**COMPARATIVE ANALYSIS OF THE TREATMENT OF GESTATIONAL TROPHOBLASTIC DISEASE WITH ETOPOSIDE AND METHOTREXATE**

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**RESUMO:** Considering the complexity and variability in the treatment of gestational trophoblastic disease (GTD), particularly in cases resistant to standard therapies such as methotrexate, there is an urgent need to explore alternative chemotherapy regimens that can effectively manage these cases. This study aims to systematically review and compare the efficacy of different chemotherapy regimens, including those based on etoposide and methotrexate, in treating both low-risk and high-risk gestational trophoblastic neoplasia (GTN). A narrative literature review was conducted, analyzing a wide range of studies and case reports that explore the outcomes of various chemotherapy protocols, such as EMA-CO, EP/EMA, and TIP, among others. The review included data from studies published between 2015 and 2021, sourced from databases such as PubMed, Scopus, and Web of Science. The results indicate that while methotrexate remains a commonly used first-line treatment, its efficacy in high-risk and resistant GTN cases is often limited, necessitating the use of alternative regimens like EMA-CO or TIP, which have shown higher complete response rates in resistant cases. Additionally, the review highlights the significant challenges associated with managing GTN with brain metastasis or other severe complications, where more aggressive treatments, including surgical interventions, may be required. It is concluded that although alternative regimens like EMA-CO and TIP offer promising results, the choice of therapy should be carefully tailored to the individual patient's risk profile and response to treatment. Further research is needed to refine these treatment strategies and develop more standardized guidelines for managing resistant and recurrent GTN, with an emphasis on balancing efficacy with toxicity.

**Palavras-Chave:** Gestational trophoblastic disease, Chemotherapy regimens, Methotrexate resistance, EMA-CO, Etoposide, TIP therapy.

**Área Temática: Medicina**

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**1. INTRODUÇÃO**

Gestational trophoblastic disease (GTD) encompasses a spectrum of pregnancy-related disorders that arise from the abnormal proliferation of trophoblastic tissue. These conditions range from benign hydatidiform moles to malignant gestational trophoblastic neoplasia (GTN), which includes invasive moles, choriocarcinoma, and placental site trophoblastic tumors. GTD is a rare yet highly treatable condition, with cure rates exceeding 90% in most cases when diagnosed early and managed appropriately. However, the treatment of GTD, particularly in cases of GTN, remains complex, especially when the disease is resistant to standard therapies such as methotrexate.

The literature on GTD highlights the effectiveness of methotrexate as a first-line treatment, particularly in low-risk GTN cases. However, resistance to methotrexate has been reported, particularly in high-risk cases, necessitating alternative chemotherapy regimens. Studies such as those by Singh, Singh, and Vardhan (2018) have demonstrated the challenges in treating methotrexate-resistant GTN, where combination regimens like EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) are employed as salvage therapies. Despite the success of these regimens, there remains a significant need for optimizing treatment protocols, as the variability in patient responses and the potential for severe side effects continue to pose challenges in clinical practice.

Further complicating the treatment landscape are cases of GTN with metastasis or other severe complications, such as brain involvement. Reports like those of Metke, Kiesel, and Witteler (2019) have highlighted the need for more aggressive treatment approaches in such scenarios, including the use of cisplatin and etoposide-based regimens. However, the lack of standardized guidelines and the limited availability of randomized controlled trials in this rare disease context leave gaps in the current understanding of the most effective treatment strategies.

This study aims to systematically review and compare the efficacy of various chemotherapy regimens, particularly those based on etoposide and methotrexate, in treating both low-risk and high-risk GTN. By synthesizing the available evidence, this research seeks to identify the most effective treatment strategies and provide recommendations for optimizing clinical outcomes in patients with resistant or recurrent GTN.

**2. MÉTODO OU METODOLOGIA**

For this study, a narrative literature review was chosen as the method, allowing for a critical and interpretative analysis of published studies on the treatment of gestational trophoblastic disease (GTD) with chemotherapy regimens, particularly those based on etoposide and methotrexate. The narrative review is particularly suitable for this topic as it enables the integration and synthesis of different chemotherapy approaches, providing a comprehensive view of the available evidence and highlighting variations in outcomes based on the regimen used and the clinical characteristics of the patients. This method is ideal for exploring both established treatments and recent advancements in managing GTD, with a focus on optimizing therapeutic strategies for cases resistant to standard treatments.

The methodology for this study was developed following guidelines established by experts in narrative review, as described by Rother (2007) and Greenhalgh (2014). These guidelines offer a robust framework for conducting narrative reviews, including the careful selection of relevant literature, assessment of the quality of included studies, and synthesis of data in a manner that acknowledges the methodological diversity and varied outcomes reported in the studies analyzed.

In line with these expert recommendations, special attention was given to identifying potential biases within the analyzed studies and ensuring a transparent and balanced presentation of the findings. The literature search was conducted in well-established academic databases, including PubMed, Scopus, and Web of Science, using specific descriptors such as "gestational trophoblastic disease," "chemotherapy regimens," "methotrexate resistance," "EMA-CO," and "etoposide," applying Boolean operators like "AND" and "OR" to refine the search results. The temporal scope considered publications from 2015 to 2021, ensuring the inclusion of a contemporary and relevant perspective on the subject.

The inclusion criteria for the articles focused on studies that provided quantitative or qualitative data on the outcomes of various chemotherapy regimens in treating GTD, including effectiveness, complications, response rates, and impacts on patient survival and quality of life. By adhering to these rigorous methodological standards, the study aims to align with the quality expectations of both academic and clinical practice, ensuring a meaningful contribution to the existing literature. Furthermore, it seeks to provide a solid foundation for future research aimed at improving treatment strategies for resistant and recurrent GTD.

**3. RESULTADOS E DISCUSSÕES**

Table 1. Comparative Analysis of the Treatment of Gestational Trophoblastic Disease with Etoposide and Methotrexate

| Author and Year | Title of the Study | Study Summary |
| --- | --- | --- |
| Yamaguchi et al., 2021 | Successful salvage treatment with paclitaxel, ifosfamide, and cisplatin in a patient with methotrexate‐resistant gestational trophoblastic neoplasia who developed hypersensitivity reaction to etoposide | Case report of a methotrexate-resistant gestational trophoblastic neoplasia treated successfully with TIP (paclitaxel, ifosfamide, and cisplatin), followed by resection of the residual mass. |
| Li et al., 2019 | Chemotherapy for gestational trophoblastic neoplasia patients with a FIGO score of 12 or greater: A multistudy analysis | Analysis of 17 studies involving 256 patients with gestational trophoblastic neoplasia with a FIGO score ≥12, comparing different chemotherapy regimens. |
| Singh, Singh and Vardhan, 2018 | A case of methotrexate resistant gestational trophoblastic neoplasia | Case of a 25-year-old woman with methotrexate-resistant gestational trophoblastic neoplasia treated with EMA-CO combination chemotherapy. |
| Alazzam et al., 2016 | Chemotherapy for resistant or recurrent gestational trophoblastic neoplasia | Systematic review to determine which chemotherapy regimens are most effective and least toxic for resistant or recurrent gestational trophoblastic neoplasia. |
| Metke, Kiesel and Witteler, 2019 | EP1139 successful treatment of choriocarcinoma with brain metastasis with cisplatin etoposid: a case report | Case report of a successful treatment of choriocarcinoma with brain metastasis using cisplatin and etoposide. |
| Li et al., 2018 | The efficacy and safety of first-line single-agent chemotherapy regimens in low-risk gestational trophoblastic neoplasia: A network meta-analysis | Meta-analysis comparing the efficacy and safety of single-agent chemotherapy regimens based on methotrexate and actinomycin-D for low-risk gestational trophoblastic neoplasia. |
| Hao et al., 2021 | Direct comparisons of efficacy and safety between actinomycin-D and methotrexate in women with low-risk gestational trophoblastic neoplasia: a meta-analysis of randomized and high-quality non-randomized studies | Meta-analysis directly comparing the efficacy and safety of actinomycin-D and methotrexate in women with low-risk gestational trophoblastic neoplasia. |
| Winder et al., 2016 | The role of surgery in the treatment of epithelioid trophoblastic tumor: A single institution case series | Case series investigating the role of surgery in the treatment of epithelioid trophoblastic tumor. |
| Breitbach et al., 2019 | Oral etoposide for metastatic choriocarcinoma: a case report and review of guidelines | Case report and review of guidelines on the use of oral etoposide for metastatic choriocarcinoma. |
| Gómez García et al., 2015 | Caesarean scar ectopic pregnancy successfully treated with methotrexate and mifepristone | Case of ectopic pregnancy in a cesarean scar successfully treated with methotrexate and mifepristone. |
| Yun et al., 2020 | Successful treatment of a high-risk nonseminomatous germ cell tumor using etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine: A case report | Case report of successful treatment of high-risk nonseminomatous germ cell tumor using the EMA-CO regimen. |
| Ranade, Aguilera-Barrantes and Quiroz, 2015 | Gestational Trophoblastic Disease and Choriocarcinoma | Case study on gestational trophoblastic disease and choriocarcinoma, detailing treatment with methotrexate and actinomycin-D. |
| Gwacham et al., 2019 | Leptomeningeal spread of gestational trophoblastic neoplasia in a 19-year old woman | Case of gestational trophoblastic neoplasia with leptomeningeal metastasis, treated with induction chemotherapy and EMA. |
| Hao et al., 2021 | Direct Comparisons of Efficacy and Safety Between Actinomycin-D and Methotrexate in Women With Low-Risk Gestational Trophoblastic Neoplasia: A Systematic Review and Meta-Analysis | Systematic review and meta-analysis comparing actinomycin-D and methotrexate in the treatment of low-risk gestational trophoblastic neoplasia. |
| Xiao et al., 2016 | Spontaneous renal hemorrhage caused by invasive mole: a case report | Case report of spontaneous renal hemorrhage caused by invasive mole, treated with EMACO chemotherapy and surgery. |

Yamaguchi et al. (2021) reported a case of a 34-year-old woman with methotrexate-resistant gestational trophoblastic neoplasia (GTN) who developed hypersensitivity to etoposide. The patient presented with a 32 mm solid mass in the right lung and a 101 mm cystic mass in the liver. Her serum human chorionic gonadotropin (HCG) level was 689,439 mIU/mL. After eight cycles of combined chemotherapy with paclitaxel, ifosfamide, and cisplatin (TIP), the HCG level decreased to 2.4 mIU/mL, and CT scans revealed the disappearance of the lung tumor and significant reduction of the liver tumor. The patient underwent left hemihepatectomy, and after three months, there was no evidence of disease, with normalized HCG levels.

Li et al. (2019) conducted a multistudy analysis of chemotherapy for GTN patients with a FIGO score ≥12. They included 17 studies with 256 patients. The most common first-line regimens were etoposide-methotrexate-dactinomycin alternating with cyclophosphamide-vincristine (EMA/CO), etoposide-platinum alternating with EMA (EP/EMA), and floxuridine-dactinomycin-etoposide-vincristine (FAEV). The complete response (CR) rates were 55.2% for EMA/CO, 60% for EP/EMA, and 63.1% for FAEV. There was no significant difference in CR rates among these regimens in the first-line setting. For patients who failed initial therapy, the most common salvage regimens were EMA/CO, EP/EMA, and paclitaxel-cisplatin alternating with paclitaxel-etoposide (TP/TE), with CR rates of 39.7%, 35%, and 11.8%, respectively.

Singh, Singh, and Vardhan (2018) presented a case of a 25-year-old woman with methotrexate-resistant GTN. Initially treated with multiple doses of methotrexate without response, she was later diagnosed with high-risk GTN (invasive mole) (I:8) and treated with the EMA-CO chemotherapy regimen (etoposide, methotrexate, actinomycin, cyclophosphamide, and oncovin). The patient responded to the treatment, became asymptomatic, and is under regular follow-up.

Alazzam et al. (2016) conducted a systematic review to determine the most effective and least toxic chemotherapy regimens for resistant or recurrent GTN. The review included various studies but found no randomized controlled trials (RCTs) due to the low prevalence of the disease and its high chemosensitivity. For methotrexate-resistant low-risk GTN, the common practice is to use five-day dactinomycin, followed by MAC (methotrexate, dactinomycin, cyclophosphamide) or EMA/CO if further salvage therapy is required. For high-risk GTN, EMA/CO is the most common first-line therapy, with platinum-etoposide combinations like EMA/EP being preferred as salvage therapy. Alternatives like TP/TE, BEP (bleomycin, etoposide, cisplatin), FAEV, and FA (5-fluorouracil, dactinomycin) may be as effective as EMA/EP with potentially fewer side effects.

Metke, Kiesel, and Witteler (2019) reported a case of successful treatment of choriocarcinoma with brain metastasis using cisplatin and etoposide. A 26-year-old patient initially treated with methotrexate for suspected ectopic pregnancy was diagnosed with gestational choriocarcinoma with pulmonary, brain, and intra-abdominal metastases. During induction therapy with cisplatin and etoposide, the patient experienced intracerebral hemorrhage. Due to complications, standard EMA/CO chemotherapy could not be administered, so the cisplatin and etoposide regimen was continued. After six cycles, the patient achieved complete remission, as indicated by HCG levels and imaging studies. The patient completed 11 cycles and is in complete remission with six months of follow-up.

Li et al. (2018) performed a network meta-analysis to compare the efficacy and safety of single-agent chemotherapy regimens based on methotrexate (MTX) and actinomycin-D (Act-D) for low-risk GTN. Seven randomized controlled trials and four retrospective studies met the eligibility criteria, including 987 patients. Treatments were grouped into weekly intramuscular MTX, five-day intramuscular MTX, five-day intravenous MTX, eight-day intramuscular MTX with folinic acid, five-day intravenous Act-D, and bi-weekly pulsed intravenous Act-D. The results indicated that Act-D-based regimens had superior efficacy, with five-day intravenous Act-D being the most effective and least toxic in terms of nausea and vomiting.

Hao et al. (2021) conducted a meta-analysis comparing the efficacy and safety of actinomycin-D (Act-D) and methotrexate (MTX) in women with low-risk GTN. The meta-analysis included eight randomized controlled trials (RCTs) and nine high-quality non-randomized studies, totaling 1674 patients. In terms of efficacy, Act-D was superior to MTX, with a complete remission rate of 80.2% for Act-D versus 65.1% for MTX. In terms of safety, Act-D had higher risks of nausea, vomiting, and alopecia, while MTX had a higher risk of liver toxicity.

Winder et al. (2016) conducted a case series to investigate the role of surgery in the treatment of epithelioid trophoblastic tumor (ETT). The retrospective study included five women treated at a gestational trophoblastic disease center from 2010 to 2015. All patients underwent hysterectomy, and three women also underwent resection of metastatic pulmonary disease. The four patients with metastatic disease received chemotherapy with platinum/etoposide regimens. All five patients are currently without evidence of disease.

Breitbach et al. (2019) reported a case and reviewed guidelines on the use of oral etoposide for metastatic choriocarcinoma. The patient, initially treated with methotrexate for gestational choriocarcinoma with pulmonary metastases, underwent hysterectomy after disease progression. She was then treated with oral etoposide, achieving complete remission after four cycles, with six years of follow-up.

Gómez García et al. (2015) described a case of ectopic pregnancy in a cesarean scar successfully treated with methotrexate and mifepristone. The patient showed significant clinical improvement and reduction in HCG levels following treatment, with the residual lung lesion attributed to scar tissue.

Yun et al. (2020) reported a case of successful treatment of high-risk nonseminomatous germ cell tumor using the EMA-CO regimen (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine). The patient, a 32-year-old man, was diagnosed with pure choriocarcinoma with metastases in the retroperitoneum, liver, and lungs. After eight cycles of EMA-CO, all residual masses were surgically removed, resulting in complete cure and ten years of follow-up without complications.

Ranade, Aguilera-Barrantes, and Quiroz (2015) described a case of gestational trophoblastic disease and choriocarcinoma. The patient was treated with methotrexate and actinomycin-D after being diagnosed with a complete hydatidiform mole in 2011. After normalization of HCG levels and a subsequent spontaneous abortion, the patient presented with persistently elevated HCG levels and was treated with multiple doses of methotrexate and actinomycin-D, resulting in normalized HCG levels.

Gwacham et al. (2019) reported a case of gestational trophoblastic neoplasia with leptomeningeal metastasis in a 19-year-old woman. The patient was treated with induction chemotherapy using etoposide and cisplatin, followed by chemotherapy with etoposide, methotrexate, and actinomycin (EMA), achieving complete response without the need for brain radiation.

Hao et al. (2021) conducted a systematic review and meta-analysis comparing actinomycin-D (Act-D) and methotrexate (MTX) in women with low-risk GTN. The meta-analysis included eight randomized controlled trials (RCTs) and nine high-quality non-randomized studies, totaling 1674 patients. The results showed that Act-D was superior to MTX in terms of complete remission rates, with higher probabilities of nausea, vomiting, and alopecia for Act-D, while MTX had a higher risk of liver toxicity.

Xiao et al. (2016) reported a case of spontaneous renal hemorrhage caused by invasive mole, treated with EMACO chemotherapy (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) and surgery. The patient underwent laparoscopically-assisted vaginal hysterectomy, laparoscopic-assisted left renal excision, and evacuation of the left perirenal hematoma, resulting in complete remission.

**4. CONCLUSÃO OU CONSIDERAÇÕES FINAIS**

This article has reviewed and compared various chemotherapy regimens used in the treatment of gestational trophoblastic disease (GTD), with a particular focus on cases resistant to standard therapies such as methotrexate. The study highlighted the effectiveness of alternative regimens like EMA-CO and TIP, which have shown higher complete response rates in resistant cases, thus offering promising options for managing this complex condition. The review also underscored the significant challenges in treating GTD with severe complications, such as brain metastasis, where more aggressive and tailored approaches are necessary to achieve favorable outcomes. These findings reinforce the critical importance of individualized treatment strategies that consider the specific risk profiles and therapeutic responses of patients.

Furthermore, the study emphasizes the practical implications of optimizing chemotherapy regimens for GTD, particularly in improving patient survival and quality of life. The variability in patient responses to different treatments and the potential for severe side effects necessitate the development of more standardized treatment protocols that can be applied across diverse clinical settings. The theoretical implications also suggest a need to refine our understanding of GTD's pathophysiology, particularly in how it influences treatment resistance and recurrence, thereby paving the way for more effective interventions.

Given the complexities and challenges discussed, there is a clear need for further research focused on refining treatment strategies for GTD, particularly in cases of methotrexate resistance and high-risk profiles. Future studies should aim to identify biomarkers that can predict patient response to different chemotherapy regimens and explore the potential of novel therapies that may offer improved efficacy with reduced toxicity. Additionally, more extensive clinical trials are needed to validate the findings of this review and establish evidence-based guidelines that can be widely adopted in clinical practice.

However, this study has certain limitations. The reliance on a narrative review approach, while allowing for a broad synthesis of available literature, also introduces potential biases in the selection and interpretation of studies. Furthermore, the limited number of randomized controlled trials in the context of GTD treatment, due to the rarity of the disease, constrains the ability to draw definitive conclusions about the superiority of specific regimens. These limitations highlight the need for more rigorous and comprehensive research efforts to build on the findings presented here.

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