Eight days versus weekly intramuscular methotrexate for the treatment of low-risk gestational trophoblastic neoplasia

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Summary

Objectives: To compare the efficacy of weekly and eight-day methotrexate (MTX) regimens for the treatment of low-risk gestational trophoblastic neoplasia (GTN). Toxicity profiles, patient satisfaction, and treatment duration were also considered for future implications. Materials and Methods: This randomized controlled trial included all patients diagnosed with low-risk gestational trophoblastic neoplasia at King Abdulaziz University Hospital over a period of four years. The primary remission rate, duration of treatment, number of treatment cycles, as well as toxicity and the change of the chemotherapeutic agent were compared following either a weekly methotrexate regimen (IM, 50 mg/m²) or an eight-day regimen (1 mg/kg IM every other day for four doses) and leucovorin calcium (0.1 mg/kg, given once, 24 hours after each dose). Results: Sixty patients (34 in the weekly IM group) were included. The eight-day protocol was associated with lesser treatment cycles (p = 0.011) and higher total methotrexate dose (p < 0.001) when compared to the weekly regimen. The eight-day protocol showed a relatively higher primary success rate when compared to the weekly protocol (84.6% vs. 70.6%), although this difference failed to reach statistical significance (p = 0.235). Only two cases of hepatotoxicity were reported in the single weekly group and no toxicity was reported in the eight-day group. Conclusion: The eight-day regimen was superior to the weekly regimen in terms of the remission rate, treatment duration, and toxicity profiles. Future studies should be based on larger sample size, investigate methotrexate effects on fertility, and the risk factors that may lead to methotrexate resistance.

Key words: Low-risk gestational trophoblastic neoplasia (GTN); Methotrexate; Success rate.

Introduction

Trophoblasts, the first differentiated cells from a fertilized oocyte, have a remarkable role in early blastocyst implantation, placental maturation and formation, and pregnancy maintenance. Gestational trophoblastic diseases (GTD) comprise a spectrum of trophoblastic proliferative abnormalities with a considerable variation in the capacity of proliferation, which ranges from non-neoplastic to neoplastic conditions. The incidence of GTD differs greatly among different countries. The highest rates have been reported in Asia (5-13 cases/1,000 pregnancies) [1] while the lowest incidence was reported in North America and Europe (0.5-1.84 cases/1,000 pregnancies) [1-3]. In Saudi Arabia, the incidence of GTD was reported as 0.3 in an earlier study in Riyadh [4], but was reported as 1.26 GTDs per 1,000 deliveries in a recent study in Jeddah [5]. The difference in GTD epidemiology is attributable to variation in consanguinity, extremes of reproductive life, previous pregnancies, socio-economic factors, and diet [6].

Generally, non-neoplastic GTDs (hydatidiform moles, or HM) are classified into complete HM, partial HM, and in-vasive moles, while neoplastic GTDs include placental site trophoblastic tumor (PSTT), gestational choriocarcinoma, and epithelioid trophoblastic tumor (ETT) [7]. For neoplastic GTDs, the International Federation of Gynecology and Obstetrics (FIGO) has employed a staging system for GTDs, where scoring ranges from confinement to the uterus (non-metastatic) to invasion into the genital tract, lungs or other metastatic sites [8]. Furthermore, the World Health Organization (WHO) modified a scoring system that includes selected risk factors for the prognosis of neoplastic GTDs. According to this system, tumors are judged to be of low risk if they are either non-metastatic, or when the score ranges between 0 and 6, whereas a score of 7 or more indicates a high-risk neoplasm [9].

Neoplastic GTDs, or gestational trophoblastic neoplasms (GTN), are rare tumors which are highly responsive to chemotherapy and are commonly viewed as the most curable malignancy in the gynecological field [10]. They usually follow HM, antecedent abortion, or ectopic gestation. Since trophoblast cells produce human Chorionic Gonadotropin (hCG), this hormone provides a useful indicator for GTN [11]. GTN diagnosis is based on the detection of elevated β-hCG after an antecedent molar pregnancy [12]. Additionally, even patients without molar pregnancy can be diagnosed with GTN when they present with high β-hCG levels along with metastasis to multiple sites, including the brain and lungs [9]. Monitoring hCG every two weeks is valuable during GTN treatment as persistent elevation for two consecutive samples indicates resistance to the therapy [13]. Once the diagnosis of GTN has been established (or

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even suspected) by elevated β-hCG levels, it is imperative to investigate for potential metastasis, including physical examination, blood count, and radiographic studies. Importantly, chest X-ray, CT, abdominal CT scan, and CT of the brain are required [14].

For low-risk GTNs, including non-metastatic tumors, chemotherapy is the treatment of choice, particularly for patients refraining from undergoing hysterectomy to maintain fertility [15]. A single chemotherapeutic, either methotrexate (MTX) or actinomycin D, is sufficient to induce remission. Indeed, the therapeutic success of MTX therapy depends mainly on the WHO score. For example, weekly intramuscular (IM) MTX therapy (50 mg/m²) was successful in 70% of patients with a WHO score of 0-1, whereas it induced a complete remission (CR) in only 40% and 12% in patients with WHO scores of 2-4 and 5-6, respectively [16, 17]. MTX administration may be associated with the development of sore eyes, oral ulcers, pleuritis, severe bone marrow toxicity, and increased risk of bleeding as it inhibits folate metabolism [18]. Therefore, an alternative to a standard MTX regimen is four doses of IM MTX every other day (for a total of eight days) at a dose of 1 mg/m² along with folinic acid (leucovorin) administration to alleviate potential adverse effects [19]. Although multiple studies have been conducted to investigate the outcomes of therapeutic approaches for patients with low-risk GTN, there is a paucity of data relevant to the treatment efficacy of non-metastatic GTN. Moreover, the results of studies comparing different MTX regimens are statistically underpowered and appear to provide conflicting outcomes [20-22]. In the present randomized trial, we aimed to compare the efficacy of single IM dosing versus eight-day MTX regimen. Furthermore, we assessed other treatment-related outcomes, such as toxicity profiles, patient satisfaction, and duration of treatment to comprehensively compare and contrast both approaches.

Materials and Methods

The study protocol was approved by the institutional review board of King Abdulaziz University (KAU). This study was designed as a randomized controlled trial, including a prospective evaluation of patients diagnosed with low-risk GTD at KAU during the period from January 2014 to December 2017. Eligible patients received adequate information about the study objectives, procedure, and risks, and they were asked to sign an informed consent. Subsequently, they were randomized by using sealed envelopes into two groups (weekly and eight-day MTX regimens).

All patients diagnosed with low-risk GTN, including invasive mole, choriocarcinoma, PSTT, and ETT, were included in this study. Patients having GTN following a HM, abortion, or full-term gestation were eligible. Only patients with scores ranging between 0 and 6 (low-risk GTN) were enrolled in the study [9]. Non-metastatic GTN was defined as tumors confined to the uterus (FIGO Stage I). Patients were excluded if they had a history of hypersensitivity to MTX, patients for whom MTX is contraindicated, or prior MTX therapy failure for a GTN. Further, patients at high risk of developing MTX-related adverse effects were not included, such as those with chronic liver disease, active pulmonary disease, peptic ulcer, or pre-existing blood dyscrasias such as bone marrow hypoplasia, leucopenia, thrombocytopenia, or significant anemia. In addition, patients who received a previous chemotherapy for other types of cancer and patients with overt or laboratory evidence of immunodeficiency were excluded from this study.

Patient demographic and clinical characteristics, including age, nationality, parity, body weight, height, and body mass index, were obtained at baseline for further analysis. Diagnosis of GTN following a molar pregnancy was performed by using three main criteria: 1) elevated β-hCG for four consecutive tests over a period of three weeks or more; 2) a rise of hCG over two weeks or more by ≥ 10% for at least three values; 3) persistent hCG after six months of molar evacuation. Development of GTN after a non-molar pregnancy indicated the presence of choriocarcinoma. After GTN diagnosis, the FIGO anatomic staging system and WHO prognostic scoring system were utilized for the staging work-up. The modified WHO scoring system was based on several parameters, including patients’ age, antecedent pregnancy, interval from the antecedent pregnancy, number and location of metastases, largest tumor, pretreatment hCG levels, and previously failed chemotherapy [23].

After establishing a confirmed diagnosis, a complete patient’s history was obtained along with a full physical examination. Subsequently, laboratory investigations were performed, including complete blood count (CBC), urea and electrolytes (U&E), liver function tests (LFT), blood typing, and quantitative β-hCG. Follow-up testing included CBC, U&E, LFT, and quantitative β-hCG. Patients with a low-risk GTN received the first-line therapy, where they were randomly assigned to two groups: the weekly regimen group receiving a weekly IM dose of MTX (50 mg/m²) and the eight-day regimen group, where the patients received an eight-day regimen of MTX (1 mg/kg IM every other day for four doses) and leucovorin calcium (0.1 mg/kg, given once, 24 hours after each dose).

In case of hematologic or hepatic toxicity incidents, the common terminology criteria for adverse events of the National Cancer Institute [24] were applied. All side effects were noted in the inpatient records. A second course of chemotherapy was given if β-hCG levels were persistent for at least three consecutive weeks or if the patient developed grade 3 or 4 toxicity. If response to MTX monotherapy was judged unsatisfactory, a second-line therapy was employed, where either dactinomycin was given intravenously (1.25 mg/m² every two weeks) or a combination therapy (etoposide, MTX, dactinomycin, cyclophosphamide, and vincristine) was given.

The patient was considered to have a complete response (CR) when he/she had three normal β-hCG levels (< 2 IU/L) over two consecutive weeks. After the attainment of CR, all patients were monitored using weekly serum β-
**Table 1. — Participants’ demographic and baseline clinical characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Category</th>
<th>Total (N = 60)</th>
<th>Weekly dose (N = 34)</th>
<th>Eight-day (N = 26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean, SD</td>
<td>35.87, 9.21</td>
<td>36.26, 9.57</td>
<td>35.35, 8.88</td>
<td>0.705</td>
</tr>
<tr>
<td>Nationality</td>
<td>Saudi</td>
<td>43, 71.7</td>
<td>24, 70.6</td>
<td>19, 73.1</td>
<td>0.832</td>
</tr>
<tr>
<td></td>
<td>Non-Saudi</td>
<td>17, 28.3</td>
<td>10, 29.4</td>
<td>7, 26.9</td>
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</tr>
<tr>
<td>Parity</td>
<td>Null</td>
<td>15, 25</td>
<td>8, 23.5</td>
<td>7, 26.9</td>
<td>0.834</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>21, 35</td>
<td>13, 38.2</td>
<td>8, 30.8</td>
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<td>≥3</td>
<td>14, 23.3</td>
<td>13, 38.2</td>
<td>11, 42.3</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>Mean, SD</td>
<td>154.29, 5.77</td>
<td>154.06, 6.45</td>
<td>154.6, 4.84</td>
<td>0.722</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean, SD</td>
<td>26.91, 6.43</td>
<td>26.18, 4.78</td>
<td>27.86, 8.11</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean, SD</td>
<td>26.60, 4.78</td>
<td>154.06, 6.45</td>
<td>154.6, 4.84</td>
<td>0.722</td>
</tr>
<tr>
<td>Pre-treatment HCG level</td>
<td>Median, P90</td>
<td>9607, 101761</td>
<td>8912.5, 68240</td>
<td>16289, 120281.8</td>
<td>0.121</td>
</tr>
</tbody>
</table>

Values are frequency/percentage, except otherwise specified. Because of missing data, all frequencies do not sum up to the total. SD: Standard deviation; P90: 90th centile; t significance level calculated using independent t-test; \( ^{\dagger\dagger} \) significance level calculated using Mann-Whitney U test (nonparametric); otherwise, test used is chi-square.

**Results**

Sixty patients were included, 34 (56.7%) were placed in the weekly dose group and 26 (43.3%) received the eight-day protocol. There was no significant difference between the two groups in age (36.26 ± 9.57 vs. 35.35 ± 8.88 years; \( p = 0.705 \)), BMI (26.18 ± 4.78 vs. 27.86 ± 8.11; \( p = 0.320 \)), and pre-treatment HCG level (median [P90] = 8,125.0 [68,240.0] vs. 16,289.00 [120,281.8] mIU/ml; \( p = 0.121 \)) among weekly dose versus eight-day protocol group, respectively. Additionally, no difference was observed in parity (\( p = 0.834 \)) (Table 1).

The eight-day protocol was associated with less treatment cycles (median [P90] = 4.00 [8.00] vs. 6.50 [12.00]; \( p = 0.011 \)) and higher total MTX dose (median [P90] = 962.50 [1,688.00] vs. 370.00 [822,50] mg; \( p < 0.001 \); Table 2). Although not statistically significant, the eight-day protocol showed a relatively higher primary success rate (84.6% vs. 70.6%; \( p = 0.235 \)) and better therapeutic results (96.2% vs. 82.4% complete remissions; \( p = 0.126 \)) vs. weekly dose protocol, respectively (Table 2). Using the weekly protocol as reference, the number needed to treat in eight-day protocol is 7.1. Using the primary success rate as the primary outcome, and given the actual sample size, the calculated statistical power for this study was 0.15. A minimum sample size of \( n = 152 \) in each group (total = 304) is required to reach a statistical power of 0.80.

Only two cases of hepatotoxicity were reported in the weekly protocol group, while no case of toxicity was reported in eight-day protocol group (Table 2). Treatment duration (\( p = 0.875 \)), as well as time for hCG normalization (\( p = 0.791 \)) were comparable between the two groups. Neither age (\( p = 0.494 \)) or BMI (\( p = 0.952 \)) were associated with primary therapeutic success. It is worthwhile to note that primary failure was associated with relatively higher pre-treatment hCG levels (median = 17,168.00 vs. 9,607.00 mIU/ml); however, the difference was not statistically significant (\( p = 0.235 \)). On the other hand, primary therapeutic failure was significantly associated with longer overall treatment duration (median = 11.50 vs. 5.00 weeks), as compared to primary success (\( p = 0.002 \)) (Table 3).

**Discussion**

Treatment of low-risk GTN has been approached by different regimens, of which MTX remains the preferred treatment. It was as early as 1956 [25] when MTX was prescribed for GTN as the first-line therapy to replace traditionally-performed hysterectomy procedures. MTX treatment is generally associated with a complete cure in women with low-risk GTN, while 86% of the patients with high-risk disease can be effectively treated with this drug [26]. The drug acts by interfering with cell proliferation by inhibiting DNA synthesis through competitive binding with dihydrofolate reductase with a binding affinity that exceeds that of folic acid [27]. Therefore, MTX is effective for treating rapidly proliferating cells, including trophoblasts, although its action may be considered non-specific in nature. A low dose of IM MTX (30-50 mg/m²) is given in the weekly therapy and is repeated until \( \beta \)-hCG normalization is achieved for three consecutive weeks. As described by
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Category</th>
<th>Weekly dose (N = 34)</th>
<th>Eight-day (N = 26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Primary success</td>
<td>Yes</td>
<td>24</td>
<td>70.6</td>
<td>22</td>
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<tr>
<td>Treatment outcome</td>
<td>Success</td>
<td>32</td>
<td>94.1</td>
<td>26</td>
</tr>
<tr>
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<td>Failure</td>
<td>2</td>
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<td>0</td>
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<td>Agent change</td>
<td>Yes</td>
<td>10</td>
<td>29.4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>24</td>
<td>70.6</td>
<td>21</td>
</tr>
<tr>
<td>Time before HCG normalization (weeks)</td>
<td>Median, P90</td>
<td>5</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>≤ 6 weeks</td>
<td>13</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>&gt; 6 weeks</td>
<td>12</td>
<td>48</td>
<td>9</td>
</tr>
<tr>
<td>Treatment duration (weeks)</td>
<td>Median, P90</td>
<td>6</td>
<td>15.5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>≤ 6 weeks</td>
<td>19</td>
<td>55.9</td>
<td>14</td>
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<td>&gt; 6 weeks</td>
<td>15</td>
<td>44.1</td>
<td>12</td>
</tr>
<tr>
<td>No. treatment cycles</td>
<td>Median, P90</td>
<td>6.5</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Total MTX dose</td>
<td>Median, P90</td>
<td>370</td>
<td>822.5</td>
<td>962.5</td>
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<tr>
<td>Overall therapeutic result</td>
<td>Complete Remission</td>
<td>28</td>
<td>82.4</td>
<td>25</td>
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<tr>
<td></td>
<td>Hysterectomy</td>
<td>6</td>
<td>17.6</td>
<td>1</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Hepatotoxicity</td>
<td>2</td>
<td>5.9</td>
<td>0</td>
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<tr>
<td></td>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>Stomatitis</td>
<td>0</td>
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<td>Alopecia</td>
<td>0</td>
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<td>0</td>
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<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

MTX: Methotrexate; *primary success = no need to change treatment; P90: 90\% centile; * statistically significant result (p < 0.05); F significance level calculated using Fisher’s exact test; M significance level calculated using Mann-Whitney U test (nonparametric).

Homesley et al. [28] the dose can be escalated from the minimum concentration (30 mg/m²) by 5 mg/m² every three doses until reaching the maximum dose to induce a reliable remission. In 1971, an eight-day regimen (also termed the Modified Bagshawe regimen) was proposed. In this therapeutic approach, MTX was combined with folinic acid, to diminish the toxic adverse effects of the MTX single-therapy [29]. In the present study, we compared the efficacy of the weekly and eight-day regimens to induce a CR and their toxicity patterns in patients with a low-risk GTN.

The primary success rate among the patients in the eight-day regimen was relatively higher than that of the weekly regimen (96.2% and 82.4%, respectively) although the difference between these two regimens was not significant. Moreover, the number of required treatment cycles was significantly lower in the eight-day regimen group, which indicates an overall shorter duration, when compared to the weekly regimen group. To our knowledge, only two studies exclusively compared both regimens with no available controlled trials. Gleeson et al. [20] found that the primary remission was attained in 75% and 69% of the patients after the eight-day (n = 13) and weekly (n = 13) regimens, respectively, with a significant difference in remission between the study groups (p < 0.001). However, there was no difference in the treatment duration. Conversely, Kang et al. [30] found that the weekly regimen was associated with a slightly increased rate of primary remission compared to the eight-day regimen (70.8% and 69.5%, respectively) in a larger study population (n=107). Additionally, chemotherapy cycles were significantly more frequent with the use of weekly MTX when compared to the eight-day regimen (p < 0.001). Furthermore, the superiority of the weekly regimen was confirmed by the shorter treatment duration (p = 0.001). Indeed, the present study suggests that long treatment duration may be primarily associated with primary therapeutic failure.

An eight-day MTX treatment regimen is most commonly used in Europe and the United States for women with low-risk GTN, suggesting that it is the most widely used regimen in the world [1]. Bagshawe et al. [19] found that all patients with low-risk GTN (n = 88) achieved better primary remission rates following the eight-day regimen when compared to medium and high-risk groups. Furthermore, the combined therapy could be completed at home by a district nurse once the patients entered into remission, as judged by normal hCG values. Despite the lack of recent studies, we propose that folinic acid rescue does not impact subsequent fertility. This is important for middle-aged productive women, and, moreover, it produced no carcinogenic effect. It has also been shown that approximately 20% of patients who developed drug resistance required therapy modification [19]. In general, this is consistent with the present study, in which the primary agent has been changed in 19.2% of patients in the eight-day regimen group as com-
pared to 29.4% in the weekly MTX group.

In addition to treatment failure and subsequent agent change, MTX therapy might be associated with several side effects. MTX produces its effects through a non-specific action during cellular replication and thus can affect every organ system. More specifically, most notable adverse effects are observed in the skin, gastrointestinal, and hematological systems, where there is normally a high turnover of cells. Therefore, MTX is commonly associated with alopecia, general erythema, photosensitivity, nausea, vomiting, diarrhea, neutropenia or generalized marrow depression [31]. Such symptoms can be alleviated with addition of folinic acid as per the findings reported in this study. None of the patients in the eight-day regimen group showed signs of MTX toxicity, while two patients from the weekly regimen group exhibited hepatotoxicity. The mechanism by which MTX-induced hepatotoxicity occurs remains unclear. Hepatic histological studies showed that MTX induces steatosis, hypertrophy of stellate cells, and hepatic fibrosis [32]. Stellate cells subsequently differentiate into myofibroblasts which release collagen and fibronectin leading to hepatotoxicity. Therefore, it is suggested that MTX should be administered at the lowest possible dosage, either as a low single dose or, to some extent, combined with folinic acid rescue.

Bagshawe et al. [19] showed that MTX toxicity was minimal in patients with low-risk GTN who were treated with the MTX-folinic acid therapy and this was associated with little alopecia. Similarly, Berkowitz et al. [33] observed that the MTX-folinic acid regimen resulted in granulocytopenia in 5.9% of the patients and thrombocytopenia was reported in only 1.6% of patients. Smith et al. [34] reported that, with the use of the eight-day regimen, bone marrow depression (as evidenced by reduced platelet and leucocyte counts) was markedly reduced along with a significant reduction of mean serum glutamic-oxaloacetic transaminase (SGOT) levels when compared to a single IM MTX injection weekly. Nevertheless, the exact reason of limited toxicity in such patients may not be related to the co-administration of folinic acid. When Rotmensch et al. [35] measured MTX levels in five patients with the combined regimens, they found that plasma MTX levels were within non-toxic ranges, which is potentially attributable to the administration of MTX in an alternating pattern. In the present study, however, the total MTX dose provided to the patients was significantly higher in the combined regimen group when compared to the single weekly regimen group.

The present study provides the first randomized controlled trial comparing the most commonly employed MTX therapies for the treatment of low-risk GTN. However, insufficient sample size limits the statistical power.

In conclusion, in the present study we demonstrated an improved response rate with the eight-day MTX regimen in patients with GTN. Moreover, this was associated with a shorter treatment duration and lower number of treatment cycles when compared to weekly MTX therapy. Additionally, the eight-day protocol was associated with higher cumulative MTX doses with no increased risk of toxicity. It is, however, recommended that future randomized controlled trials recruit larger numbers of patients to provide results with higher statistical power. Given that the eight-day MTX regimen is the most widely used therapy, it is important to investigate its impact on subsequent fertility and the potential development of other neoplasms. Finally, risk factors that may lead to drug resistance should be assessed to attain a comprehensive insight into the therapy of such rare disorder.

Conflict of Interest

The authors declare no competing interests.

References


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