Systematic Review

Actinomycin-D vs Methotrexate in Low-Risk Gestational Tropoblastic Neoplasia: Which is the better Option?

Heronimus Hansen Kaware[1], Kevin Wijaya[2], Balivia Andi Permata Hapsari[1]

[1]Faculty of Medicine Universitas Airlangga,Surabaya
[2]Faculty of Medicine Universitas Indonesia, Jakarta

Abstract

Objective: To compare the efficacy and safety of the ACT-based regimen and MTX-based regimen for LRGTN treatment.

Methods: Electronic databases were systematically searched for Randomized Controlled Trials (RCTs) and High-Quality Non-Randomized Controlled Trials (Non-RCTs) comparing ACT with MTX for patients with LRGTN. Studies without Complete Remission (CR) were excluded. The meta-analysis was carried out to quantify the efficacy and safety of each regimen based on odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results: Eight RCTs and 14 non-RCTs were included (2203 patients). Our study concludes that ACT has a higher CR than MTX (79.4% [716/902] vs 66.9%[871/1301]; OR 2.13; 95% CI 1.46-3.10, in the random-effects model). Furthermore, ACT is better in terms of efficacy compared to MTX in both the RCTs [81.2% (259/319) vs 66.1% (199/301); OR 2.17; 95% CI 1.49-3.16, in the fixed-effects model] and non-RCTs group [457/583 (78.4%) vs 672/1000(67.2%); OR 2.10; 95% CI 1.28-3.45, in the random-effects model]. Safety-wise, the use of ACT has a higher incidence of alopecia (OR 3.52, 95% CI: 1.27-9.75, in the random-effects model) compared to MTX, while MTX has a higher risk of developing liver toxicity (OR 0.54, 95% CI: 0.32-0.91, in the fixed-effects model) compared to ACT. Other side effects are not significantly different between the two groups.

Conclusion: Our meta-analysis concluded that ACT has a better efficacy compared to MTX for LRGTN patients. In terms of safety, ACT-based regimens have a higher chance of suffering from alopecia and a lower chance of suffering from liver toxicity. Future clinical studies on single-drug regimens for LRGTN should be conducted in order to produce higher-quality data.

Keywords: act, actinomycin-D, dactinomycin, methotrexate, mtx, low-risk gestational trophoblastic neoplasia, LRGTN.

Correspondence author. Hansen Kaware. Faculty of Medicine Universitas Airlangga. Surabaya.
Email; hansenkaware21@gmail.com

INTRODUCTION

Gestational Trophoblastic Neoplasia (GTN) is a malignant transformation of the placental villous trophoblast in sequelae with any type of prior pregnancy. GTN includes choriocarcinoma, invasive mole, placental site tumors, and epithelioid trophoblastic tumors. GTN has a cure rate of around 80-100% with the effective treatment regimen[1,2] GTNs' clinical presentations differ depending on the previous pregnancy type, disease progression, and histopathological classifications.[3,4]

The International Federation of Gynecology and Obstetrics (FIGO), together with the World Health Organization (WHO), developed a scoring system to assess the risk of chemotherapy resistance in gestational trophoblastic neoplasia (GTN). This system classifies GTNs into low-risk and high-risk categories. Low-risk GTNs (LRGTNs) include patients with stage I GTN according to FIGO staging, or patients with stage II–III GTN with a WHO score of 0–6. Meanwhile, GTN patients diagnosed with FIGO stage IV or FIGO stage II–III with a WHO score of ≥7 are classified as high-risk GTNs (HRGTNs). LRGTNs are often treated with single-drug regimens, whereas HRGTNs are typically treated with multidrug regimens[1,3]

Although several regimens are available for LRGTNs, single-drug regimens with either ACT or MTX remain the first choice. However, there is currently No. clear consensus on the best single-drug regimen for LRGTNs thus the choice is often made based on the institutional preference [5-7]. This meta-analysis was conducted to compare the safety and efficacy of each regimen.

METHODS

The study was done in accordance with the PRISMA.

Data Searches and Information Sources

Two investigators independently searched the electronic medical databases including PubMed/ Medline, Google Scholar, and Embase for articles written in English from January 2003 to January 2023. The keywords used were "Methotrexate, Actinomycin-D, Low-risk gestational trophoblastic neoplasia)". After the database search, the most recent studies were reviwed to identify potentially relevant publications. Full texts of these studies were then assessed for eligibility based on criteria for data synthesis.

Studies Eligibility Criteria

Eligible studies included both RCTs and non-RCTs that directly compared ACT and MTX in patients with LRGTN. Studies were if they provided detailed information on each regimens' outcomes and adverse events. Non-RCTs were included due to the rarity of RCTs on LRGTN. We excluded brief data such as abstracts, case reports, posters, and presentations of ongoing RCTs, as these lack detailed case information.

Data Extraction and Definition

The authors reviewed the main texts of each article to extract data regarding first author, publication year, region of publication, study design, total patients, chemotherapy regimens, and the number of the CR and adverse events. Complete Remission rate (CR) was made as the main inclusion criteria which is the number of patients who reached CR compared to the number of patients receiving regimens as the first line treatment. Few studies that did not include the adverse events were still included. The adverse events that show specific toxicities are used as the safety quantifier of each agent. We use Odds Ratio (OR) and 95% CI (95% Confidence Interval) to quantify the safety and efficacy of each agent.

Data Synthesis

ORs with 95% CIs were used to assess the safety and efficacy of MTX and ACT. Studies were pooled based on RCTs and non-RCTs. We applied fixed-effect models for homogeneous studies and random-effect models for studies with significant heterogeneity. Heterogeneity was assessed using the I^2 inconsistency test, with heterogeneity considered significant if the I^2 value was >50%. Forest plots were generated to provide graphical representations of the results. IBM SPSS Statistics V22.0 was used to analyze ORs, with statistical significance set at a p-value of 0.05.

RESULTS

Studies Selection and Characteristics

Results were taken from 8 RCTs [15-22] and 14 non-RCTs [23-36]. Out of all the studies there was only 1 multi-nation RCT, this may be due to the rarity of the case and the variety of regimens in different centers. FIGO/WHO 2000 Scoring System or Hammond Criteria was used as the basis of LRGTN diagnosis. The efficacy and toxicity comparison between MTX and ACT was taken from 22 papers. a total of 2203 patients were analyzed, 902 patients were given ACT while 1301 patients were given MTX.

Meta-analysis of Efficacy Profile

The regimen-based meta-analysis was done to compare the ratio of CR achieved in ACT-based regimen compared to MTX-based regimen. The final analysis shows that overall ACT-based regimen's efficacy was found higher than MTX-based regimen in complete remission (79.4% [716/902]) vs 66.9% [871/1,301]; OR 1.83, 95% CI: 1.49-2.26; I2 = 59%, P = 0.0002). The random-effects model was applied due to substantial heterogeneity, the complete remission event remained superior in the ACT-based group compared to the MTX-based group (OR: 2.13, 95% CI: 1.46-3.10). Furthermore, in the stratified analysis, we divided the studies into RCTs and non-RCTs separately. In RCT studies included, ACT-based regimen was found superior in complete remission (81.2% [259/319] vs 66.1% [199/301]; OR 2.17, 95% CI: 1.49-3.16; I2 = 41%, P = 0.10). For patients in non-RCTs, there was also a better complete remission seen in the ACT-based group (78.4% [457/583] vs 67.2% [672/1,000]; OR 1.70, 95% CI: 1.32-2.19; I2 = 66%, P = 0.0003), the results were not significantly different compared to when the random-effects model was applied due to the substantial heterogeneity (OR 2.10, 95% CI: 1.28-3.45). The meta-analysis of efficacy

profile in ACT-based group and MTX-based group can be seen in Figure 1

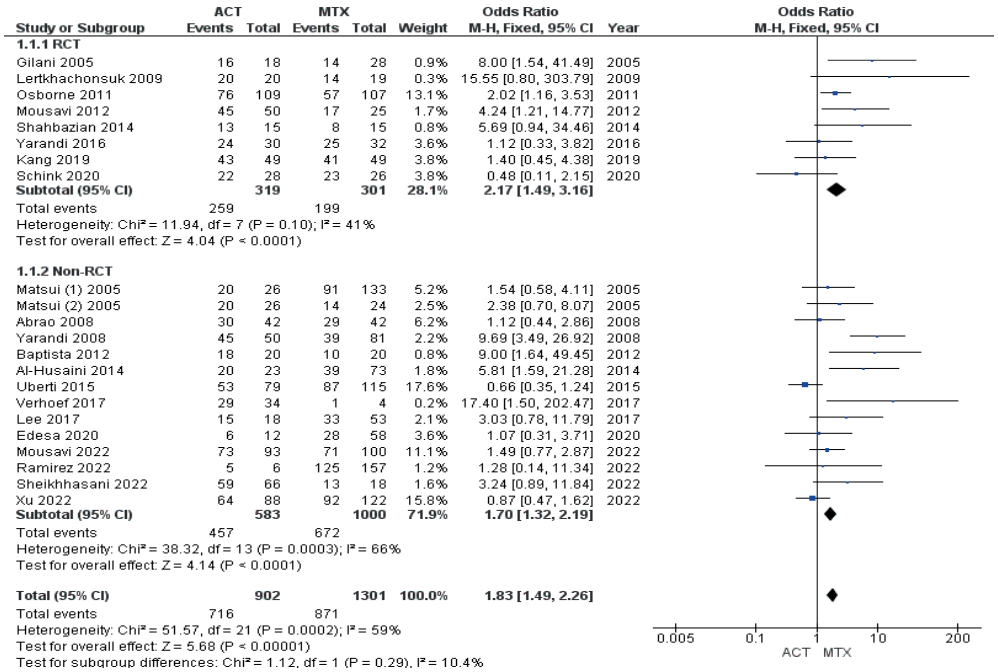

Figure 1. Meta-analysis of efficacy profile based on regimens and study type (fixed-effects model).

Meta-analysis for Toxicities

The toxicities of the regimen used were categorized into the side effects in hematological system, gastrointestinal system, reproductive system, and others.

Side Effects in Hematological System

Figure 2 demonstrated the comparison of hematological toxicities in ACT-based regimen and MTX-based regimen. The analysis shows that the patients who received ACT-based regimen have a significant lower risk of suffering leucopenia (OR 0.47, 95% CI 0.30-0.73; I2 = 83%, P = 0.0005). However, the risk of suffering leucopenia became insignificant upon the application of the random-effects model due to substantial heterogeneity (OR 0.55, 95% CI: 0.14-2.07). On the other side effects in hematological system, the final analysis showed no significant difference in anemia (OR 1.36, 95% CI 0.80-2.34; I2 = 0%, P = 0.36), neutropenia (OR 1.14, 95% CI: 0.65-2.01; I2 = 25%, P = 0.25), and thrombocytopenia (OR 1.52, 95% CI: 0.71-3.26; I2 = 32%, P = 0.21) between the two groups.

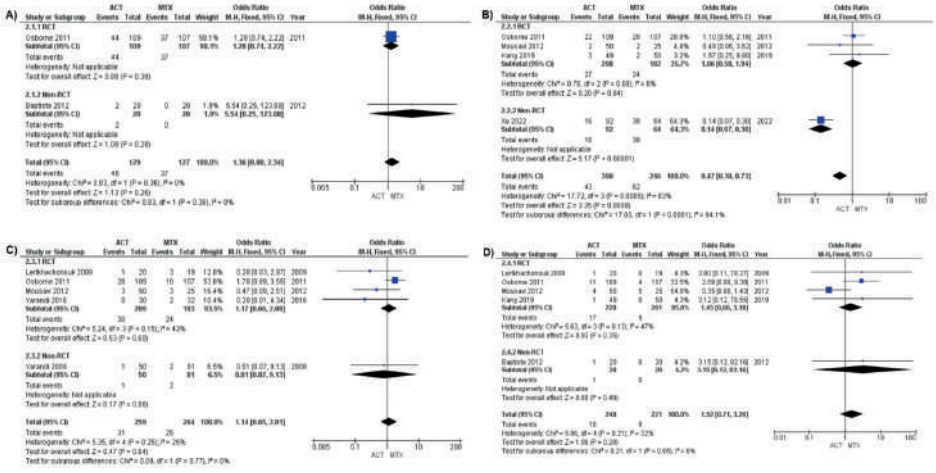

Figure 2. Meta-analysis of side effects in hematological system based on regimens and study type (fixed-effects model): (A) anemia, (B) leucopenia, (C) neutropenia, and (D) thrombocytopenia

Side Effects in Gastrointestinal (GI) System

Figure 3 shows the comparison of gastrointestinal toxicities in ACT-based regimen and MTX-based regimen. The analysis shows that the patients who received ACT-based regimen have a significantly higher risk of suffering nausea (OR 2.41, 95% CI: 1.73-3.35; I2 = 74%, P<0.0001). However, the risk of suffering nausea became insignificant upon the random-effects model application (OR 0.87, 95% CI: 0.38-1.96). The analysis also showed that ACT-based regimen increased the vomiting (OR 2.48, 95% CI: 1.69-3.65; I2 = 60%, P = 0.007). The risk of vomiting was insignificant upon the random-effect model application (OR 2.13, 95% CI: 0.97-4.67). The other pooled analysis showed that no significant difference in constipation (OR 0.92, 95% CI: 0.44-1.90; I2 = 0%, P = 0.81), diarrhea (OR 0.82, 95% CI: 0.49-1.38, I2 = 49%, P = 0.10), anorexia (OR 1.38, 95% CI: 0.58-3.29, I2 = 40%, P = 0.19), oral mucosa problem (OR 1.23, 95% CI: 0.35-4.26, I2 = 23%, P = 0.25), and other unspecified problems (OR 0.87, 95% CI: 0.40-1.90, heterogeneity test: not applicable) between the two regimen groups.

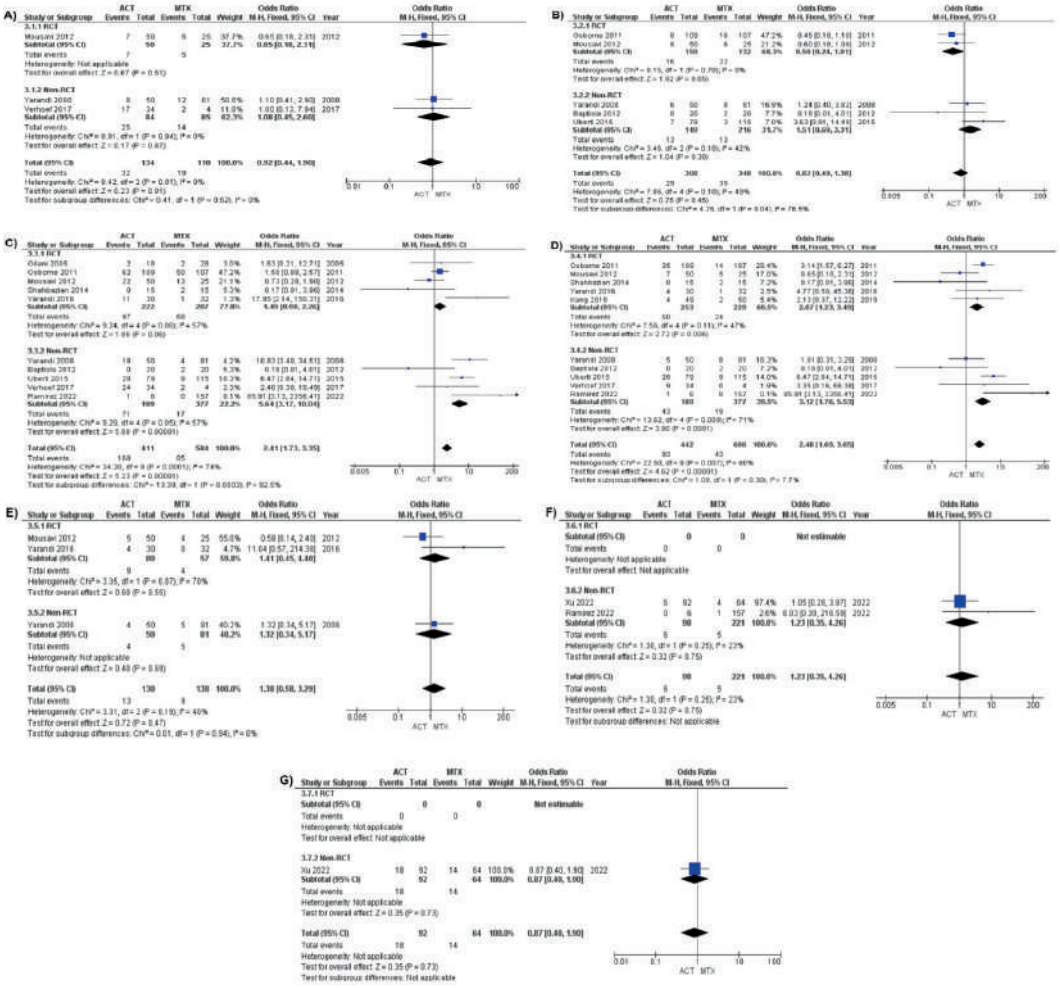

Figure 3. Meta-analysis of side effects in gastrointestinal system based on regimens and study type (fixed-effects model): (A) constipation, (B) diarrhea, (C) nausea, (D) vomiting, (E) anorexia, (F) oral mucosa problem, and (G) other unspecified disorder

Side Effects in Reproductive System

Figure 4 depicts the comparison of reproductive system toxicities in ACT-based groups with MTX-based groups. The analysis shows no significant difference of abnormalities in reproductive system, including abnormal menstrual cycle (OR 0.87, 95% CI: 0.49-1.52), change in menstrual period (OR 1.28, 95% CI: 0.68-2.42), change in menstrual volume (OR 0.78, 95% CI: 0.44-1.38), change in sexual desire (OR 1.29, 95% CI: 0.74-2.26), vaginal dryness (OR 1.06, 95% CI: 0.61-1.85), reduced sexual satisfaction (OR 0.84, 95% CI: 0.48-1.48), and sexual pain (OR 0.74, 95% CI: 0.38-1.45).

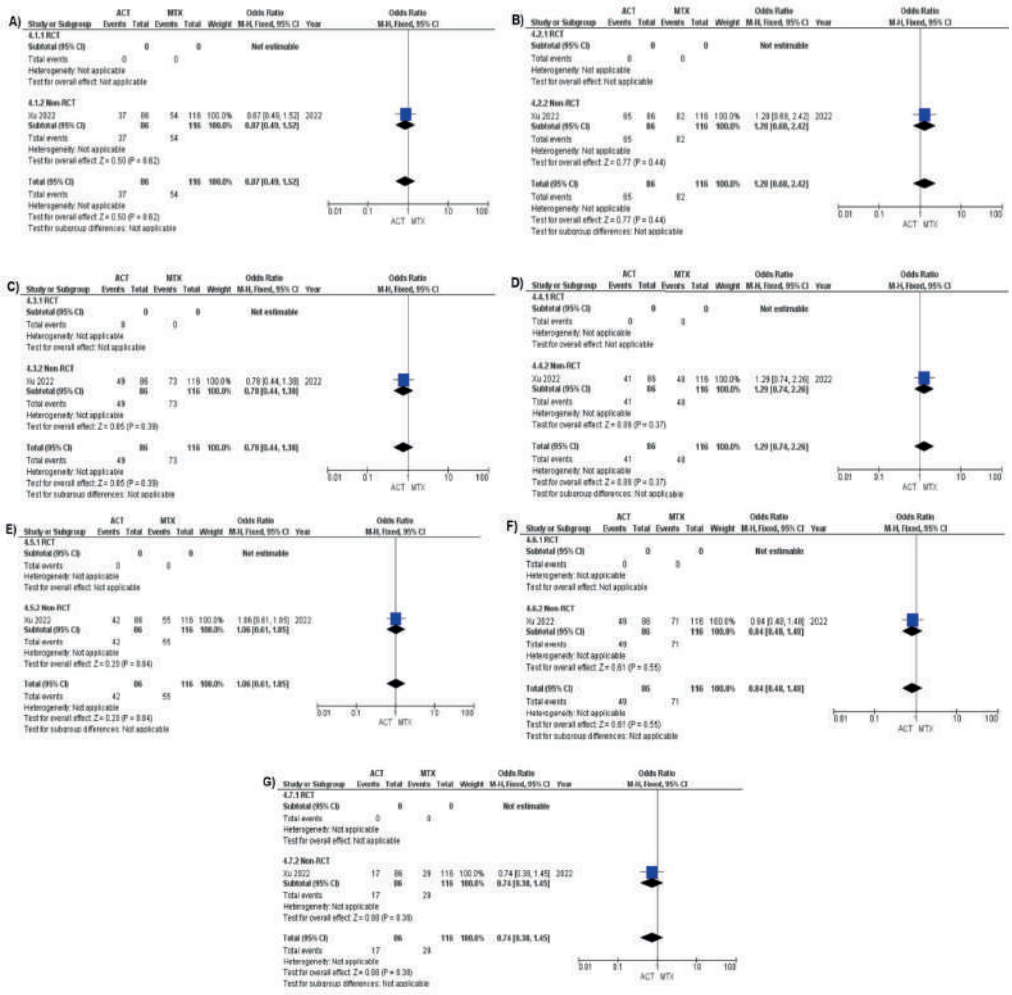

Figure 4. Meta-analysis of side effects of regimen in reproductive system abnormalities according to the regimens and study type (fixed-effects model): (A) abnormal menstrual cycle, (B) change in menstrual period, (C) change in menstrual volume, (D) change in sexual desire, (E) vaginal dryness, (F) reduced sexual satisfaction, and (G) sexual pain

Side Effects in Other System

The analysis shows that ACT-based regimen increased the risk of suffering alopecia (OR 3.21, 95% CI: 1.89-5.44; I2 = 58%, P = 0.003). The results remain significant after the application of the random-effects model due to substantial heterogeneity (OR 3.52, 95% CI: 1.27-9.75). In the stratified analysis of the total studies, the risk of suffering alopecia remained the same in RCTs (OR 2,92, 95% CI: 1.48-5.77; I2 = 63%, p = 0.05) and non-RCTs (OR 3.70, 95% CI: 1.60-8.53; I2 = 68%, p = 0.05). However, the results of each study became insignificant upon the application of random-effects model (RCTs: OR 2.81, 95% CI: 0.73-10.76 and Non-RCTs: OR 7.39, 95% CI: 0.71-77.25). Besides, the use of ACT-based regimen has a lower risk of developing liver toxicity compared to MTX (OR 0.54, 95% CI: 0.32-0.91; I2 = 0%, P = 0.43). In the stratified analysis, the risks of liver toxicity was found lower in RCTs studies (OR 0.38, 95% CI: 0.19-0.76; I2 = 0%, P = 0.55). However, the difference between the risk of liver toxicities in non-RCTs studies was found insignificant (OR 0.91, 95% CI: 0.40-2.09). Last, there is no significant difference reported in malaise symptoms between the two groups (OR 1.04, 95% CI: 0.59-1.82).

DISCUSSION

GTNs are malignant trophoblastic tumors with high sensitivity to chemotherapy. A single drug regimen of either MTX or ACT is commonly given as first-line treatment to women with LRGTN who wish to preserve fertility during chemotherapy, and the prognosis is favorable even in cases with metastasis. LRGTNs are highly curable, a CR rate approaching 100% (10-12). Currently there are still no definitive guidelines regarding the use of

single drug regimen for LRGTN. Our study which include 8 RCTs and 14 non-RCTs (2203 patients) was conducted in order to determine the safety and efficacy of each regimen. We disregarded each regimen's cycles and dosages to objectively assess the efficacy and safety of each regimens more objectively. Future studies may be needed in order to compare specific cycles and dosages of each regimen. In terms of efficacy, our findings are similar to the previous studies [8-12] confirming that ACT has a higher rate of CR compared to MTX as a single drug regimen for LRGTN patients[10-16]. Both RCTs and non-RCTs were pooled in the data analysis. In terms of safety, our study indicates that haematological and hepatic adverse events are more common in patients treated with ACT than with MTX. This finding was supported by other studies, which report that ACT may cause mild to moderate myelosuppression potentially leading to anaemia, leukopenia, neutropenia, thrombocytopaenia, or even pancytopaenia[13-18]. Conversely, LRGTN patients treated with MTX have shown more GI, reproductive system, and alopecia adverse events. Our safety analysis wa consistent with previous studies, though with slight variations. One study found that MTX-based regimen showed a higher incidence of hepatological side effects and ACT-based regimen showed a higher incidence of dermatological side effects including alopecia. Additionally, another study reported a higher incidence of nausea and vomiting with MTC regiments.[8,9,10]. Our findings also showed that MTX regiments were associated with more reproductive system adverse compared to ACT regimens. After the final analysis of the data, we concluded that ACT-based regimens have a higher chance of causing alopecia and a lower risk of liver toxicity.

This meta-analysis has some notable limitations. First, the limited number of studies required us to comnbine RCTs and non-RCT data. Although we performed pooled analyses for both RCTs and non-RCTs, the heterogeneity of the data could introduce bias. Second, there was a lack of standardization in the treatments across studies; we included all studies involving single-drug regimens of ACT and MTX regardless of dosage or regimen type. Third, there was a lack of uniform criteria for defining adverse events and CR rates among studies. Adverse events were graded using various criteria, such as WHO, Gynecologic Oncology Group Criteria, and CTCAE; some studies did not report any adverse events, which limited the sample size available for toxicity analysis and affected the assessment of drug safety.

CONCLUSION

In this study comparing the efficacy and safety of MTX and ACT in LRGTN patients, we concluded that the ACT regimen is more effective in terms of achieving complete remission, while there are no significant safety differences between the two groups. This article may serve as a valuable resource for establishing a more effective regimen for LRGTN and as a reference for future studies on LRGTN treatment.

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