The diagnostics and treatment of low-risk gestational trophoblastic neoplasia (GTN): 42-year experience

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Objective: To review the results in the surgical and chemotherapy treatment of low-risk gestational trophoblastic neoplasia (GTN) in the last 42 years in Hungary. Methods: This is a retrospective cohort study. Between 1 January 1977 and 31 December 2018, 413 patients were treated with low-risk GTN at our hospital. The patients were between 14–49 years of age with a mean age of 28.1 years. Primary chemotherapy was selected based upon the patient’s GTN stage and prognostic score. Hysterectomies were done either electively (requested by patients who completed childbearing) or to remove large uterine tumour burdens. Results: Methotrexate (MTX)/folinic acid was used as a primary therapy in 304 cases, and among these 289 patients achieved complete remission (95.1%). Nine chemotherapy-resistant patients were successfully treated with secondary MAC (MTX, Actinomycin-D (Act-D), cyclophosphamide) and 6 patients with EMA-CO (etoposide, MTX, Act-D, cyclophosphamide, vincristine) therapy. Out of 109 patients, 102 (93.6%) achieved remission following treatment with Act-D. The remaining 7 patients achieved remission with MAC (1 case) or EMA-CO (6 cases) as secondary therapy. Metastases were detected in 98 (23.7%) out of the 413 low-risk patients. Hysterectomy was performed in 28 (6.8%) patients, and among these, 10 patients were diagnosed with Stage I, 4 with Stage II, and 14 with Stage III disease. Surgical resection of metastases was necessary in 12 (2.9%) cases. Conclusions: During the study period, approximately 75% of our patients with low-risk GTN were primarily treated with MTX/folinic acid and 25% with Act-D. Single agent chemotherapy-resistant patients were successfully treated with MAC and, more recently, with EMA-CO. Hysterectomy and metastasis resection occasionally play a valuable role in the management of this disease.

Keywords
Low-risk gestational trophoblastic neoplasia; Chemotherapy; Hysterectomy; Metastasis surgery

1. Introduction

It is recognized that that an accurate and precise international staging system for gestational trophoblastic neoplasia (GTN) is essential to enable clinicians to assess their prognosis and to optimize their treatment. The International Federation of Gynecology and Obstetrics (FIGO) and the World Health Organization (WHO) proposed an anatomical staging system and a prognostic scoring system. Because of their unique biology, placental site and epithelioid trophoblastic tumors are specifically excluded from the scoring system [1, 2]. Importantly, international centers have been established to treat GTN in order to optimize therapy of this uncommon disease.

Based upon this international experience we decided to establish a center for Hungarian trophoblast patients in our institution in the mid-1970s. In our Center, we have carefully used different diagnostic methods and various chemotherapy regimens in the management of GTN while surgery, particularly in the form of hysterectomy, still plays a valuable role [3].

During the last three decades important collaboration has been established between the Hungarian Trophoblastic Disease Center (Budapest) and the Division of Gynecologic Oncology, Brigham and Women’s Hospital of Harvard Medical School (Boston, Massachusetts). As the result of our work many patients were referred to our institution with gestational trophoblastic disease from all around Hungary. In the current manuscript, we review our clinical experience in the treatment of low-risk GTN over the past 42 years for a better understanding the management of low-risk patients.
2. Materials and methods

Between 1 January 1977 and 31 December 2018 we treated 413 patients with low-risk GTN. The patients were referred to our institution from throughout Hungary. Patients were between 14–49 years of age, with a mean age of 28.1 years.

The antecedent pregnancy of low-risk GTN was hydatidiform mole (334 = 80.9%), spontaneous miscarriage (68 = 16.5%), or pregnancy termination (11 = 2.6%).

The diagnosis of post-molar low-risk GTN was made using the following FIGO/WHO criteria: (1) four or more values of a human chorionic gonadotropin (hCG) plateau over at least 3 weeks, (2) a rise in hCG of 10% or greater for 3 or more values over at least two weeks, (3) persistent hCG levels six months after molar evacuation.

Between January 1, 1977 and December 31, 2000 patients were classified by the original WHO prognostic scoring system (1983) (Appendix Table 9). However, between January 1 2001 and 31 December 2018, low-risk patients were categorized using the updated FIGO 2000 system (Appendix Table 10). Based upon these staging systems it is possible to determine accurate staging and the prognostic score. After the introduction of the FIGO 2000 classification patients with a score under 7 points were considered low-risk.

The potential presence of metastasis was evaluated by chest X-ray, computed tomography (CT) of the chest, CT or magnetic resonance image (MRI) of the brain, and ultrasound of the abdomen and pelvis or whole body positron emission tomography (PET).

After the diagnosis of low-risk GTN, we assessed the general status of the patient (complete blood count, platelet count, urinalysis and renal function studies, liver function tests, serum electrolyte determinations, blood for typing, electrocardiogram and other consultations as indicated). If necessary, we prepared the patient for treatment (e.g., whole blood or platelets transfusion, antibiotics). During diagnostic screening and treatment, if necessary, we involved other specialists such as haematologists, intensivists, surgeons, radiologists, microbiologists.

We selected primary chemotherapy based upon the patient’s GTN stage and prognostic score. Since 1977, we treat patients with low-risk GTN with methotrexate (MTX)/folinic acid (50 mg MTX i.m. on the 1st, 3rd, 5th and 7th day and 6 mg folinic-acid on the 2nd, 4th, 6th and 8th day) [4, 5]. According to the experience of Li and colleagues [6, 7], as well as other specialists, in the therapy of low-risk patients we also used Actinomycin-D (Act-D) as well (0.5 mg i.v. for 5 days). These single agent treatments are given at fixed time interval every ten days until hCG values became undetectable. Following this, 1 or 2 additional courses of consolidation therapy are administered. Both Act-D and MTX/folinic acid treatment were introduced in 1977 to treat patients at our center. At that time, and even later, it was not known which was more toxic and which was more effective. Since we did not experience significant differences in this regard, and some (but not all) studies only shed light on possible drug effect differences much later; we selected the therapy based on its availability and cost.

Patients resistant to first-line MTX or Act-D proceeded directly to treatment with combination chemotherapy.

As second line treatment of low-risk patients with resistance to prior single agent chemotherapy, we used the MAC triple combination chemotherapy (MTX, 1 mg/kg i.m. on days 1, 3, 5, and 7, folinic-acid 0.1 mg/kg on days 2, 4, 6, and 8, Act-D, 0.5 mg/day, i.v. bolus, for 5 days, cyclophosphamide, 200 mg/day, i.v. infusion for 5 days) [5, 8].

Since 1993, in patients with resistance to single agent chemotherapy, the EMA-CO (etoposide, high-dose MTX, with folinic acid rescue, Act-D, cyclophosphamide and vincristine) regimen was used as second line combination chemotherapy. The use of EMA-CO has gradually increased, especially in the last 11 years [9]. We repeated the treatments every 2–3 weeks after taking into account the status of the patient. After hCG levels become negative, we administer 1–2 additional courses of chemotherapy to reduce the risk of relapse.

During evaluation of chemotherapy toxicity, patients were categorized into the “serious complications” group if granulocytopenia (white blood cell count <2.5 × 10^9 mmol/L, granulocytes <1.5 × 10^9 mmol/L), thrombocytopenia (platelets < 50 × 10^9 mmol/L), hepatotoxicity (serum glutamic oxaloacetic transaminase (SGOT) >100 U/L), and nephrotoxicity (serum creatinine >150 µmol/L, creatinine clearance <50 mL/min), and/or serious oral ulcers, emesis, infection and gastroenteritis developed following chemotherapy.

We conduct strict follow-up of low-risk patients for one year. After completing follow-up, patients are advised that they may attempt to become pregnant.

Surgery was mainly performed to either resect sites of chemotheraphy-resistant disease or to treat acute complications. Sometimes hysterectomy or excision of metastatic foci was performed.

The prevalence of chemotherapy complications, hysterectomy and surgery for metastasis was analysed using a two-sided $\chi^2$ test.

3. Results

3.1 Results of MTX therapy with folinic acid

We treated 304 low-risk patients with the outlined MTX/folinic acid regimen (Table 1). Of these 304 patients, 289 (95.1%) achieved remission. Of the remaining 15 patients (4.9%), complete remission was achieved by using MAC (9 cases) or EMA-CO (6 cases), in some cases in association with surgery. The total number of MTX/folinic acid courses administered was 729.

3.2 Results of Act-D therapy

One hundred and nine patients received Act-D therapy (Table 2). Within this group, 102 (93.6%) achieved remission. The remaining 7 (6.4%) patients who failed primary
therapy with Act-D were successfully treated with MAC (1 case) or EMA-CO (6 cases).

The total number of Act-D courses administered was 283 courses. There was no clinically significant difference in the remission rates among patients treated primarily with Act-D or MTX/folinic (93.6% versus 95.1%).

The mean number of courses of single-agent chemotherapy given to patients prior to shifting to multiple agent chemotherapy was 3.3 courses. The median number of courses of single-agent chemotherapy given those who achieved complete remission was 2.1 courses (+1 or 2 consolidation courses). The overall remission rate for those given single-agent chemotherapy was 94.6%.

### 3.3 Result of second line MAC combination chemotherapy

We treated 10 low-risk patients (5 with stage II and 5 with stage III) with second line combination MAC chemotherapy (Table 3). All ten patients achieved complete remission (100.0%).

### 3.4 Result of second line EMA-CO combination chemotherapy

We treated 12 low-risk patients (5 with stage II and 7 with stage III) with second line EMA-CO therapy (Table 4). All 12 patients achieved complete remission (100.0%).

### 3.5 Complications due to therapy

In our study group, no patient died from chemotherapy toxicity (Table 5). Most of the minor and serious complications were bone marrow suppression (leukocytopenia and thrombocytopenia), oral ulcers, infection, alopecia, and emesis. Between 1977–2007, minor and serious complications developed in 49 (16.2%) and 11 (3.6%) in 302 low-risk patients [10], and from 2008 until 2018 minor and serious complications developed in 15 (13.5%) and 1 (0.9%) in 111 cases, respectively (for serious cases \( p < 0.05 \)). We noted somewhat higher toxicity in the Act-D group versus MTX/folinic acid group.

### 3.5 Hematologic toxicity in low-risk GTN patients during chemotherapy (primary and secondary)

Grade 1 anemia occurred in 48 patients, grade 2 in 5 patients, and grade 3 in 4 cases. Grade 1 neutropenia appeared in 9 cases, grade 2 in 4 cases, and grade 3 in 2 cases. Seven (7) grade 1, 4 grade 2 and only 1 grade 3 thrombocytopenias were recorded. Alopecia occurred in approximately half of the patients and sometimes patients presented with mild gastrointestinal symptoms (see Common Terminology Criteria for Adverse Events Version 4.0 National Cancer Institute grading system) (Appendix Table 11).
Table 4. Results of second line EMA-CO therapy (Average prognostic score: 6.1).

| Staging system of patients (anatomical stage) | Number of EMA-CO therapy patients | Number of treatments (average) | Results of treatments |
|-----------------------------------------------|-----------------------------------|--------------------------------|-----------------------|
|                                               | primary secondary total           | remission died                 |
| Stage I                                       | - -                             | - -                            | - -                   |
| Stage II                                      | - 5 low-risk                    | 2.9                            | 5 -                   |
| Stage III                                     | - 7 low-risk                    | 3.9                            | 7 -                   |
| Stage IV                                      | - -                             | - -                            | - -                   |
| Total                                         | 12 12                           | 3.4                            | 12 (100%) -           |

Table 5. Complications during cytotoxic chemotherapy.

| Number of patients | Minor complications | Percentage (%) | Serious complications | Percentage (%) |
|--------------------|---------------------|----------------|-----------------------|-----------------|
| 64                 | alopecia: 38        |                | oral ulcer: 54        |                 |
| 413                | (Act-D: 18; MTX: 20)| 15.4           | emesis: 51            | 2.9             |
|                    | (Act-D: 24; MTX: 30)|                | infection: 10         |                 |
|                    | (Act-D: 22; MTX: 29)|                | (Act-D: 5; MTX: 5)    |                 |

Table 6. Frequency of hysterectomy according to the anatomical staging system.

| Patients’ Score | Hysterectomy |
|-----------------|--------------|
| Number | Number | Percentage (%) |
| Stage I | 315 | 10 | 3.2 |
| Stage II | 35 | 4 | 11.4 |
| Stage III | 63 | 14 | 22.2 |
| Stage IV | - | - | - |
| Total | 413 | 28 | 6.8 |

3.6 Results of surgical interventions

Hysterectomy was performed in 6.8% of our low-risk patients (28/413). Out of these 28 patients, 10 had stage I, 4 stage II and 14 stage III disease. The performance of hysterectomy in stage III disease (14/63, 22.2%) was significantly higher than in stage I (10/315, 3.2%) (p < 0.05). Of the 35 stage II patients in this study, 4 (11.4%) underwent hysterectomy (Table 6). The most frequent indication for hysterectomy was uterine foci of disease resistant to single agent chemotherapy (12/28 = 42.8%) (Table 7). Four patients underwent hysterectomy for large uterine tumors, one for persistent but not life-threatening bleeding, 2 patients requested hysterectomy because of their fear of tumor propagation, and 9 did not wish further fertility. Between 1977–2007 hysterectomy was performed in 19 (6.3%) of 302 low-risk patients [10], and from 2008 until 2018 in 9 of 111 cases (8.1%).

Metastases were resected in 2.9% (12/413) patients. Metastases were excised due to the presence of drug-resistant pulmonary metastases (2 cases of lobectomies), uterine tumor propagation when the tumor involved the adnexa (4 cases) or vaginal bleeding (one case). When vaginal hemorrhage occurred embolization of the feeder vessel was used to control blood loss. In 5 cases, the vaginal nodules were resected after embolization, performing wide local excisions. They represented the only site of drug-resistant disease [11] (Table 8). All patients who underwent surgery for metastatic disease achieved remission. Between 1977–2007 metastases were resected in 10 (3.3%) of 302 cases, and from 2008 until 2018 in 2 out of 111 cases (1.8%) of low-risk GTN patients (p < 0.05).

3.6 Conclusion of therapeutic results

The summarized results of chemotherapy, surgical and other therapeutic interventions of our low-risk patients show that no patients diagnosed with low-risk GTN died of this disease. The complete remission rate is 100.0%.

4. Discussion

In the Hungarian GTD (gestational trophoblastic disease) Center our educational and publication activities made it possible for us to treat 80% of trophoblastic tumor patients from the 10.5 million person population in Hungary.

In this article, we review our 42-year experience with low-risk GTN patients in our Center. Current diagnostic methods make it possible to identify the exact extent of disease and the comparison of our treatment results with international experience. We found metastases in 23.7% (98/413) of our low-risk patients. GTNs have a tendency for early dissemination and patients with GTN require careful evaluation for metastatic disease.

MRI has an important role in the identification of invasive processes in the uterus of patients with GTN. PET imaging methods may have an advantage over MRI and CT-negative cases as it might identify occult sites of active disease [12–14].
### Table 7. The indications for hysterectomies and results of surgery.

| Indications                                                                 | Number of patients | Secondary chemoth | Remission |
|----------------------------------------------------------------------------|--------------------|-------------------|-----------|
| Large uterine tumor to reduce tumor burden to limit chemotherapy           | 4/28 (14.2%)       | MAC, EMA-CO       | 100%      |
| Chemoresistant uterine tumor (for single agent chemoth)                    | 12/28 (42.8%)      | MAC, EMA-CO       | 100%      |
| OTHERS (no further fertility, non-emergent bleeding, requested due to fear of propagation) | 12/28 (42.8%) (9, 1 and 2 cases) | MAC, EMA-CO       | 100%      |

### Table 8. Indications and chemotherapy with low-risk metastatic GTN Surgery.

| Type of metastasis resections | Indications                          | Number of patients | Secondary chemotherapy |
|------------------------------|--------------------------------------|--------------------|------------------------|
| Adnexectomy                  | Tumor propagation (bulky uterine tumor) | 4                  | 2–4 MAC or EMA-CO     |
| Lung resection (lobectomies)  | chemoresistant                        | 2                  | 1–4 MAC or EMA-CO     |
| Vaginal nodules              | 1 vaginal bleeding, 5 elective resections | 6                  | 2 or 3 courses MAC or EMA-CO |

Our experience is similar to other investigators in the field in that MTX/folinic acid or Actinomycin-D should be the primary treatment in patients with non-metastatic or metastatic low-risk GTN [15]. During the period encompassed by our study, approximately 75% of our patients with low-risk GTN were initially treated with MTX/folinic acid and 25% with Act-D monotherapies. With these monotherapies, remission rates are high and the toxicity levels are low. Importantly, those patients with resistance to single agent chemotherapy regularly achieve remission with minimal toxicity when given combination chemotherapy (i.e., MAC or EMA-CO). As to the pregnancy rate following therapy, there are no exact data available in our Center, owing to the fact that after completing patients’ serum hCG follow up, further patient data were unavailable. Nevertheless, we estimate that of the 385 patients who did not undergo a hysterectomy, approximately one-third had a subsequent delivery.

Our data indicate that during the last 11 years, the dominant use of EMA-CO as secondary chemotherapy significantly decreased chemotherapy-induced serious complications, as well as the resection of metastases. As in other international GTN Centers, the EMA-CO protocol is regarded as our current second-line treatment for single agent chemotherapy-resistant low-risk GTN [16].

Hysterectomy may be necessary in low-risk patients with large or chemoresistant uterine tumors, uterine tumor propagation, and/or prolonged uterine bleeding. Furthermore, in patients with bulky uterine tumors, hysterectomy may reduce the tumor burden and decrease the number of chemotherapy courses needed to achieve remission [17, 18].

Surgical resection of metastasis in selected circumstances may also be important in the management of metastatic low-risk disease including the thorax and pelvis. Resection of metastases may contribute to complete remission by controlling local complications such as hemorrhage or resecting sites of drug-resistant tumor [19].

The importance of early GTN diagnosis and therapy is critically important. Chemotherapy, surgical intervention, or other supplementary treatments may result in 100% success rate in cases of non-metastatic and metastatic low-risk disease.

When pregnant patients experience systemic symptoms or irregular vaginal bleeding, it is essential to consider the possibility of GTN. It is also important to emphasize careful hormonal follow-up after molar pregnancy.

We developed a regional referral center for GTN to consolidate patient care in a setting in which clinicians had specialized interest and experience in treating and studying this uncommon disease. Based upon international data, we anticipated that patient care under the direction of experienced clinicians would optimize the opportunity for cure and minimize morbidity. A regional center also fosters research to advance our understanding of the natural history and biology of GTN. The establishment of a specialized national referral center for GTN in Hungary has substantially contributed to improved patient outcomes. GTN is a rare disease and optimal care was facilitated in our referral regional center. We are encouraged by our results over the past 42 years, and hope that treatment and understanding of this disease will continue to improve in the future.

5. Conclusions

During the study period, approximately 75% of our patients with low-risk GTN were primarily treated with MTX/folinic acid and 25% with Act-D. Single agent chemotherapy-resistant patients were successfully treated with MAC and, more recently, with EMA-CO. Hysterectomy and metastasis resection occasionally play a valuable role in the management of this disease.

**Author contributions**

VF—conceived and designed the study, main writer of the manuscript. IS—collected and categorized patients’ data. JS—collected the data. EL—collected part of treatment data. GV—served part of patients’ data included in the paper. JD—participated in manuscript writing and sometimes in patients’ data consultations. ZP—analyzing chemotherapy treatments data. RSB—participated in study design, writing (as a native English) the paper. All authors read and approved the final manuscript.
Table 9. WHO prognostic scoring system for GTN (1983).

| Score | 0 | 1 | 2 | 4 |
|-------|---|---|---|---|
| Age (years) | <39 | >39 | - | - |
| Antecedent pregnancy | Mole | Abortion | Term pregnancy | - |
| Interval (AP to start of chemotherapy) in months | 4 | 4–6 | 7–12 | >12 |
| Pretreatment hCG (log) | <3 | <4 | <5 | >5 |
| ABO groups (female x male) | - | 0xA | A0 | B AB | - |
| Site of metastases | - | Spleen, kidney | Gastro-intestinal tract, liver | Brain |
| Largest tumor (diameter–cm) | - | 3–5 | 5 | - |
| No. of metastases identified | - | 1–4 | 4–8 | >8 |
| Previous failed chemotherapy failed | - | - | Single drug | Two or more drugs |

≤4, low risk; 5–7, medium risk; >7, high risk.

Risk factors: parity, lymphocytic infiltration of the tumor, immune status were left out.

Table 10. Placental Site Trophoblastic Tumor (PSTT) is categorized separately from other GTN FIGO classification for GTN (2000).

| A. Staging | B. Scoring |
|-----------|-----------|
| Stage I  | Disease confined to the uterus |
| Stage II | GTN extends outside the uterus, but is limited to the genital structures (adnexa, vagina, and broad ligament) |
| Stage III | GTN extends to the lungs, with or without known genital tract involvement |
| Stage IV | All other metastatic sites |
| Scoring | 0 | 1 | 2 | 4 |
| Age (years) | <40 | ≥40 | - | - |
| Antecedent pregnancy | Mole | Abortion | Term | - |
| Interval months from index pregnancy | <4 | 4 to <7 | 7 to <13 | ≥13 |
| Pretreatment serum hCG (IU/L) | <10<sup>3</sup> | 10<sup>3</sup> to <10<sup>4</sup> | 10<sup>4</sup> to <10<sup>5</sup> | ≥10<sup>5</sup> |
| Number of metastases | - | 1–4 | 5–8 | >8 |
| Site of metastases | Lung | Spleen, kidney | Gastro-intestinal | Liver, brain |
| Largest tumor size (cm) (including uterus) | <3 | 3 to <5 | ≥5 cm | - |
| Previous failed chemotherapy | - | - | Single drug | Two or more drugs |

Table 11. WHO risk table.

| Adverse reaction | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|------------------|---------|---------|---------|---------|---------|
| Anemia | Hb < LLN to 10.0 g/dL | Hb <10.0 g/dL to 8.0 g/dL | Hb <8.0 g/dL; transfusion indicated | Life-threatening consequences; urgent intervention indicated | Death |
| Neutro-penia | Neutrophils < LLN to 1500/mm<sup>3</sup> | Neutrophils <1500 to 1000/mm<sup>3</sup> | Neutrophils <1000 to 500/mm<sup>3</sup> | Neutrophils <500/mm<sup>3</sup> | N/A |
| Thrombo-cytopenia | Platelets < LLN to 75,000/mm<sup>3</sup> | Platelets <75,000 to 50,000/mm<sup>3</sup> | Platelets <50,000 to 25,000/mm<sup>3</sup> | Platelets <25,000/mm<sup>3</sup> | N/A |

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Medical Centre, Hungarian Defense Forces (HDF), Budapest (approval number: 307-114/2021).

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Conflict of interest

The authors declare no conflict of interest.

Appendix

See Tables 9, 10, 11

Financial disclosure

The authors have no connection to any companies or products mentioned in this article.
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