Comparison of pulsed actinomycin D versus 5-day methotrexate for the treatment of low-risk gestational trophoblastic disease

Azamsadat Mousavi a, Fatemeh Cheraghi a,⁎, Fariba Yarandi b, Mitra Moderess Gilani a, Hadi Shojaei b

a Department of Gynecological Oncology, Vali-e-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran
b Department of Gynecological Oncology, Mirza-Koochak-Khan Hospital, Tehran University of Medical Sciences, Tehran, Iran

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Objective: To determine the effectiveness of 2 standard chemotherapy regimens for low-risk gestational trophoblastic disease according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. Methods: From 2008 until 2010, 75 women with low-risk gestational trophoblastic disease received either pulsed actinomycin D (n=50) or 5-day methotrexate (n=25). The primary remission rate, the duration of treatment, the number of treatment courses, and the adverse effects were compared. Results: The complete remission rates were 90% for the actinomycin D group and 68% for the methotrexate group (P=0.018). The mean number of chemotherapy courses administered to achieve complete remission (including courses of second-line therapy) was 3.1 in the methotrexate group and 5.3 in the actinomycin D group (P=0.01). No major adverse effects were experienced in either treatment group and there were no significant differences in terms of adverse effects. Second-line chemotherapy was indicated for 11 patients. Conclusion: Based on the present study, pulsed actinomycin D seems to be an appropriate first-line treatment for patients with low-risk gestational trophoblastic disease.

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1. Introduction

Gestational trophoblastic disease (GTD) is a proliferative neoplasia of trophoblastic cells. It includes a spectrum of interrelated conditions ranging from hydatidiform mole to choriocarcinoma. Gestational trophoblastic disease is highly sensitive to chemotherapy and is recognized as the most curable gynecologic malignancy [1].

The choice of an appropriate therapeutic regimen has an important role in the treatment of this disease. Single-agent chemotherapy is accepted as first-line therapy for low-risk GTD. Since the early 1960s, methotrexate and actinomycin D have been used as the main drugs for the treatment of patients with low-risk GTD [2]. Many different protocols and regimens have been proposed by the reference centers. Methotrexate regimens include a 5-day regimen of intramuscular methotrexate, an 8-day schedule of methotrexate and folinic acid rescue given on alternate days, and pulsed therapy [3,4]. Actinomycin D can be used as a 5-day regimen or as a pulsed regimen [5,6]. Over the years, the 5-day regimens of methotrexate and actinomycin D have been replaced by pulsed regimens for reduced toxicity and ease of administration [1,7,8].

Single-drug regimens as a standard regimen for low-risk GTD are successful in approximately 60%–90% of patients [9], despite the fact that approximately 25% of patients require second-line chemotherapy because of resistance to the first-line drug or adverse effects [1,3,5,10]. Most patients can be cured with multiple-agent chemotherapy; however, this regimen has significant toxicity [11].

Currently, there is no universal agreement regarding the selection of the best regimen for patients with low-risk GTD. The present study was undertaken to compare the efficacy of 2 standard chemotherapy regimens for this condition, namely 5-day methotrexate and pulsed actinomycin D.

2. Materials and methods

The present study was conducted at Vali-e-Asr Hospital in Tehran, Iran, from January 1, 2008, until December 31, 2010. It included patients with a diagnosis of low-risk GTD according to the modified WHO prognostic scoring system for gestational trophoblastic neoplasia as adapted by the International Federation of Gynecology and Obstetrics (FIGO) [12]. Other inclusion criteria were FIGO stage I, II, or III disease, a WHO risk score of 6 or less, and a rise in the serum beta-human chorionic gonadotropin (β-hCG) level of more than 10% in the 3 weeks following termination of the last pregnancy or a β-hCG level plateau for at least 4 consecutive weeks. Exclusion criteria were prior chemotherapy and prior hysterectomy. Institutional Review Board approval for the present study was obtained from the Tehran University of Medical Sciences Committee on Human Research. Informed consent was obtained from all patients.

⁎ Corresponding author at: Department of Cynecological Oncology, Vali-e-Asr Hospital, Bager-Khan St, Keshavarz Boulevard, PO Box 1417613151, Tehran, Iran. Tel./fax: +98 21 66909309.
E-mail address: dr.cheraghi@ajums.ac.ir (F. Cheraghi).
Before the start of chemotherapy, all patients with persistent trophoblastic disease were submitted to a complete physical examination, determination of the blood cell count and serum β-hCG, renal function tests, liver function tests, thoracic X-ray, and pelvic and abdominal ultrasound. Computed tomography examination of the thorax, abdomen, and brain were performed in the case of pelvic or lung metastasis.

The patients were randomized to receive an intramuscular injection of 0.4 mg/kg methotrexate per day for 5 days or an intravenous bolus of 1.25 mg/m² actinomycin D. Both chemotherapy regimens were repeated every 2 weeks until normal β-hCG levels (less than 5 IU/L) were obtained. Complete remission was confirmed if the β-hCG levels were within the normal range for 3 consecutive weeks and the patient was asymptomatic. After the initial normalization of the serum β-hCG levels, 1 further course of chemotherapy was given. Patients used an effective contraceptive method before completing 1 year of follow-up.

Second-line chemotherapy was used in cases of nonresponse. The criteria for nonresponse to first-line chemotherapy were based on the weekly β-hCG titers (plateau or increasing levels for 2 consecutive weeks). Patients treated with a single agent who presented with resistance were crossed over to the other single-agent regimen. Adverse effects were classified according to the Gynecologic Oncology Group toxicity criteria [6].

The outcome measures were the primary remission rate, other efficacy measures such as need for second-line chemotherapy and overall duration of treatment, and the toxicity in the 2 groups.

The statistical analysis was performed using SPSS version 18.0 (SPSS, Chicago, IL, USA). Comparisons were carried out by the Mann–Whitney U test, the Fisher exact test, or the independent-sample t test. P<0.05 was considered statistically significant.

3. Results

Of 75 patients with low-risk GTD enrolled in the study, 50 were randomized to receive pulsed actinomycin D and 25 to receive 5-day methotrexate. The 2 treatment groups were similar in terms of age, number of days from diagnosis to treatment, pretreatment concentration of serum β-hCG, and size and number of lung metastases (Table 1). The preceding pregnancy was a molar pregnancy in 45 (90.0%) patients in the actinomycin D group and 22 (88.0%) patients in the methotrexate group. Two (4.0%) patients in the actinomycin D group and 1 (2.0%) patient in the methotrexate group had a term pregnancy. Pulmonary metastasis was present in 6 (12.0%) patients in the actinomycin D group and in 4 (16.0%) patients in the methotrexate group; the difference was not significant (P=0.08; χ² test). None of the patients in either arm underwent hysterectomy as part of their first-line treatment.

The overall remission rate after first-line chemotherapy was 82.7% (n=62). The remission rate was 90.0% (n=45) in the actinomycin D group and 68.0% (n=17) in the methotrexate group (P=0.018). All patients completed their first-line chemotherapy.

Overall, 11 (14.7%) first-line treatment failures were observed; all affected patients received a second-line therapy. Of the 8 (32.0%) patients resistant to methotrexate, 6 (75.0%) patients responded to treatment with actinomycin D and the 2 (25.0%) remaining patients underwent multiple-agent chemotherapy. In the actinomycin D group, resistance to the first-line therapy was observed in 5 (10.0%) patients, all of whom switched to methotrexate.

The mean number of chemotherapy courses administered to achieve a complete response (including courses of second-line therapy) was 3.1 in the methotrexate group and 5.3 in the actinomycin D group (P=0.01; Table 2).

In a subgroup analysis, no significant differences between responders and nonresponders were found in terms of age, number of days from diagnosis to treatment, largest uterus size, and presence of lung metastases. However, the pretreatment serum β-hCG concentration was lower among responders (P=0.006).

There were no major adverse effects in the 2 treatment groups. The most prevalent adverse effect was fatigue (Table 3). There were no significant differences between the 2 groups in terms of adverse effects.

4. Discussion

Several different regimens and protocols for the treatment of low-risk GTD have been reported; however, the best protocol for this condition remains to be determined because of the challenge of balancing effectiveness, toxicity, and patient convenience and preference.

Etoposide (VP16) is the most effective single-agent cytotoxic drug in the treatment of low-risk GTD [13,14]. Matsui et al. reported a remission rate of 90% with etoposide, in contrast to rates of 73.6% and 84% with methotrexate and actinomycin D, respectively [13]. However, the high frequency of adverse effects—myelosuppression, gastrointestinal disturbances, alopecia, and an increased risk of a second neoplasia—associated with etoposide resulted in replacement of this agent with drugs such as methotrexate and actinomycin D as first-line therapies in the treatment of low-risk GTD [14,15].

Various methotrexate and actinomycin D protocols for the treatment of low-risk GTD have been studied. In 3 randomized clinical trials [16–18], the primary complete remission rates for pulsed methotrexate (49–53%) were significantly lower than those for pulsed actinomycin D (69–90%). Two retrospective studies [19,20] compared 5-day intramuscular methotrexate with the 8-day methotrexate–folinic acid regimen. In the study by Smith et al. [19], the response rate was 92% in methotrexate alone group versus 72% in the methotrexate–folinic acid group. The remission rate was 76% in the study by Wong et al. [20] and there was no significant difference between 2 groups. In a randomized study [21]

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methotrexate (n=25)</th>
<th>Actinomycin D (n=50)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>25.2±7.2</td>
<td>26.8±4.6</td>
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<td>Preceding pregnancy</td>
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<td>Mole</td>
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<td>Abortion</td>
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<tr>
<td>Ectopic pregnancy</td>
<td>0 (0.0)</td>
<td>2 (4.0)</td>
<td></td>
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<tr>
<td>Term pregnancy</td>
<td>1 (4.0)</td>
<td>2 (4.0)</td>
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<tr>
<td>Pretreatment β-hCG level ≤10⁴ IU/L</td>
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<td>29 (58.0)</td>
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<td>&gt;10⁴ IU/L</td>
<td>9 (36.0)</td>
<td>21 (42.0)</td>
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<td>47 (94.0)</td>
<td>0.61</td>
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<tr>
<td>&gt;4 months</td>
<td>2 (8.0)</td>
<td>3 (6.0)</td>
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<tr>
<td>Uterine mass</td>
<td>10 (40.0)</td>
<td>18 (36.0)</td>
<td>0.23</td>
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<tr>
<td>Lung metastasis</td>
<td>4 (16.0)</td>
<td>6 (12.0)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Abbreviations: β-hCG, beta-human chorionic gonadotropin.

* Values are given as mean±SD or number (percentage).
that compared 5-day actinomycin D with 8-day methotrexate-folinic acid for the treatment of non-metastatic GTD, the complete response rate was 100% in the actinomycin D group and 74% in the methotrexate-folinic acid group.

Patients with low-risk GTD who were treated with 5-day regimens of actinomycin D or methotrexate or with a combination of actinomycin D and methotrexate were analyzed in a retrospective study by Abrão et al. [22]. There was no significant difference in the remission rates between these 3 groups (61.4%, 69%, and 79.1%; respectively). The rates of adverse effects were 62.5% with the combination therapy, 28.6% with 5-day methotrexate, and 19% with 5-day actinomycin D (P = 0.0003).

To our knowledge, no retrospective, prospective, or randomized study has previously compared the efficacy of 5-day methotrexate with that of pulsed actinomycin D. In the present study, the remission rate with 5-day intramuscular methotrexate was only 68%, which is lower than the rate reported in other studies [19,20,23]. However, the response rate for first-line chemotherapy with pulsed actinomycin D was 90%. The Gynecologic Oncology Group tested pulsed biweekly actinomycin D in a prospective phase III trial [17] and reported a complete remission rate of 73%, compared with a rate of 58% with pulsed weekly methotrexate. Biweekly intravenous actinomycin D was statistically superior to weekly intramuscular methotrexate. Kohorn et al. [24] reported a treatment failure rate of 20% for patients treated with pulsed actinomycin D, in contrast to a failure rate of 8% with 5-day actinomycin D.

The number of chemotherapy courses in the present study was higher with pulsed actinomycin D than with the 5-day methotrexate regimen (mean number of courses 6.3 versus 3.1). However, treatment once every 14 days has obvious advantages such as cost savings and convenience. According to other studies, the median number of treatment courses required to achieve a complete response is 2–8 with methotrexate [1] and 4 with actinomycin D [5,6,25].

In the present study, the most significant prognostic factor for response to first-line chemotherapy was the pretreatment serum β-hCG level. This result is similar to that reported by Yarandi et al. [18] and Kwon et al. [26].

Although the present findings indicate that the efficacy of pulsed actinomycin D for the treatment of low-risk GTD is higher than that of 5-day methotrexate, a comparison with other regimens with larger sample sizes is required to determine the optimal single-agent therapy. However, actinomycin D is the least toxic agent [17,22] and might offer the best treatment option for patients with low-risk GTD.

Conflict of interest

The authors have no conflicts of interest.

References


[14] Rustin GJ, Newlands ES, Lutz JM, Holden L, Bagshawe KD, Hiscox JG, et al. Combination of actinomycin D or methotrexate or with a combination of actinomycin D and methotrexate were analyzed in a retrospective study by Abrão et al. [22]. There was no significant difference in the remission rates between these 3 groups (61.4%, 69%, and 79.1%; respectively). The rates of adverse effects were 62.5% with the combination therapy, 28.6% with 5-day methotrexate, and 19% with 5-day actinomycin D (P = 0.0003).

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