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Single-Agent Therapy for Low Risk Gestational Trophoblastic Neoplasia (LRGTN): A Preliminary Report on a Randomized Clinical Trial to Compare Pulse-Methotrexate versus Pulse-Dactinomycin

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ABSTRACT

The efficacy of single-agent chemotherapy for patients with low risk gestational trophoblastic neoplasia (LRGTN) with methotrexate or dactinomycin is well established, but efforts continue to reduce the toxicity, the patients' time and cost of treatment. In a randomized clinical trial, we evaluated and compared the efficacy, toxicity and cost effectiveness of pulse-methotrexate versus pulse-dactinomycin as single-agent therapy in LRGTN. Forty low risk GTN patients were randomly assigned to receive pulse-methotrexate (30 mg/m^2 weekly intramuscularly) (20 cases) or pulse-dactinomycin (1.25 mg/m^2 every two weeks intramuscularly) (20 cases). Treatment continued if no major toxicity was encountered and beta human chorionic gonadotropin (β-hCG) values were lower than 5mIU/m^2 in three consecutive weeks. Seventy percent of methotrexate group and 90% of dactinomycin group responded to treatment (100% remission was achieved with no recurrence in one-year follow-up). The mean time to response was 43 days for methotrexate and 66 days for dactinomycin group (*P-value* = 0.001). Patients achieved remission after receiving an average of 8 courses of therapy in methotrexate versus 6 courses in dactinomycin group (*P-value* = 0.002). The average cost of treatment per course was about 7 US$ for methotrexate and 62 US$ for dactinomycin group (*P-value* < 0.001). There were no cases of major toxicity in methotrexate or dactinomycin groups. Overall, both methotrexate and dactinomycin were associated with good remission rate. Based on our results, LRGTN treatment with dactinomycin is somewhat more effective than that with methotrexate, but methotrexate is more cost-effective for both patients and the health system. As the effectiveness of both pulse-methotrexate and pulse-dactinomycin does not differ significantly, pulse-dactinomycin is recommended as first-line treatment.

Keywords: G*estational trophoblastic neoplasia, Single-agent chemotherapy, Methotrexate, Dactinomycin*

Single-agent chemotherapy is the first-line choice in the treatment of women with low risk gestational trophoblastic neoplasia (LRGTN), thereby avoiding the greater morbidity associated with multiagent therapies [1]. Single-agent methotrexate with or without citrovorum factor rescue has a very high remission rate, with toxicity comparable to that of single-dose dactinomycin [2, 3]. Gynecologic Oncology Group (GOG) studied the efficacy, toxicity and cost effectiveness of weekly intramuscular (IM) methotrexate and reported 74% complete response rate with a median of 7 weeks duration of therapy among patients with non-metastatic GTN (NM-GTN). No major toxicity occurred and they concluded weekly IM methotrexate for NM-GTN is efficacious, minimally toxic and cost effective [4]. Through a prospective trial of single-dose dactinomycin given IV at 1.25 mg/m^2 every 2 weeks for NM-GTN, the response rate was 94% with a median of 4 and mean of 4.4 courses of therapy. No life threatening toxicity occurred [5]. Based on several studies, the GOG clinical trials indicate that both weekly IM methotrexate and single-dose pulsed dactinomycin offer safe, effective, inexpensive and convenient therapy for patients with LRGTN [6].

Almost all patients with LRGTN can be cured with chemotherapy. The most important aspect of their cure

is to correctly determine their risk for single-agent failure and then administer the appropriate treatment. Also, the patients' convenience and financial burdens should not be ignored. In this randomized clinical trial, we compared the efficacy, toxicity and cost effectiveness of pulse-methotrexate and pulse-dactinomycin as single-agent therapy in patients with LRGTN.

METHODS

This study was carried out on patients who were referred to Gynecologic Oncology Clinic in Mirza Koochak Khan Hospital, Tehran University, during the period of September 2000 to September 2002. Patients with untreated LRGTN were eligible for study if they had a low risk score (score ≤ 6) according to modified WHO prognostic scoring system as adapted by FIGO [7] (Table 1), had a plateau or rising serum β-hCG level after termination of last pregnancy and had evidence of low risk metastatic disease during or following a molar pregnancy. Patients with previous chemotherapy, hematologic disorders such as idiopathic thrombocytopenic purpura (ITP), chemotherapy just after hysterectomy or dilatation and curettage (D&C) and hepatic or renal diseases were excluded from the study.

Table 1. Modified WHO prognostic scoring system for gestational trophobalstic neoplasia as adapted by FIGO [7].

Prognostic factor	Score			
	0	1	2	4
Age	<40	≥40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	<4	4-<7	7-<13	≥13
Pre-treatment serum β-hCG (IU/mL)	$<10^3$	10^3-$<10^4$	10^4-$<10^5$	$\geq 10^5$
Largest tumor size (cm)	-	3-<5	≥5	-
Site of metastasis	Lung	Spleen, Kidney	Gastro-intestinal	Liver, Brain
Number of metastases	-	1-4	5-8	>8
Previous failed chemotherapy	-	-	Single drug	2 or more drugs

Forty patients (of total of 61 patients diagnosed as having GTN) met these criteria and entered the study. Informed written consent was obtained and approved by the Medical Ethical Committee in Tehran University of Medical Sciences. A physical examination including chest X-Ray, uterine ultrasound, serum β-hCG level, hematologic, hepatic and renal function tests, paternal and maternal ABO blood typing were performed before therapy.

Patients were randomly assigned to receive methotrexate (20 subjects) or dactinomycin (20 subjects). Methotrexate was administered intramuscularly (IM) at a dose of 30 mg/m^2/week.

Dactinomycin was administered intravenously (IV) at a dose of 1.25 mg/m^2 every two weeks. Antiemetics were administered during hydration in dactinomycin group. Hematologic, hepatic and renal function tests along with β-hCG titers were repeated weekly. To initiate the treatment, these laboratory values were required: white blood cell (WBC) > 3000/ μL, polymorphonuclear cells (PMN) > 1500/ μL, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) < 2.5 times of normal concentration, bilirubin and creatinine at normal level. Chemotherapy was repeated until documented remission or non-responding therapy occurred. Remission was defined as three consecutive weekly β-hCG titers lower than 5mIU/ml. Patients received two courses of chemotherapy after the first normal β-hCG level was obtained. Non-responding therapy was defined as the appearance of new metastases, β-hCG plateau (decrease of less than 10%) in 3 consecutive weeks or an increase of 20% of its titer over two weeks. In non-responsive patients, if any, chemotherapeutic agent were changed to alternative second agent. Multi-agent chemotherapy was administered after failure of second chemotherapeutic agent. All patients used oral contraceptive (low dose) pills (OCP) to prevent pregnancy during the course of treatment.

Statistical analysis compared two treatment groups by T-test for continuous and Chi-square test for categorical variables or Fisher's exact test if it was appropriate (level of significance < 0.05).

RESULTS

In this randomized clinical trial on women with LRGTN, 20 patients as methotrexate treatment group were compared with 19 patients as dactinomycin treatment group (one patient decided to discontinue her treatment). Two treatment groups were comparable in terms of age, blood group, size of tumor, β-hCG level before treatment and duration between ends of pregnancy to beginning of treatment (Table 2). The antecedent pregnancy was molar pregnancy in all of the patients. Four cases of lung metastasis were observed during study period (3 in methotrexate and 1 in dactinomycin group).

Table 2. Patients characteristics in two treatment groups.

Characteristics	Methotrexate n=20	Dactinomycin n=19	Significance
Age (yr) ≤ 39	20 (100%)	16 (84.2%)	NS*
Maternal blood group			
A and O	15 (75%)	10 (52.6%)	NS*
B and AB	5 (25%)	9 (47.4%)	
Rh positive	20 (100%)	16 (84.2%)	
Size of tumor < 3 cm	20 (100%)	18 (94.7%)	NS*
Duration between end of pregnancy and beginning of treatment (months)			
< 4	15 (75%)	13 (68.4%)	NS*
4-6	4 (20%)	4 (21.2%)	
7-12	1 (5%)	2 (10.5%)	
β-hCG level (mIU/ml) before treatment:			
< 1000	13 (65%)	10 (52.6%)	NS*
1000-10000	5 (24%)	4 (21.1%)	
10000-100000	2 (10%)	5 (26.3%)	

*not-significant

Table 3. Efficacy of single-agent chemotherapy in low-risk metastatic gestational trophoblastic tumors (LRGTN).

Treatment group	LRGTN cases with remission		LRGTN cases without remission	
	Number of cases	*Percent*	*Number of cases*	*Percent*
Methotrexate	14	70	6	30
Dactinomycin	17	89.5	2	10.5
Total	31	79.5	8	20.5

Fourteen patients (70%) in methotrexate group and 17 (89.5%) in dactinomycin group responded to treatment (no statistically significant difference), as shown in Table 3. Six patients in methotrexate group, who did not respond to methotrexate, were switched to alternative therapy with dactinomycin; among them one patient did not respond to the second regimen and went on multiple-agent therapy. Two patients in dactinomycin group did not respond to dactinomycin and they were switched to methotrexate. One of these two patients did not respond to methotrexate either and was given multiple-agent chemotherapy. A 100% remission was achieved in all patients with no recurrence in one-year follow-up. The mean time to respond was 43 days (SD: 13.9) for methotrexate and 65.7 (SD: 22.6) for dactinomycin group (*P-value* = 0.001), as indicated in Table 4. Remission required a mean of 7.6 (SD: 1.3) courses of therapy in methotrexate and 5.7 (SD: 1.5) courses of therapy in dactinomycin group (*P-value* = 0.002). The cost of treatment was 52,710 Rials (7 US$) per course for methotrexate and 499,750 Rials (62 US$) for dactinomycin group (*P-value* < 0.001). There were no cases of major toxicity in any of these groups.

Table 4. Number of courses and duration needed to achieve remission in patients with low-risk gestational trophoblastic tumors.

Treatment group	Mean duration of therapy in responding patients (days)	Mean Number of courses in responding patients
Methotrexate	42.95 (SD = 13.89)	7.36 (SD = 1.28)
Dactinomycin	65.74 (SD = 22.56)	5.65 (SD = 1.50)
P-value	0.001	0.002

DISCUSSION

Primary single-agent chemotherapy is a reasonable treatment option in patients with low-risk GTN, as it has been associated with high rate of remission with low morbidity in most cases. Both methotrexate and dactinomycin have achieved an excellent remission rate with low levels of toxicity. The question is which one is better for first-line choice in the treatment of LRGTN.

Methotrexate was the first chemotherapeutic agent used for patients with LRGTN [8]. Later, dactinomycin was introduced for treatment of methotrexate-resistant LRGTN [9]. Alternating methotrexate and dactinomycin was tested for patients with LRGTN in various studies [10-12]. Based on these studies, 100% of patients achieved complete remission, but increased rate of toxicity was reported as well. In recent years, single-agent therapy for management of patients with LRGTN seems reasonable with excellent outlook [3-4, 13-15]. Eighter methotrexate or actionmycin has been used for LRGTN single-agent therapy, providing excellent and comparable remission rates with acceptable levels of toxicity [1, 6].

The first objective of this trial was to estimate and compare the efficacy of pulse methotrexate and pulse dactinomycin. During the two-year study of all GTN cases referred to our clinic (61 cases), 40 patients were scored as LRGTN. As our clinic is one of the main referral centers for patients with GTN in Iran, we visit a great number of these rare cases every year. Among 19 cases of LRGTN treated with dactinomycin, 17 (90%) achieved remission after receiving about 6 courses of therapy, without any major toxicity. In a GOG study using single-dose dactinomycin for LRGTN, the response rate was 94%. Remission required about 4.4 courses of therapy, and 81% of patients experienced toxicity. Most of adverse effects were mild to moderate, only 8% were severe and none were life-threatening [5].

The response rate for methotrexate was 70% in our study, after receiving a mean of 8 courses of therapy with a mean of 6 weeks to response. In two GOG weekly intramuscular methotrexate trails for LRGTN, time to achieve response was about 7 weeks, with a range of 3-19 weeks [4, 16]. In the initial study, there was an 81% complete response rate in 53 patients with 30-50 mg/m^2/weeks of IM methotrexate. In the second study with rapid escalation to 50 mg/m^2, the complete response rate was 74%. Weekly IM methotrexate for NMGTD at maximum dose of 60 mg/m^2 induced remission in 12 (60%) of 20 patients in 2-12 (median of 8) weeks. There were no cases of major toxicity [3]. In our trial, the response rate was somehow higher in dactinomycin group (90%) compared with methotrexate (70%). The mean courses of therapy to achieve remission were significantly lower in dactinomycin group with longer time to get response in comparison with methotrexate group. (6 courses in 66 days versus 8 courses in 43 days), considering dactinomycin was administered every two weeks versus weekly administration of methotrexate. Two treatment groups were similar according to toxicity of drugs without any important toxicity. We calculated cost for treatment based on drugs and administration expenses per course of therapy in average. All of our patients were house wives and they did not pay for child care. Methotrexate costs about 88% less than dactinomycin per course of therapy. In the case of lack of response, some workers suggest switching to dactinomycin while some believe patient should be given the same chemotherapy as a 5-day course [17-18]. We switched to alternative therapy with one failure in each treatment group, who went on multi-agent chemotherapy.

In conclusion, Pulse dactinomycin every 2 weeks provides safe and effective therapy for LRGTN, although it is expensive. On the other hand weekly IM methotrexate at a dose of 30 mg/m^2 is safe and cost effective as single-agent therapy for LRGTN. As the efficacy of dactinomycin in the treatment of LRGTN is somewhat higher than that of methotrexate, it might be appropriate to start the LRGTN treatment with dactinomycin. On the other hand, as both methotrexate and dactinomycin achieved excellent and comparable remission rate, the choice would be based on what physician and patients think is best in their situation. The other

factor is availability of the drug. We had an experience of no-access to either dactinomycin or methotrexate in a certain period of time. In that case, we start the treatment with the available drugs in our market. Although, based on the current study, it seems that both dactinomycin and methotrexate could be selected as the first-line treatment for patients with LRGTN, a larger clinical trial is required to determine the optimal treatment for LRGTN.

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