy was required.

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Short-term complications arising secondary to treatment was noted in 16 patients. Of these, 12 patients (70%) received primary combination EMACO chemotherapy, whereas four (57%) had received low-dose induction EP chemotherapy. The most common complication noted was febrile neutropenia seen in nine (37%) patients. Complications were seen in lesser percentage of patients receiving low-dose induction EP chemotherapy. One death was noted in each of the study group. Patients in the group receiving primary combination EMACO chemotherapy expired secondary to massive hemorrhage following chemotherapy. In the patient that received low-dose induction EP chemotherapy death occurred secondary to pulmonary hemorrhage and embolism. Table 6 summarizes the morbidity and mortality in the study cohort.

**Discussion**

GTN has excellent remission rates. However, as the stage and prognostic score increases, there is a decrease in the percentage of patients who attain complete remission. Low-risk GTN are noted to have cure rates approaching 100%, whereas in case of high-risk GTN cure rates of up to 85%.[3] In addition to decline in cure rates in cases of high-risk GTN, these patients require combination chemotherapy to achieve remission and are at an increased risk of recurrence. A number of factors have been associated with reduced long-term survival, often as a consequence of the development of drug resistance. The advanced disease has been implicated as a risk factor for early death in patients with GTN secondary to fatal hemorrhage and/or organ failure.[7,10] With increased understanding of both clinical and pathological aspects of disease, attempts are made to reduce both complications and drug resistance during treatment.
In the current study, the mean age was found to be 26.9 years and mean serum beta hCG was found to be 745,845.5 IU. It was seen that the mean interval from previous antecedent pregnancy was 17.5 months in case of the “ultra-high risk” group as compared to 12 months for patients of high-risk GTN excluding the above cohort. Powles et al. following a retrospective analysis have suggested that the interval since the last antecedent pregnancy is a prognostic factor for the development of drug resistance.\(^{[6,7]}\)

Patients with ultra-high-risk GTN are at increased risk of morbidity and mortality. In the current study, these patients either received primary combination chemotherapy in the form of EMACO or low-dose induction chemotherapy, EP followed by EMACO. Low-dose induction EP was introduced in patients with a high burden of disease at presentation to enable a more gradual reduction in tumor bulk in the initial weeks of treatment to minimize the risk of early death.\(^{[1]}\)

Alifrangis et al. conducted a retrospective study at Charring Cross Hospital, UK.\(^{[4]}\) Between 1979 and 1995, overall survival with EMACO in high-risk GTN at their institute was 85.4%, with a significant proportion of early deaths (<4 weeks). They tried to determine whether survival rates improved in a more recent patient cohort (1995–2010). Four hundred and thirty-eight patients received EMA/CO between 1995 and 2010. EP induction chemotherapy was given to 23.1% of high-risk patients (33 of 140 patients) with a large disease burden, and the early death rate was only 0.7% compared with 7.2% in the pre-1995 cohort. Despite the limitation of nonrandomized design, their results strongly suggest that the reduction in early deaths was attributable to EP chemotherapy.

There was no difference in the mean dose of EMACO utilized for treatment in the two groups (5.7 vs. 6). May et al.\(^{[5]}\) reported that significant part of patients treated with EMACO did require salvage chemotherapy with a platinum-containing regimen.\(^{[2,6,7]}\) Patients treated with only EMACO regimen had increased incidence of resistance/relapse as compared to those patients who received low-dose induction EP (41% vs. 28%). This could be explained by the fact that the patients receiving low dose received the definitive combination chemotherapy in the form of EMACO. Furthermore, in patients receiving only EMACO, resistance to second-line chemotherapy was noted in two patients.

Despite the high effectiveness of EMACO, progressive disease or relapse of the disease has been reported in up to 30%–40% of the patients. Different risk factors for developing resistance include patients presenting with metastases in the liver and brain.\(^{[9]}\) Ultra-high-risk GTN is associated with a higher frequency of resistance to standard first-line methotrexate and etoposide based regimens. This is especially the case in patients with liver metastases, multiple brain metastases and those with a prolonged time from the antecedent pregnancy. These are associated with increased toxicity and morbidity. EP/EMA, the second line chemotherapy utilized is very toxic and great attention to renal and bone marrow function is required.\(^{[2,4,10]}\) In the current study, resistance to first-line chemotherapy was noted in nine patients. Two patients had an antecedent pregnancy beyond 2.8 months, and another patient had liver and brain metastasis. Majority of the patients developing resistance had a WHO score >12 (5/9), and 2 patients had hCG value >1000,000; signifying increased disease burden.

Furthermore, two patients in the EMACO group required surgical intervention. One underwent bilateral internal iliac artery embolization due to torrential hemorrhage secondary to vaginal metastasis. The second patient required hysterectomy due to relapse of disease following five cycles of EMACO chemotherapy. EMACO therapy, the standard regimen for high-risk patients can lead to catastrophic hemorrhage during the first few weeks of treatment due to rapid destruction of tumor following chemotherapy.\(^{[1]}\)

In the current study, increased morbidity was noted in patients receiving upfront EMACO therapy versus initial
low dose chemotherapy. Febrile neutropenia was the most common complication probably secondary to the effects of chemotherapy. Authors have reported those patients with massive disease burden, starting with standard chemotherapy may have severe marrow suppression leading to bleeding, septicemia, and even multiple organ failure.[1] There have been previous reports, wherein patients treated with EMA/CO more often had anemia, neuropathy, and hepatotoxicity.[9] In both the subgroups one death was noted. In the cohort receiving primary combination chemotherapy, EMA/CO death occurred following administration of first cycle of chemotherapy, secondary to massive hemorrhage. The particular patient had a high tumor burden, and as noted in literature following administration of chemotherapy there was rapid tumor destruction leading to massive hemorrhage. In the group receiving low-dose induction EP chemotherapy, death was secondary to pulmonary hemorrhage and embolism. Clinically, the morbidity is much less with low-dose EP induction chemotherapy, though there is no statistical significance noted.

Conclusions

The management of high-risk GTN has evolved with introduction of low-dose EP induction chemotherapy, primarily to reduce the risk of early death. In the present study, one death is noted in the group receiving low-dose EP; however, sample size limits drawing of any conclusions. The previous study by Alifrangis et al.[4] reported a decrease in mortality in patients receiving low-dose induction chemotherapy with EP. In our study, we noted decrease in the proportion of patients developing resistance to primary chemotherapy and adverse effects in patients receiving initial low-dose induction EP chemotherapy. However, the study is limited by its small sample size, and further studies will have to be undertaken to statistically validate the observation.

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Conflicts of interest

There are no conflicts of interest.

References