Archives of Gynecology and Obstetrics (2019) 299:1115–1119
https://doi.org/10.1007/s00404-018-5016-x

GYNECOLOGIC ONCOLOGY

Oral etoposide for metastatic choriocarcinoma: a case report and review of guidelines

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Received: 11 October 2018 / Accepted: 12 December 2018 / Published online: 19 December 2018

Abstract

Background and purpose Choriocarcinoma (CCA) is a rare form of malignant trophoblastic disease. Systemic polychemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMA/CO) is the mainstay of treatment for metastatic disease. Due to the rarity of the condition, however, the evidence basis for this management is small and other chemotherapy regimens may also be effective. The reported case presents anecdotal evidence of an effective etoposide monotherapy treatment.

Method: case presentation We report the case of a patient with gestational choriocarcinoma and pulmonary metastases initially treated with methotrexate. Due to local disease progression, she underwent hysterectomy and continued treatment with methotrexate. After pulmonary progression, she was switched to oral etoposide.

Results After four cycles of etoposide monotherapy at a oral dosage of 100 mg d1–7, q28, the patient had no evidence of disease according to human chorionic gonadotropin serum levels and imaging studies. The treatment was well tolerated with World Health Organization (WHO) grade 2 alopecia and hot flushes as the most prominent side effects. The patient has achieved a sustained complete remission with a follow-up of 6 years.

Conclusion Oral etoposide may be an effective treatment alternative to EMA/CO in selected patients with oligometastatic CCA.

Keywords Choriocarcinoma · Etoposide · Chemotherapy · Angioinvasion · Metastasis

Introduction

Choriocarcinoma (CCA) is a rare malignant trophoblastic tumor with a prevalence of 2–5 cases per 100,000 live births [1, 2]. CCA is characterized by the biphasic growth of mononuclear cytotrophoblastic stem cells and multinucleated syncytiotrophoblasts and typically exhibits central necroses and hemorrhages, high mitotic counts, and marked angioinvasion without fibrinoid vessel wall degeneration [3]. Human chorionic gonadotropin (hCG) is produced by the syncytiotrophoblast and reaches high serum levels > 100,000 U/l in most cases [1]. The majority of CCA is gestational and occurs subsequently to a specific gestational event such as hydatidiform mole, normal pregnancy, or spontaneous abortion in decreasing frequency [2]. Non-gestational CCA, on the other hand, is very rare and may arise from pluripotent germ cells in the gonads or midline structures such as the mediastinum or they may even develop in poorly differentiated carcinomas of the cervix, endometrium, or the gastrointestinal tract [4, 5]. CCA is a chemosensitive tumor and, therefore, after histological diagnosis, CCA is treated with chemotherapy. Systemic monotherapy with methotrexate (MTX) is the mainstay of treatment for low-risk cases with low risk

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defined as a Fédération Internationale des Gynècologues et Obstétriciens (FIGO) risk score < 7 [6]. In contrast, patients with high-risk CCA defined as a FIGO score ≥ 7 are usually treated with systemic polychemotherapy consisting of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMA/CO) [7]. The success rate of EMA/CO is high but this therapy carries a considerable toxicity. Alifrangis et al. reported an overall survival rate of 94% after a median follow-up of 4 years in a large retrospective cohort study of 438 patients with various forms of high-risk or relapsed trophoblastic diseases treated with EMA/CO [7]. However, up to 35% of patients undergoing EMA/CO experienced significant toxicity with WHO grade 3/4 events, mostly alopecia, nausea, emesis, diarrhea, myelosuppression, and fatigue [7, 8].

While the efficacy of EMA/CO has been confirmed in numerous studies of patients with high-risk trophoblastic disease [8], the specific role of EMA/CO in patients with CCA is less well documented. Low-risk CCA can be successfully treated with MTX monotherapy and may even spontaneously regress without any chemotherapy at all as demonstrated in a retrospective study by Taylor et al. [9]. In this study, 24 out of 65 low-risk CCA showed a spontaneous regression while on a watch and wait strategy. Therefore, it is reasonable to speculate that less aggressive forms of chemotherapy may also be effective in selected patients with high-risk CCA. Etoposide, for example, is a candidate for such a systemic monotherapy approach in patients with CCA, because it has been shown to be active when used as induction chemotherapy before the initiation of EMA/CO [7]. Here, we report the case of a patient with high-risk gestational CCA and pulmonary metastases successfully treated with oral etoposide as a monotherapy. This experience may add to the treatment choices faced by patients with CCA.

Case report

A 44-year-old patient presented to the clinic in November 2012 after an outpatient uterine curettage due to miscarriage with a gestational age of 18 weeks according to uterine size. An hCG serum level of 618,000 U/l was recorded. Histopathological examination of the curettage material demonstrated CCA. Staging was performed including abdominal, thoracic, and brain computed tomography (CT) demonstrating diffuse peripheral nodules in both upper pulmonary lobes up to a diameter of 10 × 10 mm. Abdominal and brain CAT scan showed no evidence of disease. Despite a FIGO score of 12, the patient was started on a methotrexate monotherapy after deliberate shared decision-making. The course of disease including serial serum hCG values and chemotherapy interventions is demonstrated in Fig. 1. Specifically, the treatment scheme consisted of intravenous MTX 50 mg/day d1, 3, 5, 7, q14 with folinic acid 15 mg/day on days 2, 4, 6, and 8. After three cycles of MTX, hCG dropped to 52,100 U/l. After the third cycle, hCG rose to 130,000 U/l. The MTX dosage was, therefore, increased to 75 mg/day. A thoracic CT showed no more evidence of pulmonary metastases. After the fifth cycle and a serum hCG value of 87,000 U/l, the patient was hospitalized because of strong pelvic pain. At admission, a gynecological examination demonstrated no vaginal bleeding, but an enlarged and painful uterus with a size according to week of gestation 18. Transvaginal ultrasound revealed cloudy hyporeflexive

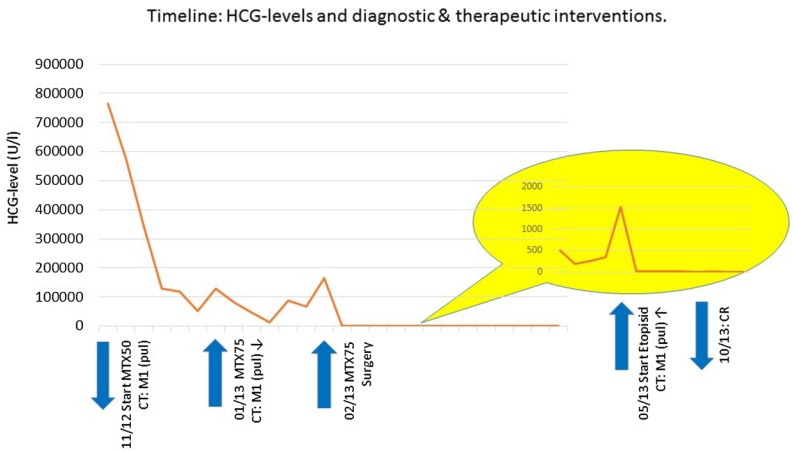

Fig. 1 Timeline of serial serum hCG evaluations and therapeutic interventions

Abbreviations: MTX50=methotrexate 50 mg, MTX75=methotrexate 75 mg, CT=computed tomography, downward arrow=disease remission, upward arrow=disease progression, CR=complete remission

masses in the uterine cavity, which seemed to penetrate the uterus at its ventral isthmic part. Laboratory parameters showed leucocytosis and high C-reactive protein (CRP) levels. The patient's temperature was > 39 °C. She was started on antibiotic treatment and open hysterectomy with bilateral salpingectomy was performed. The intraoperative course was uneventful. No perforation of the uterus and no peritoneal tumor spread were noted. Figure 2 shows a macroscopic image of the uterus with the uterine cavity filled with CCA tumor masses.

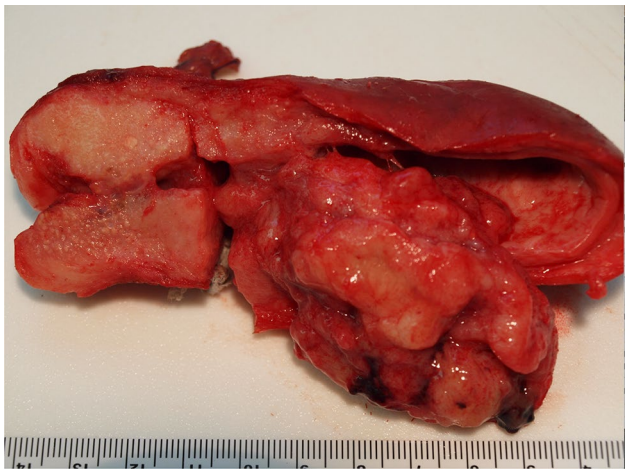

Fig. 2 Macroscopic image of a choriocarcinoma within the uterine cavity and infiltration of the caesarian scar

Pathologic–anatomic assessment showed a uterus of 169 g measuring 8.5 × 6.6 × 4 cm with a soft tumor mass of 5.5 × 4.3 × 4.2 cm, infiltrating the inner part of the myometrium and the uterine isthmus, leaving a 4-mm tumor-free zone under the uterine serosa. Within the intraepithelial and stromal areas of the uterus, neutrophilic granulocytes, a lympho-plasmacellular infiltrate, and single siderophages were found. The parametric tissue was tumor free. Figure 3 shows histopathologic images of the CCA demonstrating necrosis, hemorrhage, and angioinvasion. The final histopathologic report described a choriocarcinoma of 5.5 cm in the largest diameter with angiotropism and angioinvasion. The pTNM tumor stage was pT1, V1, L0, R0, NX, MX.

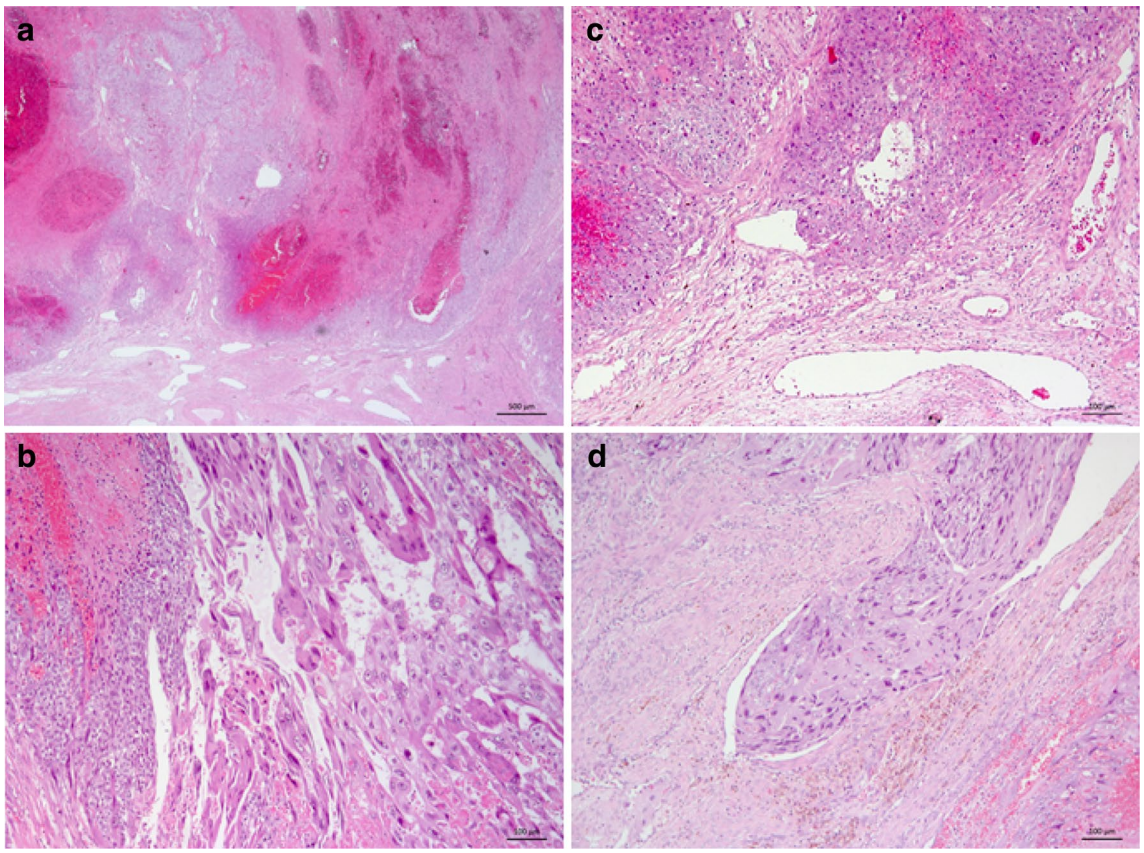

Fig. 3 Histopathologic images of a choriocarcinoma with myometrial invasion, necrotic areas and hemorrhage (magnification × 2.5) (**a**), trimorphic pattern of cytotrophoblast on the left (smaller cells) and syncytiotrophoblast (large multinucleated cells) and intermediate trophoblast (medium sized cells) in the center and on the right and marked cytological atypia (magnification × 10) (**b**), tumor cells surrounding blood vessels demonstrating angiotropism (magnification × 10) (**c**), and angioinvasion (magnification × 10) (**d**)

After an uneventful recovery, the patient was dismissed from the hospital. At the time of the next appointment, 14 days after discharge, the patient presented in good general condition only reporting occasional hot flushes. Serum hCG was 508 U/l and again a shared decision was made to resume MTX monotherapy. Whereas a further decline to 182 U/l was observed after two cycles, the following hCG controls revealed rising hCG values of 1520 U/l after another cycle. At that time, abdominal and thoracic CT scans were performed and showed a new small peripheral pulmonary nodule in the left upper lobe of the lung with 13 mm in the largest diameter (Fig. 4). Subsequently, the patient was started on oral etoposide at a dosage of 100 mg d1–7, q28 in May 2013. After four additional cycles of etoposide, serum hCG dropped below the detection level and a thoracic CT demonstrated complete remission of the pulmonary metastasis (Fig. 4). No adverse events World Health Organization (WHO) grade ≥ 3 were noted. The patient had alopecia WHO grade 2 and hot flushes. The chemotherapy was stopped and the patient underwent monthly serum hCG controls until March 2015, when a control CT of the thorax confirmed sustained remission. Afterwards, she underwent 3-monthly serum hCG controls. In September 2014, ovarian function resumed. From 2016 to March 2018, she underwent 6-monthly serum hCG controls demonstrating sustained complete remission.

Discussion

In this case report, oral etoposide was chosen as treatment in a patient with high-risk CCA and pulmonary metastases achieving a sustained complete remission. Being aware of the guideline recommendation of EMA/CO chemotherapy in high-risk CCA the therapeutic decision was discussed thoroughly with the patient who after all refused to comply with the toxic therapy asking for a less toxic modification. The observed complete remission suggests that etoposide may be an effective single-agent chemotherapy in selected patients with oligometastatic CCA not eligible for EMA/CO, thus sparing these patients the considerable toxicity associated with this form of polychemotherapy. Of note, up to 35% of patients undergoing EMA/CO have been reported to experience significant toxicity with WHO grade 3/4 events, mostly alopecia, nausea, emesis, diarrhea, myelosuppression, and fatigue [7, 8]. Clearly, EMA/CO is the standard of care for high-risk CCA and has been proven to be efficacious and safe with success rates of 94% after a median follow-up of 4 years [7]. However, some patients may not be able or willing to undergo polychemotherapy and some patients may have to undergo early termination of EMA/CO due to side effects. For these patients, oral etoposide may be considered based on the positive experience described in this case report.

CCA is a rare entity, but it displays characteristic histopathological features. In our case, the microscopic aspects of the tumor showed a trophoblastic cell mass with deep myometrial infiltration, abundant hemorrhages, and necrotic areas with a characteristic trimorphic pattern of

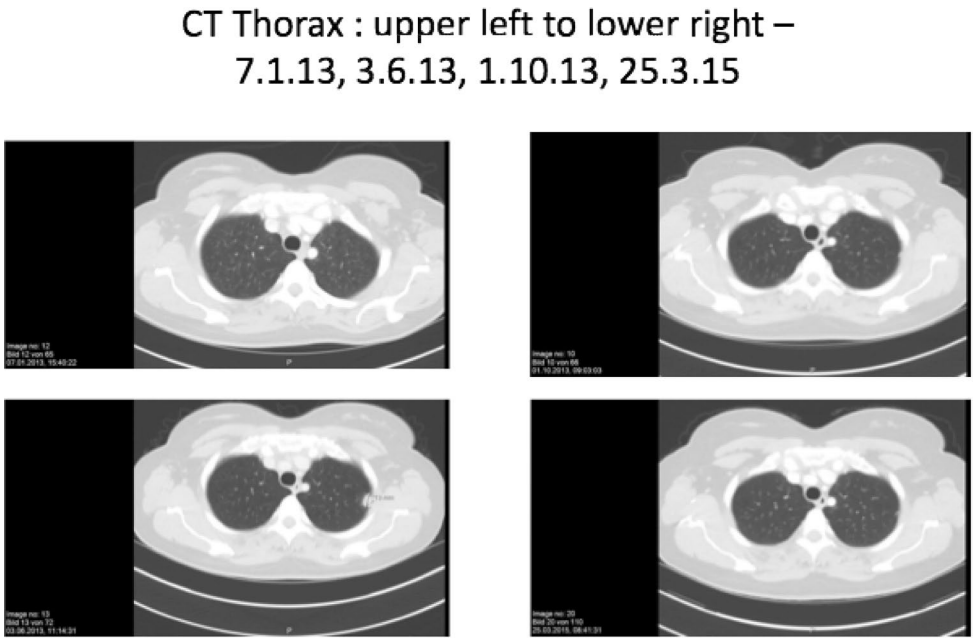

Fig. 4 Thoracic computed tomography scans at different time points during the course of treatment demonstrating lung metastasis of choriocarcinoma in the left upper lobe

cytotrophoblast, syncytiotrophoblast with hCG positivity, and intermediate trophoblast. In addition, marked cytological atypia, angiotropism, and angioinvasion were noted, signaling the invasive and metastatic potential of this rare tumor. Focal neutrophilic granulocytes, a lymphoplasmacellular infiltrate, and single siderophages were also seen, presumably as sequelae of myometritis and parametritis. Clearly, CCA is difficult to diagnose, especially when only curettage material is available. In accordance, interobserver variability in the diagnosis of trophoblastic tumors is considerable and has been reported in the literature to be between 59 and 100% [10]. Therefore, due to the histopathological complexity of CCA and the difficulty associated with its histopathological diagnosis, a second opinion regarding the histopathological diagnosis may be obtained to confirm the diagnosis before the start of any chemotherapy regimen.

The optimal chemotherapy for high-risk CCA is not well evidence based due to the rarity of this tumor. The recommendation to use MTX in low-risk cases and EMA/CO in high-risk cases is extrapolated from other low- and high-risk gestational diseases [2, 7] and may be an overtreatment in some cases. Thus, treatment alternatives for selected patients who cannot or are not willing to undergo the recommended treatments are clinically warranted. Based on our case report, we provide anecdotal evidence that oral etoposide may be a treatment alternative for patients with high-risk CCA in selected cases.

Author contributions GPB: protocol/project development, data collection and management, data analysis, manuscript writing. PS: data collection and management. CV: images collection and management, histopathological data analysis. SDC: project development, data analysis. WK: manuscript review, editing. EFS: manuscript review, editing. IJ-B: data analysis, manuscript writing, editing. CT: data analysis, manuscript writing, editing.

Funding This study was not funded.

Compliance with ethical standards

Conflict of interest All of the authors (Georg-Peter Breitbach, Panagiotis Sklavounos, Christian Veith, Serban-Dan Costa, Walther Kuhn, Erich-Franz Solomayer, Ingolf Juhasz-Boess, Clemens Tempfer) declare that they have no conflict of interest.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent for publication of this case report was received and personally signed from the patient on 2017-09-07.

References

1. Ngan HY, Bender H, Benedet JL, Jones H, Montruccoli GC, Pecorelli S, FIGO Committe on Gynecologic Oncology (2003) Gestational trophoblastic neoplasia: FIGO 2000 staging and classification. Int J Gynaecol Obstet. 83(Suppl. 1):175–177
2. Brown J, Naumann RW, Seckl MJ, Schink J (2017) 15 years of progress in gestational trophoblastic disease: scoring, standardization, and salvage. Gynecol Oncol 144(1):200–207
3. Fisher RA, Newlands ES, Jeffreys AJ, Boxer GM, Begent RH, Rustin GJ et al (1992) Gestational and nongestational trophoblastic tumors distinguished by DNA analysis. Cancer 69(3):839–845
4. Dilek S, Pata O, Tok E, Polat A (2004) Extraovarian nongestational choriocarcinoma in a postmenopausal woman. Int J Gynecol Cancer. 14(5):1033–1035
5. Ramarajapalli ML, Rao NA, Murudaraju P, Kilara NG (2012) Ovarian choriocarcinoma with concurrent metastases to the spleen and adrenal glands first case report. J Gynecol Surg. 28(2):153–155
6. FIGO Oncology Committee (2002) FIGO staging for gestational trophoblastic neoplasia 2000. Int J Gynaecol Obstet 77:285–287
7. Alifrangis C, Agarwal R, Short D, Fisher RA, Sebire NJ, Harvey R et al (2013) EMA/CO for high-risk gestational trophoblastic neoplasia good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. J Clin Oncol 31(2):280–286
8. Alazzam M, Tidy J, Osborne R, Coleman R, Hancock BW, Lawrie TA (2016) Chemotherapy for resistant or recurrent gestational trophoblastic neoplasia. Cochrane Database Syst Rev 1:CD008891
9. Taylor F, Short D, Winter MC, Tidy J, Savage PM, Sarwar N, Hancock BW, Seckl MJ, Coleman RE (2015) A retrospective study to evaluate single agent methotrexate treatment in low risk gestational choriocarcinoma in the United Kingdom. Gynecol Oncol 136(2):258–263
10. Gupta M, Vang R, Yemelyanova AV, Kurman RJ, Li FR, Maambo EC, Murphy KM, DeScipio C, Thompson CB, Ronnett BM (2012) Diagnostic reproducibility of hydatidiform moles: ancillary techniques (p57 immunohistochemistry and molecular genotyping) improve morphologic diagnosis for both recently trained and experienced gynecologic pathologists. Am J Surg Pathol 36(12):1747–1760