Research Article

Prognosis of Gestational Trophoblastic Neoplasia in Women at 40 Years Old and Above: A Multicentre Retrospective Study

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ABSTRACT

Purpose: To investigate the outcome of different treatment strategies in patients with gestational trophoblastic neoplasia (GTN) in women at 40 years old and above.

Patients and Methods: We analysed a historical cohort from 5 referral centres from 5 countries, including all women with GTN treated between 2012 and 2017, who were 40 years old and older. Baseline characteristics and outcome of different treatment strategies were recorded and evaluated. The patients were categorized into low-risk non-metastatic, low-risk metastatic and high-risk, based on the FIGO classification.

Results: A total of 141 cases were identified, of which 112 cases fulfilled the inclusion criteria. Mean age was 45.4 years ± 4.2SD. Of 80 patients with LR non-metastatic GTN, 46 women received single agent chemotherapy and 34 a hysterectomy with or without (n = 4) chemotherapy. Higher remission rate and shorter treatment duration (P<0.001) was seen in the group that underwent hysterectomy. Seven of the 14 patients with low-risk, metastatic GTN were cured with methotrexate. Two of the 18 high-risk patients died during chemotherapy treatment, four were treated with polychemotherapy; two of them needed second line chemotherapy for incomplete response. Two cases received induction with methotrexate followed by EMA/CO. Ten high-risk patients were treated with hysterectomy and chemotherapy, of these six achieved complete remission, three needed second line chemotherapy, and one patient died during chemotherapy treatment.

Conclusion: In this cohort of women with GTN at 40 years old or above, we found high proportions of metastatic and high-risk cases, of methotrexate resistance, and of need for multiple treatment lines. In all groups, hysterectomy was performed, but its role remains controversial in metastatic low-risk and high-risk disease.

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Introduction

The incidence of gestational trophoblastic neoplasia (GTN) increases with age; however, its treatment in women aged 40 years and above is poorly studied. Post-molar GTN after suction evacuation of molar pregnancies has been reported in 23 to 37% of women older than 40 years and 31 to 56% of women above 50 years of age [1]. In contrast, GTN following complete and partial moles have been reported in 20%
and 5% of young women, respectively [2]. Moreover, Savage et al. reported a strong association of non-molar gestational choriocarcinoma with rising maternal age. The incidence relative to viable pregnancies was 1:80 227 for ages 30-34 in contrast to 1:1197 for women aged over 45 [3]. In elderly women, complete moles are generally aneuploid, which is a risk factor for GTN [4].

To reduce this malignant sequel, prophylactic single-agent chemotherapy after molar evacuation has been recommended for “high-risk” moles in patients having maternal age above 40 years [5]. However, Jiang et al. and Geng et al. have reported no significant decrease in post-molar GTN after prophylactic chemotherapy [6, 7]. Primary hysterectomy reduces the tumor bulk and has been recommended in older patients with molar pregnancies to reduce the risk of developing GTN and need for chemotherapy [8]. However, Giorgione et al. reported that such treatment did not reduce the incidence of GTN [9]. The International Federation of Obstetrics and Gynaecology (FIGO) scoring system stratify patients with GTN to treatment decisions; one of the items included is the patient’s age [10]. For the treatment of older GTN patients, it is debatable whether upfront hysterectomy should be performed to reduce tumor bulk or chemotherapy should be conducted without hysterectomy [11, 12]. Hysterectomy is recommended for placental-site trophoblastic tumors (PSTT) and epithelioid trophoblastic tumors (ETT) since both are often confined to the uterus and exhibit poor response to chemotherapy [13]. In the absence of international guidelines, treatment in most cases depends on nationwide guidelines, expert opinion, local hospital protocols, and the availability of resources in low-resource settings.

As of now, there are no established guidelines for the management of GTN at advanced age. Thus, we conducted this multicentre retrospective study to investigate the outcome of different treatment strategies in low-risk (LR) non-metastatic, LR metastatic, and high-risk (HR) GTN in patients aged 40 years or more.

Patients and Methods

This study included all newly diagnosed patients with GTN from April 2012 to March 2017 in five referral centres (from Egypt, Saudi Arabia, Ukraine, Canada, and Indonesia). The Institutional Review Board of the faculty of Medicine, Mansoura University (Number.R.18.04.142), Mansoura, Egypt, gave central study approval.

I Study Population

The study included patients with GTN, i.e., invasive mole, choriocarcinoma, and post-molar GTN, and aged 40 years and older at the time of admission to any of the participating centres. Histopathological diagnosis was done by a team of specialized gynaecological pathologists in the participating centres. GTN cases were staged and classified according to the FIGO 2000 staging and classification guidelines [14]. Patients who refused initial permission to use their data for future research and patients whose histologic examination proved other pathologies rather than GTN were excluded. Since PSTT and ETT are rare and different tumor types that need a different approach, we decided to exclude these from this analysis.

II Study Design

From the patient charts, we retrieved age, parity, antecedent pregnancy, pre-treatment serum human Chorionic Gonadotropin (hCG) levels, presence of metastases, FIGO score, the need for single- and multi-agent chemotherapy, the number of courses necessary to achieve normalization of hCG concentrations, surgical procedures, histopathology, and outcome of treatment. FIGO score < 7 is considered low-risk and ≥ 7 is considered high-risk. Since treatment rationale for metastatic versus non-metastatic disease might be different, we categorized the patients into three groups: LR non-metastatic, LR metastatic, and HR.

For each group, the following treatment modalities were recognized: single-agent chemotherapy with or without second curettage, polychemotherapy, and hysterectomy with or without adjuvant chemotherapy. Treatment outcome was accordingly evaluated. Resistance to chemotherapy was defined as plateauing or rising serum hCG for 3 consecutive weeks. Disease recurrence was defined as a rise in serum hCG values after previous normalization, in the absence of a new pregnancy. Follow-up duration was considered to be at least 12 months after normalization of serum hCG. Complications of chemotherapy were (in retrospect) graded according to the Common Terminology Criteria for Adverse Events (CTCAE, V. 3.0) [15].

III Statistical Methods

Data were anonymized, imputed in an Excel database, and analysed using Statistical Package of Social Sciences (SPSS) software version 20.0 (IBM, Armonk, NY, USA). Qualitative data were described using numbers and percentages. Quantitative data were described using median (minimum, maximum and interquartile range) for non-parametric data. For parametric data, mean, standard deviation and 95% confidence interval (CI) were used. Normality was tested using Kolmogorov-Smirnov test. Significance of the obtained results was judged at 5% level, and all tests were two-tailed. Chi-square test was used for categorical variables to compare between different groups as appropriate. To compare parametric quantitative variables, the student’s t test was used, and for non-parametric quantitative variables, the Mann-Whitney and Fischer exact tests were used. No core outcome sets were relevant for this study. Furthermore, there was no patient involvement in this retrospective study.

Results

Data of 141 patients from the participating centres were reviewed. Twenty-three cases were excluded: eight cases did not meet the time frame, seven cases had incomplete clinical data, two cases concerned a non-gestational choriocarcinoma, three cases were PSTT and three cases ETT. Finally, 112 cases with GTN who fulfilled the inclusion criteria were analysed (30 from Egypt, 13 from Ukraine, 14 from Canada, 30 from Saudi Arabia, and 25 from Indonesia). Complete details of the patients are given in the supplementary table. The mean age (years) was 45.4±4.2 SD (range; 40.0-55.0), and the median hCG at initial diagnosis of GTN was 2686 (range; 11-9609) IU/L. Ninety-four cases (83.9%) followed molar pregnancies, and 18 (16.1%) followed other pregnancy events.
Table 1: Demographic characteristics of the studied case.

| Age (years) (mean ± SD) | 45.4 ± 4.2, range 40.0 - 55.0 |
|------------------------|-------------------------------|
| Parity median (range)  | 4 (0-12)                      |
| Weight (kg) (mean ± SD)| 67.8 ± 17.8                   |
| Serum HCG (IU/l) median (range) | 2686 (11 - 9609) |
| FIGO SCORE median (range) | 2.7 (1-13)                    |

| Antecedent pregnancy                          | Number | %     |
|-----------------------------------------------|--------|-------|
| Unknown                                       | 5      | 4.5   |
| Abortion                                      | 8      | 7.1   |
| Complete mole                                 | 80     | 71.4  |
| Partial mole                                  | 14     | 12.5  |
| Term pregnancy                                | 5      | 4.5   |

| Histopathology Specimen                       |        |
|-----------------------------------------------|--------|
| 2nd curettage                                 | 14     |
| hysterectomy                                  | 53     |
| endometrial biopsy                            | 9      |

| Diagnosis                                      |        |
|-----------------------------------------------|--------|
| Choriocarcinoma                               | 23     |
| Molar tissues                                 | 20     |
| Invasive mole                                 | 33     |

| Presentation *                                |        |
|-----------------------------------------------|--------|
| Raised hCG                                    | 63     |
| Plateau hCG                                   | 8      |
| Vaginal bleeding                              | 55     |
| Abdominal mass                                | 4      |
| Abdominal pain                                | 4      |
| Other                                         | 3      |

| Metastasis. Site of metastases *              | N = 25 |
|-----------------------------------------------|-------|
| Lung                                          | 20    |
| Liver                                         | 1     |
| Vagina                                       | 1     |
| Renal                                         | 2     |
| Urinary bladder                               | 1     |
| Fallopian tube                                | 1     |
| Bone                                          | 1     |

| Treatment duration (days) median (range)      | 84.5(14-245) |
| Follow up(months) median (range)              | 17.5(1-72)   |

| Outcome                                       |        |
|-----------------------------------------------|--------|
| Uneventful                                    | 97     |
| Cured after relapse                           | 5      |
| Death                                         | 3      |
| Lost follow up                                | 7      |

*Presentation: Categories are not mutually exclusive; *Metastases: Some cases had more than one site.

The commonest presentation was a raising hCG level after evacuation of a molar pregnancy, as it was observed in 63 cases (56.2%). LR non-metastatic GTN was observed in 80 (71.4%) cases, LR metastatic in 14 cases (12.5%) and HR in 18 cases (16.1%). FIGO stage I was observed in 50% cases. Metastases were diagnosed in 25 cases (22.3%), predominantly lungs (n = 20). Histopathological diagnoses were available for 76 cases either retrieved through second curettage (n = 14), a hysterectomy (n = 53), or after endometrial biopsy for abnormal uterine bleeding (n = 9). The commonest diagnosis was invasive mole (43.4%). The median follow-up duration was 17.5 months (range: 1-72 months). Seven cases (6.3%) were lost to follow-up within one year after normalization of serum hCG. Other sociodemographic data are shown in (Table 1).

### I Low-Risk Non-Metastatic GTN

The mean FIGO score in this subgroup was 3.2 (range, 1-6). Of the 80 patients with LR non-metastatic GTN, 46 patients received single-agent chemotherapy, in 14 preceded by a second curettage because of participation in a clinical trial [16]. Remission was achieved in 29 patients (63%). Sixteen (20%) patients needed second-line chemotherapy, one was cured with actinomycin-D as second-line single-agent therapy, 14 cases received polychemotherapy, and two underwent hysterectomy.

| Diagnosis                                      |        |
|-----------------------------------------------|--------|
| Choriocarcinoma                               | 23     |
| Molar tissues                                 | 20     |
| Invasive mole                                 | 33     |

| Presentation *                                |        |
|-----------------------------------------------|--------|
| Raised hCG                                    | 63     |
| Plateau hCG                                   | 8      |
| Vaginal bleeding                              | 55     |
| Abdominal mass                                | 4      |
| Abdominal pain                                | 4      |
| Other                                         | 3      |

| Metastasis. Site of metastases *              | N = 25 |
|-----------------------------------------------|-------|
| Lung                                          | 20    |
| Liver                                         | 1     |
| Vagina                                       | 1     |
| Renal                                         | 2     |
| Urinary bladder                               | 1     |
| Fallopian tube                                | 1     |
| Bone                                          | 1     |

| Treatment duration (days) median (range)      | 84.5(14-245) |
| Follow up(months) median (range)              | 17.5(1-72)   |

| Outcome                                       |        |
|-----------------------------------------------|--------|
| Uneventful                                    | 97     |
| Cured after relapse                           | 5      |
| Death                                         | 3      |
| Lost follow up                                | 7      |

Table 2: Outcome of treatment of low-risk cases (n=80 cases).

| Diagnosis                                      |        |
|-----------------------------------------------|--------|
| Choriocarcinoma                               | 23     |
| Molar tissues                                 | 20     |
| Invasive mole                                 | 33     |

| Presentation *                                |        |
|-----------------------------------------------|--------|
| Raised hCG                                    | 63     |
| Plateau hCG                                   | 8      |
| Vaginal bleeding                              | 55     |
| Abdominal mass                                | 4      |
| Abdominal pain                                | 4      |
| Other                                         | 3      |

| Metastasis. Site of metastases *              | N = 25 |
|-----------------------------------------------|-------|
| Lung                                          | 20    |
| Liver                                         | 1     |
| Vagina                                       | 1     |
| Renal                                         | 2     |
| Urinary bladder                               | 1     |
| Fallopian tube                                | 1     |
| Bone                                          | 1     |

| Treatment duration (days) median (range)      | 84.5(14-245) |
| Follow up(months) median (range)              | 17.5(1-72)   |

| Outcome                                       |        |
|-----------------------------------------------|--------|
| Uneventful                                    | 97     |
| Cured after relapse                           | 5      |
| Death                                         | 3      |
| Lost follow up                                | 7      |

In 34 cases, upfront hysterectomy was performed. In four patients, a wait-and-see policy was successful. However, in most participating hospitals, the policy was to prescribe adjuvant chemotherapy, either a fixed number of courses (1 or 2) or based on regression of hCG levels. Therefore, instant chemotherapy followed in 30 patients, mainly single methotrexate with folic acid rescue (MTX/FA) (n = 29) for 1-12 courses. In 29 of 30 cases (96.7%), complete remission with uneventful follow-up was observed. In one patient, MTX/FA failed, but second-line etoposide was successful. Compared to single-agent chemotherapy (with or without a second curettage), primary hysterectomy with or without single-agent chemotherapy was associated with a higher remission rate (P=0.001), a shorter mean treatment duration (P=0.001), and less number of total chemotherapy courses (mean 2.5 versus 5; P < 0.001) as shown in (Table 2).

### II Low-Risk Metastatic GTN

The mean FIGO score in this subgroup was 4.0 (range 2-6). Eight of the 14 women with LR metastatic GTN were initially treated with MTX/FA. Four of them reached complete remission, and four had incomplete
responses. Of these four patients, one was cured after second-line single-agent actinomycin-D, one successfully received second-line polychemotherapy, one received second-line polychemotherapy combined with hysterectomy, and one received 7 courses of etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine polychemotherapy (EMA/CO) and underwent excision of vaginal metastases. In this patient, a relapse that occurred 2 years later was cured with EMA/CO.

In six patients, a hysterectomy was performed, followed immediately by MTX/FA. This resulted in complete response with uneventful follow-up in three patients. Two were cured with second-line chemotherapy EMA/CO, and the third failed on second-line single carboplatin but achieved complete remission with third-line EMA/CO. This patient had a pulmonary relapse after 7 months, which was again treated with EMA/CO. Only 7 of the 14 patients with LR metastatic GTN were cured with MTX/FA chemotherapy, 3 of whom also underwent a hysterectomy. All others needed second- or third-line chemotherapy, and two developed a relapse.

### III High-Risk GTN

The mean FIGO score in this subgroup was 8.3 (range, 7-13). Two high-risk patients died before treatment could start due to distant metastases. In six patients, chemotherapy was started; two cases were started with induction MTX/FA due to bad general condition, followed by EMA/CO. Relapse occurred in one patient who was treated again with EMA/CO. In four patients, treatment started with EMA/CO chemotherapy; two of them had incomplete response and subsequently received second-line etoposide, MTX/FA, actinomycin-D, etoposide, and cisplatin (EMA/EP).

Ten cases (62.5%) underwent hysterectomy and mono or poly chemotherapy as first-line. One patient died during chemotherapy treatment, six (60%) showed complete response, one of them developed renal metastases, which was successfully treated with nephrectomy and EMA/CO, and three (30%) needed second-line treatment to achieve a complete response. The complications of chemotherapy could be retrieved for 42 cases (37.5%) only. Grade 3 complications were reported in 4 cases (9.5%) including renal failure, respiratory failure, deep venous thrombosis, and severe anaemia.

### Discussion

We presented the experience of five different centres in five countries on four continents (Africa, Asia, Europe, and North America) in managing GTN in patients aged 40 years and above. In the current study, 44% of cases with LR non-metastatic GTN did not achieve remission with initial treatment with MTX/FA, which is higher than the expected 10% in all age categories [17]. In an analysis of 359 patients with low-risk GTN treated between 1979 and 2006 at the Brewer Trophoblastic Center (Chicago), approximately 80% of women were cured with first-line single-agent therapy, mainly MTX/FA [18]. In our study, 11 of 14 cases (69.6%) with LR non-metastatic disease achieved complete remission after second curettage plus MTX/FA. Most of these cases were included in a randomized study conducted by Hemida et al. [16]. Overall, this study did not find a significant reduction in the number of chemotherapy courses among patients who underwent second curettage and who did not. The study did not stratify for age, and a subgroup analyses for older aged patient was not performed. Thus, we would recommend hysterectomy over second curettage. For LR metastatic disease, complete remission was observed only in 50% of cases with single-agent chemotherapy with or without hysterectomy.

Goldstein et al. reported that patients with low-risk metastatic GTN (Stages II and III; score < 7) were treated with single-agent chemotherapy with cure rates of 80-90% for all ages [1]. Our result is, however, in line with two cohort studies: Dutch and British studies that reported higher MTX resistance and recurrence rates in patients with lung metastases than in patients without lung metastases [19, 20]. This may denote a poorer response to single-agent chemotherapy regardless of age and would plead for larger, preferably prospective, cohort studies.

A higher acceptance of hysterectomy is observed in the older age group when compared to the younger group with a wish to preserve fertility. Hysterectomy was performed in 43% LR cases, regardless of the presence or absence of metastases. This resulted in a remission rate of 97% in the 34 non-metastatic LR GTN, opposed to 50% in the six LR metastatic disease. This result is in line with the findings of Bolze et al., who reported a retrospective analysis on 74 patients who underwent hysterectomy as first-line treatment; 82% of them did not require any further salvage chemotherapy [21]. These results are better than the findings of Eysbouts et al., who reported complete remission after hysterectomy in 47.8% patients [22]. The high cure rate after hysterectomy in our LR non-metastatic group may be attributed to the prophylactic use of 1-2 courses of MTX/FA with hysterectomy in most participating centres in this study. Rodriguez et al. also supported this concept [23]. The role of hysterectomy in the LR metastatic group is less clear; Eysbouts et al. reported that no cases with metastatic GTN achieved remission with hysterectomy alone [24].

In our study, hysterectomy was often chosen at the start of treatment, regardless of the low- or high-risk status and presence of metastasis. Hysterectomy is thought to reduce the burden of disease and, therefore, improve outcome in terms of reduction of the number of chemotherapy courses and less failure of first-line chemotherapy. It remains debatable whether this applies to patients with metastatic disease as surgery should not delay the prompt start of chemotherapy since it is the cornerstone of treatment in metastatic disease.

In the current study, 15% were categorized as high-risk GTN, which is more than the results reported by other authors who reported 10% incidence of HR GTN in all age groups [17]. Ten of 18 (55.6%) HR patients were initially treated with hysterectomy with chemotherapy in contrast to only four patients (22.2%) who started with combination chemotherapy alone. This indicates the more frequent use of hysterectomy in this age group. Adjuvant hysterectomy is likely to benefit cautiously selected patients with high-risk GTN, but polychemotherapy is the standard of care [24]. Fear for deterioration of the clinical condition in cases with a high tumor burden was at stake in some cases, resulting in the adaptation of the chemotherapy schedule. In our study, two cases of HR received MTX/FA induction prior to EMA/CO. Alifrangis et al. used etoposide-cisplatin induction
chemotherapy before EMA/CO in 23% of high-risk patients with a large disease burden [25].

We reported a relapse rate of 4.6%, which is in agreement with that reported by other authors [24]. Three fatal cases were reported in the current study (2.7%), which is twice the mortality rate reported by Ozlap et al. in a retrospective study involving GTN cases in all age groups in Turkey [17]. However, when we compare our results with the published data; the groups may not be directly comparable. Our study demonstrates that the majority of the participating centres use nationwide or local hospital protocols in the absence of international guidelines for the treatment of GTN at 40 years of age and above. Thus, there is an urgent demand for international guidelines [20].

The limitations of the current study include its retrospective design, missing data (i.e., chemotherapy toxicity was retrieved for only 37% of patients from the charts), heterogeneity of data as reported by different centres, and different local hospital protocols for management. Unfortunately, the central pathology review of histopathology could not be obtained, but all cases were treated in a national or regional center, where experienced pathologist examined the available specimens. Uniform international definition and treatment would make it easier to combine datasets from different global cohorts and address certain topics currently unanswered in the community [20].

The strength of the study is that it reflects a relatively large group of patients from tertiary centers across the world. It, therefore, reflects practice as performed under different circumstances. The unexplained high number of hysterectomies in LR metastatic and HR disease is of concern since this might delay the start of (poly) chemotherapy and impact outcome.

Conclusion

GTN at 40 years old or above may have a poorer prognosis than women of younger age, with a larger proportion of metastatic, high-risk, and MTX resistant disease. Hysterectomy with MTX/FA for LR non-metastatic disease was successful with a remission rate above 90%. Hysterectomy was also widely used in metastatic LR and HR disease, but its role remains controversial in these groups and chemotherapy should not be delayed because of the surgery. A large, randomized study is needed to investigate the optimal treatment strategy.

Conflicts of Interest

None.

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Author Contributions

RH, PS, NT, HvD: design, planning, conduct, data analysis, and manuscript writing; HP, NA, NE, and KS: planning, conduct, data analysis; HvD: study design and manuscript editing. All authors agreed on the latest version of the manuscript.

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