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Treatment of low-risk gestational trophoblastic neoplasia comparing biweekly eight-day Methotrexate with folinic acid versus bolus-dose Actinomycin-D, among Brazilian women

Tratamento da neoplasia trofoblástica gestacional de baixo-risco, comparando aplicação quinzenal de oito dias de Metotrexato com ácido folínico versus Actinomicina D em bolo, em mulheres brasileiras

Original Article

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Abstract

PURPOSE: To compare two single-agent chemotherapy (ChT) regimens evaluating, in first-line treatment, response and side effects and, in final single-agent treatment, the outcomes, among Brazilian patients with low-risk gestational trophoblastic neoplasia (GTN), according to International Federation of Gynecology and Obstetrics (FIGO) 2002. **METHODS:** Retrospective analysis of two concurrent cohorts with 194 low-risk GTN patients: from 1992 to 2012, as first-line treatment, 115 patients received 4 intramuscular doses of methotrexate alternated with 4 oral doses of folinic acid (MTX/FA) repetead every 14 days and, since 1996, 79 patients received an endovenous bolus-dose of actinomycin D (Act-D), biweekly. At GTN diagnosis, patient opinion was taken into consideration when defining the initial single-agent ChT regimen, and when there was resistance or toxicity to one regimen, the other drug was used preferentially. This study was approved by the Irmandade da Santa Casa de Misericórdia de Porto Alegre Ethical Committee. **RESULTS:** Both groups were clinically similar ($p>0.05$). In first-line treatments, frequency of complete response was similar (75.7% with MTX/FA and 67.1% with bolus Act-D); the number of ChT courses —median 3 (range: 1–10) with MTX/FA and 2 (range: 1–6) with bolus Act-D — and the time to remission —median 9 weeks (range: 2–16) with MTX/FA and 10 weeks (range: 2–16) with bolus Act-D) — were not different between the groups. In both groups, first-line side effects frequency were high but intensity was low; stomatitis was higher with MTX/FA ($p<0.01$) and nausea and vomit with Act-D ($p<0.01$). Final single-agent ChT responses were high in both groups (94.8% with MTX/FA and 83.5% with bolus Act-D; $p<0.01$) and 13% higher in the group initially treated with MTX/FA. Rates of hysterectomy and of GTN recurrence were low and similar. No patient died due to GTN. **CONCLUSION:** The two regimens had similar first-line ChT response. Final single-agent response rates were high and similar in both groups but the final single-agent remission rate was higher in the MTX/FA group.

Resumo

OBJETIVO: Em mulheres brasileiras com neoplasia trofoblástica gestacional (NTG) de baixo-risco, de acordo com a Federação Internacional de Ginecologia e Obstetrícia (FIGO) 2002, comparar dois regimes de quimioterapia (Qt) por agente único avaliando resposta e efeitos colaterais no tratamento de primeira linha, e a eficácia no tratamento final por agente único de Qt. **MÉTODOS:** Análise retrospectiva de duas coortes concorrentes com 194 pacientes com NTG de baixo risco: de 1992 a 2012; como primeira linha, 115 pacientes receberam 4 doses intramusculares de metotrexato alternado com 4 doses orais de ácido folínico (MTX/FA) repetidos a cada 14 dias e, desde 1996, 79 pacientes receberam quinzenalmente dose em bolo de actinomicina D (Act-D) por

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via endovenosa. No momento do diagnóstico da NTG, a opinião da paciente foi levada em consideração para definir o regime de Qt por agente único inicial e, quando havia resistência ou toxicidade a um regime, o outro fármaco era usado preferentemente. Este estudo foi aprovado pelo Comitê de Ética da Irmandade da Santa Casa de Misericórdia de Porto Alegre. **RESULTADOS:** Ambos os grupos eram clinicamente semelhantes (p>0,05). Nos tratamentos de primeira linha, a frequência de resposta completa foi semelhante (75,7% com MTX/FA e 67,1% com Act-D em bolo); não houve diferença entre os grupos quanto ao número de séries de Qt — mediana 3 (intervalo: 1–10) com MTX/FA e 2 (intervalo: 1–6) com Act-D em bolo — e ao tempo para remissão — mediana 9 semanas (intervalo: 2–16) com MTX/FA e 10 semanas (intervalo: 2–16) com Act-D em bolo. Em ambos os grupos, foi elevada a frequência de efeitos colaterais no tratamento de primeira linha, mas com intensidade baixa; estomatite foi mais frequente com MTX/FA (p<0.01) e náuseas e vômitos com Act-D (p<0.01). A resposta final à Qt por agente único foi alta nos dois grupos (94,8% com MTX/FA e 83,5% com Act-D em bolo; p<0,01) e 13% maior no grupo inicialmente tratado com MTX/FA. As frequências de histerectomia e de recorrência da NTG foram baixas e semelhantes. Nenhuma paciente morreu devido à NTG. **CONCLUSÃO:** Os dois regimes tiveram resultados semelhantes no tratamento de primeira linha. A resposta final ao tratamento por agente único foi alta e semelhante, mas a taxa final de remissão foi maior no grupo iniciado por MTX/FA.

Introduction

Gestational trophoblastic disease (GTD) describes a rare and highly curable group of tumors pathologies that arise from tissues of placental origin and results from abnormal conception caused by aberrant fertilization[1]. Most GTD cases include the two types of hydatidiform moles (HM) that have a variable potential to progress into the rare malignant disease, called gestational trophoblastic neoplasia (GTN)[2,3]. GTN has become a highly curable tumor, with an overall 90% of patient survival, due to the possibility of early diagnosis and treatment monitoring, ideally in Reference Centers (RC), and the individualized chemotherapy (ChT) based on prognostic factors, according scoring system of the International Federation of Gynecology and Obstetrics (FIGO) 2002[1-7].

The FIGO 2002 defined that low-risk GTN could be treated with single-agent ChT, resulting in final survival rates approaching 100%[3,7]. Several studies with Methotrexate (MTX) and Actinomycin D (Act-D) protocols have been used for treatment of low-risk GTN[8-12]; nevertheless, few studies compared these two drugs in the management of low-risk GTN[13-16]. Osborne et al.[16] has recently published a randomized study that suggests that the use of a bolus dose of Act-D every 15 days might be more effective than the administration of a weekly dose of MTX[16]. A randomized multi-center trial (GOG0275) is underway to compare pulsed Act-D with other MTX administration schemes[17]. To our knowledge, no study has evaluated the use of biweekly 8-day MTX alternated with folinic acid (MTX/FA) and bolus-dose Act-D. This retrospective study compared the results of these regimens, administered as first-line and as total single-agent ChT, to two concurrent cohorts of Brazilian patients with FIGO 2002 low-risk GTN.

Methods

From March 1985 to September 2012, from 1,678 cases with GTD and after excluding 70 patients (4.2%) due to pre-remission loss to follow-up (45 cases — 2.7%) and due to transfers to other RC (25 cases — 1.5%), 300 GTN patients (17.9 %) were retrospectively analysed in the Trophoblastic Disease Center of Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCMPA), in Southern Brazil.

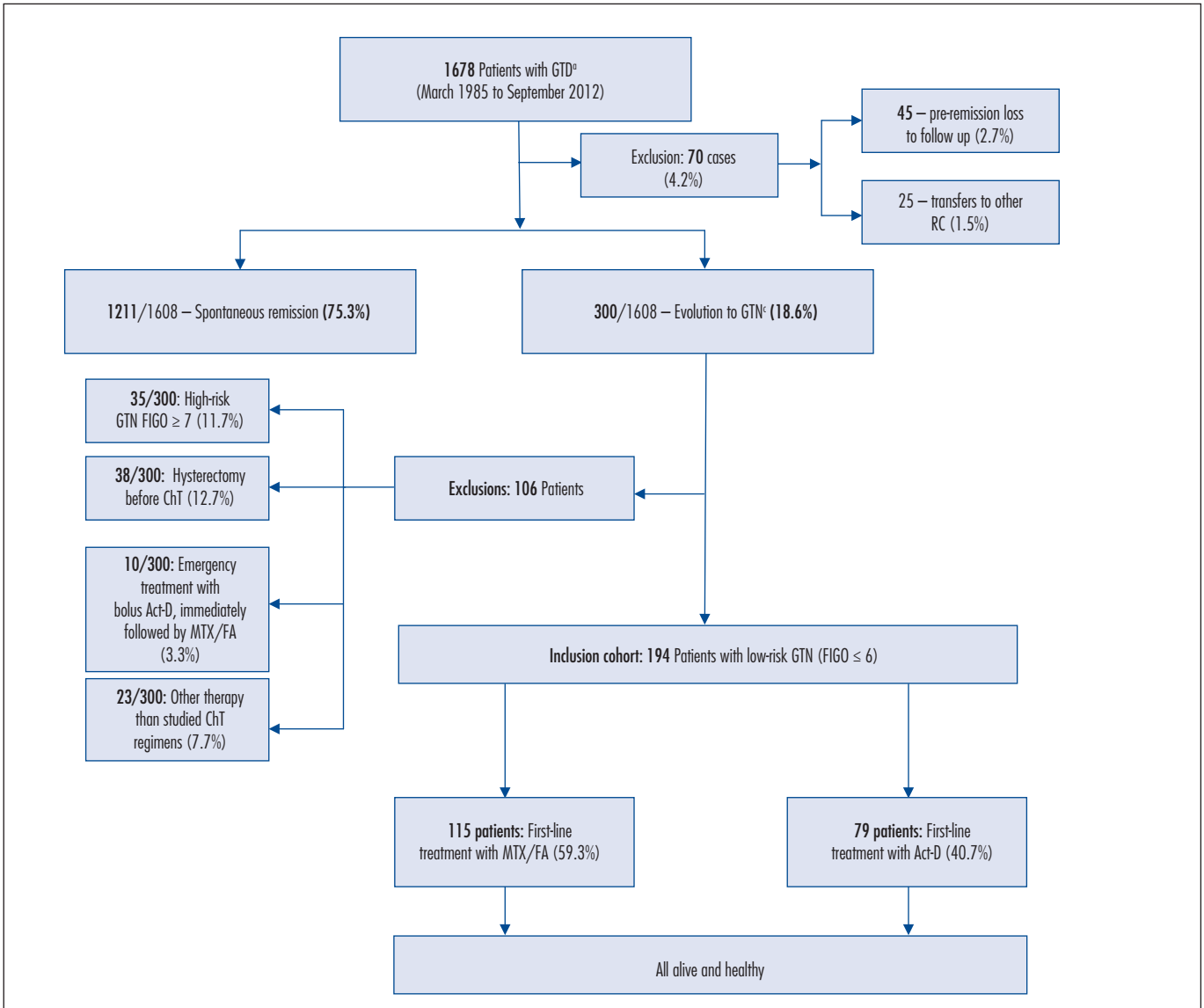
The GTN patients met FIGO 2002 criteria and had an hCG plateau of ±10% for at least 3 consecutive weeks, a rise of hCG >10% for 2 consecutive weeks, a high hCG for 6 months or longer[7,18], or other Charing Cross Hospital indications for ChT in GTD[1,3]. After the diagnosis of GTN was established, a staging evaluation was performed, using clinical, laboratorial and radiology resources, as recommended by FIGO 2002. Then, patients with GTN were categorized according to the FIGO 2002 criteria into a low (≤6) or high-risk (≥7) group. FIGO stage and score were retrospectively determined in patients treated prior to 2002. Complete response or remission was diagnosed after 3 consecutive weekly hCG levels were within normal range (<5 mIU/mL) and sustained remission, when the hCG level remained at that same level for 1 year[1,2,4,5,7,18].

Our management protocol is shown in Figure 1. We excluded 106 patients: 35/300 patients (11.7%), due to high-risk GTN; 38/300 patients (12.7%), due to hysterectomy before ChT; 10/300 patients (3.3%), due to emergency treatment with bolus Act-D, immediately followed by 8-day MTX/FA; 23/300 patients (7.7%), due to other therapy than the studied ChT regimens.

A final cohort population with 194 low-risk GTN patients was included in the study. All patients were primarily treated as outpatient with one of the two single-agent ChT regimens described here, and, at GTN diagnosis, patient opinion was taken into consideration when defining the initial single-agent ChT regimen: Group A (GA): from October 1992 to September 2012; for 115 patients (59.3%), the first-line single-agent ChT was the 8-day MTX/FA regimen, which consisted of 4 intramuscular doses of 1 mg/kg MTX every other day

plus 0.1 mg/kg to 15 mg of oral folinic acid in the intervening day, recycled every 14 days until hCG remission and then, after one normal hCG value (<5 mUI/mL), treatment was maintained for 6 weeks post-remission. Group B (GB): from September 1996 to September 2012; for 79 patients (40.7%), the first-line single-agent ChT was the pulsed Act-D regimen, which consisted of administration of intravenous Act-D (1.25 mg/m^2; maximum dose: 2.0 mg), recycled every 14 days until hCG remission and then, after one normal hCG value, ChT treatment was maintained for more 6 weeks post-remission. When there was resistance or toxicity to one regimen, the other drug was used preferentially.

GTN surveillance during treatment included bi-weekly measurements of serum hCG levels on the first day of each course of treatment. The regression hCG curve for each patient was compared with the standard curve established by Schlaerth et al.[19]. Regardless of hCG serum levels, when evidence of resistance or toxicity to first-single-agent ChT was identified, patients received the other single-agent ChT regimen. All patients required advice about pregnancy prevention and they generally received contraceptive pills every month. After the first normal hCG, the patients received two to three cycles of the last ChT regimen as treatment consolidation[18,20]. After ChT completion,



GTD: gestational trophoblastic disease; RC: Reference Centers; GTN: gestational trophoblastic neoplasia; FIGO: International Federation of Gynecology and Obstetrics; ChT: individualized chemotherapy; Act-D: Actinomycin D; MTX/FA: Methotrexate alternated with folinic acid.

Figure 1. Management and outcome of patients with low-risk gestational trophoblastic neoplasia treated with single-agent high-dose Methotrexate alternated with folinic acid or bolus dose of Actinomycin D, repeated each two weeks

the patients underwent clinical examination and hCG measurements as recommended by Bagshawe[20]. One year after ChT completion, the patients were released to become pregnant[1,2,5,7,18].

When a third-line GTN treatment was necessary, most patients received the EMA/CO multi-agent ChT regimen (etoposide + MTX/FA + Act-D + vincristine + cyclophosphamide)[1,2,5,7], but a few patients chose to undergo secondary hysterectomy associated with single-agent ChT[18,21].

Patient and disease characteristics, including age, parity and hCG serum level before treatment, FIGO 2002 anatomic staging and risk score, response rate with first-line single-agent ChT (time to achieve GTN remission, number of ChT courses, frequency and intensity of toxic treatment effects according to the National Institute of Health standard toxicity criteria), response rate to alternative single-agent ChT in second-line ChT, overall percentage of response to first- and second-line ChT treatment were analysed. Finally, data about secondary hysterectomy rates, discharge conditions, duration of follow-up and compliance to treatment were also collected, as well as GTN recurrence. Patient adherence to follow up was evaluated up to December 2013.

Categorical variables were analyzed and described using frequency rates, followed by the analysis of quantitative variables; results were described as means and standard deviations or medians and inter-quartile ranges. The Pearson χ^2 test was used to compare qualitative variables and to identify possible associations between them. The Student's t-test was used to compare means between two independent groups; in case continuous variables had an asymmetric distribution, the Mann-Whitney test was used. The level of significance was set at $p<0.05$ for all tests. All analyses were conducted using the Statistical Package for the Social Sciences 17.0 (IBM, Armonk, NY, USA). This study was approved by the Institutional Review Board of ISCMPA (Registration number: 3625/11), and an institutional confidentiality term was adopted.

Results

In both groups, most patients were classified as FIGO 2002 stage I (GA=92.2% and GB=91.1%), and risk scores were lower than 5 (GA=95.6% and GB=94.9%). There were no differences between groups in age, parity, weight, histopathology, FIGO 2002 stage/score and serum hCG levels at the beginning of treatment (Table 1). Because in the three cases of FIGO 2002 stage II patients the chosen initial treatment was with bolus-Act-D, the time to diagnosis was significantly shorter in GB than in GA.

Table 1. Sample characteristics

Variables	Total sample (n=194) n (%)	MTX/FA (n=115) n (%)	Bolus Act-D (n=79) n (%)	p-value
Age (years) (mean±SD)	29.0±8.0	28.1±7.4	30.3±8.6	0.05*
Age (range)	(13–54)	(13–45)	(13–54)	
Age (years)				
≤19	23 (11.9)	15 (13.0)	8 (10.1)	0.2**
20–34	127 (65.5)	79 (68.7)	48 (60.8)	
≥35	44 (22.7)	21 (18.3)	23 (29.1)	
Parity				
0	82 (42.3)	50 (43.5)	32 (40.5)	0.7**
1	63 (32.5)	38 (33.0)	25 (31.6)	
≥2	49 (25.3)	27 (23.5)	22 (27.8)	
Weight (kg) (mean±SD)	60.6±11.2	60.8±11.0	60.3±11.6	0.7*
HP				
CHM	163 (84.0)	95 (82.6)	68 (86.1)	0.5**
PHM	21 (10.8)	12 (10.4)	9 (11.4)	
Other HP result	6 (3.1)	5 (4.3)	1 (1.3)	
No HP result	4 (2.1)	3 (2.6)	1 (1.3)	
FIGO 2002 Risk Score				0.9**
0	15 (7.7)	9 (7.8)	6 (7.6)	
1	55 (28.4)	35 (30.4)	20 (25.3)	
2	53 (27.3)	31 (27.0)	22 (27.8)	
3	34 (17.5)	17 (14.8)	17 (21.5)	
4	28 (14.4)	18 (15.7)	10 (12.7)	
5	5 (2.6)	3 (2.6)	2 (2.5)	
6	4 (2.1)	2 (1.7)	2 (2.5)	
FIGO 2002 stage				0.08**
I	178 (91.8)	106 (92.2)	72 (91.1)	
II	3 (1.5)	0 (0.0)	3 (3.8)	
III	13 (6.7)	9 (7.8)	4 (5.1)	
hCG serum levels (UI/L) (median±iQR) 0.09*** (range)	4 465 (17 180) (27–1, 415,000)	3 435 (13 375) (48–147,000)	5 520 (19 534) (27–1, 415,000)	0.09***
Time to diagnosis (weeks) (median±iQR) <0.01*** (range)	7 (5) (0–38)	7 (4) (1–36)	5 (6) (0–38)	<0.01***

*Student's t-test; **Pearson χ^2 test; ***Mann-Whitney test.

MTX/FA: 8-day high-dose Methotrexate with folinic acid rescue; Act-D: Actinomycin D; SD: standard deviation; CHM: complete hydatidiform mole; PHM: partial hydatidiform mole; HP: Histopathology; FIGO: International Federation of Gynecology and Obstetrics; hCG: human chorionic gonadotropin; iQR: interquartile range.

Treatment results are shown in Table 2. There were no differences in the comparison of first-line single-agent ChT complete response rate (75.7x67.1%), number of courses (median, 3x2 cycles) and time to GTN remission (median, 9x10 weeks) between GA and GB, respectively. As secondary therapy, the complete response rate was 75% (21/28) in GA (alternatively treated now with Act-D) and 50% (13/26) in GB (now received MTX/FA). However, the overall complete response to sequential single-agent ChT was 94.8% in GA and 83.5% in GB (p=0.02). According to the Poisson regression, after adjustments to the hCG serum levels, time to diagnosis, age and FIGO 2002 stage, a higher response to first + second line remained significantly associated with GA (p=0.02). Patients who begin the GTN treatment with MTX/FA have 13% more probability of response in first + second line (RR=1.1; confidence interval of 95% – 95%CI 1.0–1.2). As a third-line treatment in the total sample, 15/194 patients (7.7%) received the EMA/CO multi-agent ChT regimen as salvage treatment after both single-agent ChT failure and the EMA/CO use rate was higher in GB (2.6% in GA and 15.2% in GB, p<0.01). In both groups, the frequency of surgical treatment with secondary hysterectomy and the GTN recurrence rate — respectively, 2.6% (3 patients) in GA and 1.3% (1 patient) in GB — were low and similar.

Table 2. Treatment results

Variables	Total sample (n=194) n (%)	MTX/FA (n=115) n (%)	Pulsed Act-D (n=79) n (%)	p-value
First-line ChT complete response rate				
Yes	140 (72.2)	87 (75.7)	53 (67.1)	0.1*
No	54 (27.8)	28 (24.3)	26 (32.9)	
Time from GTN diagnosis to GTN remission (complete response) using first-line ChT (weeks)				
Median±iQR	9.5±7	9±14	10±6	0.9**
Range	(2–26)	(2–26)	(2–26)	
First-line ChT courses				
Median±iQR	3 (2)	3 (2)	2 (2)	0.05**
Range	(1–10)	(1–10)	(1–6)	
Second-line ChT response rate	n=54	n=28	n=26	
Yes	34 (63.0)	21 (75.0)	13 (50.0)	0.1*
No	20 (37.0)	7 (25.0)	13 (50.0)	
Second-line ChT courses				
Median±iQR	2±3	2±1	3±2	<0.01**
Range	1–8	(1–5)	1–8	
First + second-line ChT response rate				
Yes	175 (90.2)	109 (94.8)	66 (83.5)	
No	19 (9.8)	6 (5.2)	13 (16.5)	
Consolidation of ChT courses				
mean±SD	2.0±0.8	1.9±0.8	2.1±0.7	0.07***
Final treatment results				
Only single-agent ChT	175 (90.2)	109 (94.8)	66 (83.5)	0.01*
Only ChT	190 (97.9)	112 (97.4)	78 (98.7)	0.6****
ChT + hysterectomy	4 (2.1)	3 (2.6)	1 (1.3)	
GTN recurrence rate*****	4 (2.1)	3 (2.6)	1 (1.3)	0.6****

*Pearson χ^2 test; **Mann-Whitney test; ***Student's t-test; ****Fisher exact test; *****4/5 (80%) patients also underwent hysterectomy.

MTX/FA: 8-day high-dose Methotrexate with folinic acid rescue; Act-D: Actinomycin D; ChT: chemotherapy; GTN: gestational trophoblastic neoplasia; iQR: interquartile range.

The frequency of response to first-line single-agent ChT according to the drug used and FIGO 2002 showed similar response rate between groups when FIGO 2002 score was below 5 (GA=77.3%, GB=69.3%). When second-line response according the hCG serum levels (Table 3) was evaluated, even when these levels were above 300 mIU/mL and although the case numbers were few (GA=7 patients; GB=23 patients), the frequency of response to the alternative single-agent ChT was good and similar (GA=28.6%; GB=43.5%), averting in these cases the use of multi-agent ChT.

Only 3 patients (2.6%) required a change from MTX/FA to pulsed Act-D due to grade 3 mouth ulcers, but no patients required hospital admission for treatment of toxicity. In both groups, total percentage of collateral effects was high, but their intensity was low (grade 1 or 2); they were easy to manage and more frequent in the pulsed Act-D group (p=0.04), especially nausea and vomits (p<0.01). However, in the MTX/FA group, there were higher percentages of mild stomatitis (mouth ulcers) (66.7%; p<0.01), pleuritis (14.8%; p<0.01) and sore eyes (33.3%; p=0.03) (Table 4).

In the total sample, the follow-up duration was high and similar between the groups — median (range): GA=5 years (1.4–16.6) and GB=4.5 years (1.1–11.3). Also, the frequency of medical discharge and of adherence to complete follow-up were elevated and not different among both groups (respectively, 86.9x96.2% and 93.1x96.3%). Almost all patients were alive and healthy (99.5%). The only death occurred in a patient in the Act-D group: it occurred 10 months after GTN remission and was due to adult immunodeficiency syndrome's gastrointestinal complications (bowel hemorrhage).

Table 3. Second-line single-agent chemotherapy success rate according to human chorionic gonadotropin serum levels

hCG (mUI/mL)	n	MTX/FA to bolus Act-D		Success rate (%)	p-value	Bolus Act-D to MTX/FA		Success rate (%)	p-value
		Number	Response			Number	Response		
<300	24	21	19	90.5		3	3	100.0	
≥300	30	7	2	28.6	<0.01*	23	10	43.5	0.22*
Total	54	28	21	75.0		26	13	50	
<100	15	14	12	85.7		1	1	100.0	
≥100	39	14	9	64.3	0.38*	25	12	48.0	1.00*
Total	54	28	21	75.0		26	13	50.0	

*Fisher exact text

MTX/FA: 8-day high-dose Methotrexate with folinic acid rescue; Act-D = Actinomycin D; hCG: human chorionic gonadotropin.

Table 4. Treatment toxicity during first-line chemotherapy on low-risk gestational trophoblastic neoplasia patients

Variables	Total sample (n=131) n (%)	MTX/FA (n=77) n (%)	Pulse Act-D (n=54) n (%)	p-value
Side effects				
Yes*	101 (77.1)	54 (70.1)	47 (87.0)	0.04**
No	30 (22.9)	23 (29.9)	7 (13.0)	
Side effects type				
Mouth ulcers	53 (52.5)	36*** (66.7)	17 (36.2)	<0.01**
Nausea and vomit	37 (36.6)	9 (16.7)	28 (59.6)	<0.01**
Diarrhea	10 (9.9)	3 (5.6)	7 (14.9)	0.1****
Pleuritic pain from serositis	8 (7.9)	8 (14.8)	0 (0.0)	<0.01****
Stomach ache	15 (14.9)	8 (14.8)	7 (14.9)	1.0**
Sore eyes	24 (23.8)	18 (33.3)	6 (12.8)	0.02**

*Most patients had toxicity grade 1 or 2; **Pearson χ^2 test;***three patients (3.8%) changed the ChT due to this toxicity (grade 3); ****Fisher exact test.

MTX/FA: 8-day high-dose Methotrexate with folinic acid rescue; Act-D: Actinomycin D.

Discussion

To our knowledge, no study had evaluated the two analysed single-agent ChT regimens in low-risk GTN patients as we did in this concurrent cohort retrospective analysis. In this study, the first-line results for biweekly 8-days MTX/FA and pulsed Act-D among patients with a similar low-risk GTN FIGO 2002 were resemble. The hCG levels normalized in both groups in the same time and the patients received similar number of treatment cycles (p=0.06).

For nearly all low-risk GTN patients, single-agent ChT with either MTX or Act-D is the preferred treatment[1,2,5,7,9,18]. A variety of regimens have been developed, in which non-randomized, mostly retrospective studies demonstrate a 50–90% chance of inducing remission[22]. Osborne et al.[16] have suggested that pulsed Act-D is more likely to induce remission than weekly MTX but this randomized study has been underpowered. We are waiting for the results of an larger international trial run by the Gynecology Oncology Group in the United States, begun in 2013 (NCT01535053), evaluating quality of life and acceptability of treatment with the objective of helping to define the optimum single-agent approach[17,23]. However, this trial did not include the chosen MTX regimen as we used in this study.

As the success rates of treating GTN with known agents are high, investigators have evaluated modified protocols for administering MTX to limit systemic toxicity, to reduce overall time to remission and costs, with no hospitalization[2-7]. According to Osborne and Gerulath[24], the MTX regimen, most commonly used in Europe and the rest of the world, excluding North America, is the Charing Cross modified Bagshawe 8-day regimen: a fixed dose of 50 mg MTX repeated every 14–16 days; on the results of 10 studies using MTX/FA in 1,238 patients, they reported a primary resistance in 20.3% (our results, 24.3%); a number of ChT series ranging from 1.4 to 8.0 (our results, median 3(2)); a toxicity that required a change of ChT regimen in 1% (our results, 2,6%) and total primary cure of 79.2% (our results, 75.7%).

Act-D is one of the two most used drugs in the treatment of low-risk GTN[1,2,5]. Usually, it is administered using a 5-day EV schedule in the cases of MTX resistance or toxicity[8,11,12]. In order to reduce the high rate and intensity of collateral effects with 5-day Act-D schedule, several authors have investigated the use of the so-called pulsed Act-D regimen[15,16]. When used as first-line ChT for low-risk GTN patients, pulsed Act-D had the following results in 4 studies: mean number of courses was 4.9 — our results, median 2; resistance was 8–24% — our results, 32.9%; and cure rate ranged from 76% (low-risk metastatic GTN) to 86% (non-metastatic GTN) —our results, 67.1%, with most patients in stage I of FIGO 2002[12,13,16].

Kohorn[25] and others[10,11] recommended abandoning the use of combination ChT, as an immediate second-line treatment for primary single-agent failure. We agree with

his recommendation and we have tried to use the alternative single-agent ChT regimen, irrespective of the hCG level, before the administration of multi-agent ChT. We had a high overall response rate of 94.8 and 83.5% in patients respectively initially treated with MTX/FA and pulsed Act-D (p=0.019); and patients that begin the GTN treatment with MTX/FA have 13% more probability of response in first + second line (RR=1.1; 95%CI 1.0–1.2).

Although a few patients were submitted to a second-line treatment (respectively, 28 with MTX/FA and 26 with pulsed Act-D), in Act-D group the response to alternative second-line treatment was not different when serum hCG levels were above or below 300 mIU/mL (p=0.2); nevertheless, with this management of second-line treatment, we could avoid the multiagent ChT in 2/7 patients (28.6%) in GA and in 10/23 patients (43.5%) in GB. In our RC, we will continue evaluating the second-line treatment responses to the studied single-agent ChT in low-risk GTN patients[12,25], which may protect some patients against the effects of the more toxic multi-agent ChT.

Adverse events were relatively modest on either regimen. There was an observed increase in grades 1 and 2 gastrointestinal adverse effects in patients receiving pulsed Act-D. In patients receiving MTX/FA, there were higher grade 2 stomatitis, pleural pain due to serositis, and sore eyes, especially after the first cycle of ChT. Alopecia was not observed with MTX/FA and was not significant with pulsed Act-D.

To reduce the rate of recurrence, we used a mean of 2–3 consolidation ChT with the last used ChT scheme (respectively, 1.9±0.8 cycles with MTX/FA and 2.1±0.7 cycles with pulsed Act-D; p=0.07), and our recurrence rates (MTX/FA=2.6%, pulsed Act-D=1.3%; p=0.64) were similar to the overall recurrence rate of 4–8% reported in the literature[1,2,4].

In our patients with low-risk GTN, clinical treatments with only ChT, without hysterectomy, promote excellent healing rates — in final treatment, 97.4% in the MTX/FA group and 98.7% in the pulsed Act-D (p=0.64). Our results strongly suggest that the single-agent ChT for low-risk GTN, as studied here, had good and similar first-line single-agent treatment effectiveness, and final first + second-line single-agent ChT response rate was high in both groups, but higher in the group of initial MTX/FA. We are waiting for the GOG0275 randomized trial results[17], hoping that the single-agent ChT remission rates be similar or better than ours results, clarifying this GTN treatment challenge: higher efficiency associated with lower morbidity.

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References

1. Seckl MJ, Sebire NJ, Fisher RA, Golfier R, Massuger L, Sessa C, et al. Gestational trophoblastic disease: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi39-50.
2. May T, Goldstein DP, Berkowitz RS. Current chemotherapeutic management of patients with gestational trophoblastic neoplasia. Chemother Res Pract. 2011;2011:806256.
3. Froeling FE, Seckl MJ. Gestational trophoblastic tumours: an update for 2014. Curr Oncol Rep. 2014;16(11):408.
4. Biscaro A, Braga A, Berkowitz RS. Diagnosis, classification and treatment of gestational trophoblastic neoplasia. Rev Bras Ginecol Obstet. 2015;37(1):42-51.
5. Lurain JR. Gestational trophoblastic disease II: classification and management of gestational trophoblastic neoplasia. Am J Obstet Gynecol. 2011;204(1):11-8.
6. FIGO Oncology Committee. FIGO staging for gestational trophoblastic neoplasia 2000. Int J Gynaecol Obstet. 2002;77(3):285-7.
7. Ngan HY, Kohorn EI, Cole LA, Kurman RJ, Kim SJ, Lurain JR, et al. FIGO report 2012: trophoblastic disease. Int J Gynaecol Obstet. 2012;119 Suppl 2:S130-6.
8. Chapman-Davis E, Hoekstra AV, Rademaker AW, Schink JC, Lurain JR. Treatment of nonmetastatic and metastatic low-risk gestational neoplasia: factors associated with resistance to single-agent methotrexate chemotherapy. Gynecol Oncol. 2012;125(3):572-5.
9. Growdon WB, Wolfberg AJ, Goldstein DP, Feltmate CM, Chinchilla ME, Lieberman ES, et al. Evaluating methotrexate treatment in patients with low-risk postmolar gestational trophoblastic neoplasia. Gynecol Oncol. 2009;112(2):353-7.
10. Covens A, Filiaci VL, Burger RA, Osborne R, Chen MD; Gynecologic Oncology Group. Phase II trial of pulse dactinomycin as salvage therapy for failed low-risk gestational trophoblastic neoplasia: a Gynecologic Oncology Group study. Cancer. 2006;107(6):1280-6.
11. Lurain JR, Chapman-Davis E, Hoekstra AV, Schink JC. Actinomycin D for methotrexate-failed low-risk gestational trophoblastic neoplasia. J Reprod Med. 2012;57(7-8):283-7.

12. Petrilli ES, Twiggs LB, Blessing JA, Teng NH, Curry S. Single-dose actinomycin D treatment for nonmetastatic gestational trophoblastic disease. A prospective phase II trial of the Gynecologic Oncology Group. Cancer. 1987;60(9):2173-6.

13. Lertkhachonsuk AA, Israngura N, Wilailak S, Tangtrakul S. Actinomycin d versus methotrexate-folinic acid as the treatment of stage I, low-risk gestational trophoblastic neoplasia: a randomized controlled trial. Int J Gynecol Cancer. 2009;19(5):985-8.

14. Abrão RA, de Andrade JM, Tiezzi DG, Marana HR, Candido dos Reis FJ, Clagnan WS. Treatment for low-risk gestational trophoblastic disease: comparison of single-agent methotrexate, dactinomycin and combination regimens. Gynecol Oncol. 2008;108(1):149-53.

15. Mousavi A, Cheraghi F, Yarandi F, Gilani MM, Shojaei H. Comparison of pulsed actinomycin-D versus 5-day methotrexate for the treatment of low-risk gestational trophoblastic neoplasia. Int J Gynecol Obstet. 2012;116(1):39-42.

16. Osborne RJ, Filiaci V, Schink JC, Mannel RS, Alvarez Secord A, Kelley JL, et al. Phase III trial of weekly methotrexate or pulsed dactinomycin for low risk gestational trophoblastic neoplasia: a gynecologic oncology group study. J Clin Oncol. 2011;29(7):825-31.

17. Schink J. Methotrexate or dactinomycin in treating patients with low-risk gestational trophoblastic neoplasia [Internet]. 2015 [cited 2015 Jan 15]. Available from: <http://www.cancer.gov/about-cancer/treatment/clinical-trials/search/view?cdrid=725211&version=HealthProfessional>

18. Uberti EMH, Diestel MCF, Guimarães FE, Lacerda ME, Rosa MW, Nápoli G, et al. Conduta no Tumor Trofoblástico Gestacional (TTG): experiência de 10 anos de um centro de referência. Acta Oncol Bras. 2000;20(2):53-62.

19. Schlaerth JB, Morrow CP, Kletzky AO, Nalick RH, D'Ablaing GA. Prognostic characteristics of serum human chorionic gonadotropin titer regression following molar pregnancy. Obstet Gynecol. 1981;58(4):478-82.

20. Bagshawe KD. Choriocarcinoma: a model for tumour markers. Acta Oncol. 1992;31(1):99-106.

21. Pires LV, Uberti EM, Fajardo MC, da Cunha AG, Rosa MW, Ayub AC, et al. Role of hysterectomy in the management of patients with gestational trophoblastic neoplasia: importance of receiving treatment in reference centers. J Reprod Med. 2012;57(7-8):359-68.

22. Alazzam M, Tidy J, Hancock BW, Osborne R, Lawrie TA. First-line chemotherapy in low-risk gestational trophoblastic neoplasia. Cochrane Database Syst Rev. 2012;7:CD007102.

23. Taylor F, Grew T, Everard J, Ellis L, Winter MC, Tidy J, et al. The outcome of patients with low risk gestational trophoblastic neoplasia treated with single-agent intramuscular methotrexate and oral folinic acid. Eur J Cancer. 2013;49(15):3184-90.

24. Osborne R, Gerulath A. What is the best regimen for low-risk gestational trophoblastic neoplasia? A review. J Reprod Med. 2004;49(8):602-16.

25. Kohorn EI. Is lack of response to single-agent chemotherapy in gestational trophoblastic disease associated with dose scheduling or chemotherapy resistance? Gynecol Oncol. 2002;85(1):36-9.