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Effectiveness and toxicity of first-line methotrexate chemotherapy in low-risk postmolar gestational trophoblastic neoplasia: The New England Trophoblastic Disease Center experience

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HIGHLIGHTS

- The study provides the most complete toxicity review of methotrexate in low-risk GTN.
- 8-day MTX-FA caused more toxicity but most toxicities were mild.
- 8-day MTX-FA had a higher remission rate than MTX infusion.

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ABSTRACT

Objectives. To assess the outcomes and toxicity of first-line methotrexate (MTX) chemotherapy in low-risk postmolar gestational trophoblastic neoplasia (GTN) patients receiving 8-day methotrexate or one-day methotrexate infusion regimens.

Methods. This retrospective cohort study was conducted at the New England Trophoblastic Disease Center (NETDC), between 1974 and 2014, and included 325 patients with FIGO-defined low-risk postmolar GTN receiving first-line 8-day MTX/folinic acid (FA) or one-day MTX infusion and FA. Demographics, disease presentation, initial treatment plan, treatment outcome, and treatment-related adverse events were assessed.

Results. Sustained remission (84% vs 62%, $p < 0.001$) and need to switch to second-line therapy due to treatment-related adverse events (5.3% vs 0%, $p = 0.001$) were higher for 8-day MTX/FA compared to one-day MTX infusion. MTX resistance, however, was more frequent with one-day MTX (34.5%) than with 8-day MTX/FA (7.3%, $p < 0.001$). Relapse rates were similar with both regimens (3.0%). Compared to one-day MTX infusion, 8-day MTX/FA was associated with significantly higher gastrointestinal disorders (48% vs 24%), abnormal laboratory findings (48% vs 28%), eye disorders (37% vs 19%) and general disorders (22% vs 5%) ($p < 0.001$). Only infection frequency did not differ between 8-day MTX/FA and one-day MTX infusion (20% vs 12%, $p = 0.083$).

Conclusions. This is one of the largest studies to comprehensively catalogue toxicities associated with 8-day MTX/FA and one-day MTX infusion. Although treatment-related adverse events were more frequent with 8-day MTX/FA, these were all self-limited and resolved with no long-term sequelae. Given this and its higher effectiveness, 8-day MTX/FA remains the treatment of choice at NETDC for patients with low-risk postmolar GTN.

1. Introduction

Patients with gestational trophoblastic neoplasia (GTN) are classified into two prognostic groups on the basis of the extent of disease,

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level of human chorionic gonadotropin (hCG), duration of disease, nature of the antecedent pregnancy, and extent of prior treatment [1–4]. Based on the staging system of the International Federation of Gynecology and Obstetrics (FIGO 2002) [5], including the World Health Organization (WHO) scoring system, low-risk GTN is defined as having a FIGO/WHO prognostic risk score lower than seven. Patients with a score of 0–6 are more likely to respond to single-agent therapy. Patients with a score >6 have a higher risk of resistance to single-agent chemotherapy, and are best treated with combination chemotherapy [1–4].

Most patients with low-risk GTN are cured with single-agent chemotherapy, using either methotrexate (MTX) or actinomycin-D (ActD). Several single-agent regimens have been developed with comparable remission rates [6–10]. However, non-randomized, retrospective studies [11] assessing these regimens have suggested wide variability in outcome. This variability probably results from differences in dose, frequency, route of administration and patient selection [12]. Randomized prospective trials comparing ActD with weekly MTX or 5-day MTX have shown that pulse ActD achieved significantly better response rates than weekly MTX [7], but was comparable to 5-day MTX [13]. Nonetheless, the choice of both the drug and the regimen is usually institution specific [7], and there is no consensus on the best single agent regimen.

At the New England Trophoblastic Disease Center (NETDC), an 8-day regimen alternating intramuscular MTX and folinic acid (FA) has been the preferred single-agent regimen since the early 1970s [14–16] because it is well tolerated, efficacious, and cost effective [6,16–18]. MTX infusion has also been utilized at the NETDC to both shorten and simplify the treatment [19]. While MTX has been used as primary therapy in about 90% of patients with low-risk GTN in our institution [6,20], ActD is used as first-line therapy in patients with evidence of preexisting hepatic dysfunction and as second-line therapy if there is an adverse reaction to MTX or MTX resistance.

Although the most important objective of treatment is complete remission, other considerations such as toxicity are also relevant. Chemotherapy for GTN has been associated with adverse events such as bone marrow suppression, alopecia, stomatitis/mucositis, nausea and vomiting, neuropathy, and alterations in hepatic and renal function [7,13,21]. However, prior analyses of MTX toxicity have been primarily restricted to cases requiring change in regimen due to adverse events [9,22–24].

Preferences in MTX dosing regimens have varied at our center over time. To appropriately evaluate effectiveness, it is important to reassess treatment outcomes and toxicity periodically. Thus, the purpose of this study was to evaluate both the outcomes and toxicity of first-line methotrexate chemotherapy in low-risk postmolar gestational trophoblastic neoplasia patients receiving 8-day methotrexate versus one-day methotrexate infusion regimens.

2. Methods

This retrospective study consisted of 355 patients with FIGO-defined low-risk postmolar GTN (stage I and stages II–III, score < 7) [5] receiving first-line methotrexate chemotherapy who were registered in the Donald P. Goldstein, M.D., Trophoblastic Tumor Registry of the New England Trophoblastic Disease Center (NETDC) from 1974 to 2014. A final study population of 325 patients was identified after 30 patients were excluded due to using first-line therapy with weekly intramuscular MTX ($n = 23$) or MTX 0.4 mg/kg (max. 25 mg) intravenously for 5 days ($n = 7$).

All electronic and paper charts for the patients were reviewed. Gestational trophoblastic neoplasia was diagnosed using FIGO 2002 criteria: an hCG level plateau of more or <10% for at least 3 weeks, an elevation in serum hCG level >10% over 2 weeks, or histologic evidence of choriocarcinoma. Clinical, radiologic, and laboratory assessments were carried out as described elsewhere [20,25]. Lung metastases were diagnosed by chest X-ray rather than chest CT. Magnetic resonance imaging or computed tomography scan of the brain and abdomen were performed when pulmonary involvement, liver function abnormalities, or relevant symptoms were present.

First-line therapy consisted of 8-day MTX/folinic acid [16], or one-day MTX infusion and folinic acid [19] administered as either one single course or multiple courses followed by consolidation therapy [25]. The 8-day MTX/FA regimen consisted of MTX at 1 mg/kg intramuscularly on days 1, 3, 5, 7 alternating with folinic acid 0.1 mg/kg orally 24 h after each dose of methotrexate on days 2, 4, 6, 8. For the one-day MTX infusion regimen, methotrexate was administered at a dose of 100 mg/m^2 as an intravenous bolus over 30 min followed by a dose of 200 mg/m^2 in a 12-hour intravenous infusion. Twenty-four hours after beginning methotrexate infusion, folinic acid was administered at a dose of 0.1 mg/kg orally every 12 h for four doses. If the hCG did not decline by one log and then plateaued for at least 2 consecutive weeks or re-elevated, the patient was considered resistant to MTX and switched to ActD. If the hCG did decline by 1 log or more and then plateaued or re-elevated, the patient was then again treated with the same first-line MTX regimen. Serum hCG levels were closely monitored after each course of chemotherapy. In the earlier years of this experience (1974–2009), an initial single course of methotrexate chemotherapy was administered and no further chemotherapy was given as long as the hCG level was progressively falling. If the hCG level plateaued for at least 2 consecutive weeks, re-elevated or did not decline by >1 log within 18 days of the completion of the initial treatment, the patient was considered resistant to MTX and was switched to ActD. From 2010 onwards, multiple courses of methotrexate chemotherapy were administered at fixed intervals until hCG remission, followed by 1–3 courses of consolidation chemotherapy. If the hCG level plateaued for at least 2 consecutive weeks or re-elevated, the patient was considered resistant to the first-line MTX and switched to ActD.

Chemotherapy dosing for all patients (including overweight/obese patients) was calculated based on either actual body weight or body surface area throughout the study.

Clinical data collected included age, race, BMI (weight/height^2 in kg/m^2), history of prior mole, molar histology (complete or partial), time to persistence, pretreatment serum hCG level, use of D&C at persistence, presence of metastatic disease, FIGO stage/risk score, first-line chemotherapy regimen (8-day MTX/FA or one-day MTX infusion) and initial treatment plan (one single course or multiple courses with consolidation), treatment outcome, and treatment-related self-reported and witnessed adverse events.

Race was self-reported as defined by the National Institutes of Health [26]. BMI was classified into 2 BMI categories [27]: overweight/obese (BMI ≥ 25 kg/m^2) and non-overweight/obese (BMI < 25 kg/m^2). Time to persistence (days) was defined as the time between molar evacuation and postmolar GTN diagnosis. Dilatation and curettage (D&C) at persistence was defined as occurring within 7 days after GTN diagnosis. Treatment outcome was categorized as success or failure based on the following definitions:

- Treatment success: sustained complete remission;
- Treatment failure: need to switch regimens due to resistance, relapse, substantial toxicity;
- Sustained complete remission: normalization of serum hCG levels for 3 consecutive weeks and then monthly for 1 year;
- Resistance: hCG plateau of ±10% over the course of 2 weeks or a re-elevation in at least one measurement of hCG level;
- Relapse: hCG re-elevation after three normal weekly tests, in the absence of a new pregnancy;
- Substantial toxicity: treatment-related grade 3–4 adverse event requiring need to switch to second-line chemotherapy.

Adverse events were defined and classified according to standardized criteria (Common Terminology Criteria for Adverse Events-CTCAE v4.0). Complete blood cell count, platelet count, and renal (serum

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