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Are different methotrexate regimens as first line therapy for low risk gestational trophoblastic neoplasia more cost effective than the dactinomycin regimen used in GOG 0174?

Caela R. Miller^{a,*}, Nicole P. Chappell^a, Caitlin Sledge^a, Charles A. Leath III^b, Neil T. Phippen^c, Laura J. Havrilesky^d, and Jason C. Barnett^a

^a San Antonio Military Medical Center, Ft Sam Houston, TX, United States

^b University of Alabama at Birmingham, Birmingham, AL, United States

^c Walter Reed National Military Medical Center, Bethesda, MD, United States

^d Duke University Medical Center, Durham, NC, United States

Abstract

Objectives—Gynecologic Oncology Group (GOG) 0174 compared weekly intramuscular methotrexate (MTX) with biweekly pulsed intravenous dactinomycin (Act-D) as single-agent chemotherapy for low-risk gestational trophoblastic neoplasia (GTN). Act-D had a higher rate of initial complete response (CR) (70% vs. 53%, $p = 0.01$), but multi-day regimens of MTX have higher historic success rates. We assessed the cost-effectiveness of Act-D vs. MTX per GOG 0174 and explored multi-day MTX regimens.

Methods—A cost effectiveness decision model was constructed with data from GOG 0174. Outcome was cost per first-line treatment success expressed in terms of incremental cost-effectiveness ratio (ICER). Front-line failures were assumed to receive cross-over single agent therapy, second line failures; multi-agent chemotherapy. GOG 0174 had no quality of life (QOL) evaluation, so equal QOL (utility 1.0) was assumed but varied in sensitivity analysis. A second exploratory model included 5-day and 8-day MTX regimens.

Results—Act-D (\$18,505) was more expensive compared to weekly MTX (\$8950) with an ICER of \$56,215 per first-line treatment success compared to weekly MTX. Small decreases in QOL dramatically increased the ICER during sensitivity analysis. Models with multi-day MTX regimens were also more cost-effective than Act-D. If effectiveness was redefined as avoidance of multi-agent chemotherapy, weekly MTX was more effective.

* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, San Antonio Military Medical Center, 3551 Roger Brooke Drive, JBSA Fort Sam Houston, TX 78324, United States. caela.r.miller.mil@mail.mil, caelamiller@hotmail.com (C.R. Miller).

Conflict of interest statement

Portions of this data and content were presented in a poster presentation at the Society for Gynecologic Oncology Annual Clinical Meeting, March 2015 in Chicago, Illinois. The authors have nothing to disclose. There is no off label use of any medical device in this manuscript. No proprietary interest is mentioned. The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, Department of Defense or the U.S. Government.

Conclusions—With a complete cure rate for low-risk GTN regardless of initial agent, our model supports provider hesitation toward first line Act-D for low risk GTN. While Act-D is more effective for first line treatment success, it is more costly, and does not decrease rate of multi-agent chemotherapy use.

Keywords

Low risk gestational trophoblastic neoplasia; Cost-effectiveness; GOG0174; Actinomycin D; Methotrexate

1. Introduction

Gynecologic Oncology Group (GOG) trial 0174 was a phase III randomized controlled trial that compared biweekly pulsed intravenous (IV) dactinomycin (Act-D) 1.25 mg/m² to weekly intramuscular (IM) methotrexate (MTX) 30 mg/m², in an attempt to define the most effective single-agent chemotherapy for low risk gestational trophoblastic neoplasia (GTN). Currently, low-risk GTN is defined as patients who have a World Health Organization (WHO) prognostic index score of <7 [1]. 240 women were enrolled in this multicenter trial and complete response after first line treatment favored Act-D (70% vs. 53% p = 0.01) [2]. An early criticism of this study was that there are alternative regimens of MTX with higher historic success rates than the 30 mg/m² weekly MTX dose used in the trial [3]. All of these historic regimens' success rates have been documented in single center phase II trials [4,5,6,7] and recent single center phase III trials [8,9] with questionable reporting of bias and severe adverse side effects [10]. Importantly, regardless of first agent used, low-risk GTN remains almost completely curable [3]. Patients whose tumor fails to respond to primary therapy with either MTX or Act-D receive single agent therapy with the other agent [11]; patients without a complete response on two single agent therapies are then treated with multi-agent therapy. Most centers give the EMA/CO regimen: (etoposide 100 mg/m² IV days 1 & 2), MTX (100 mg/m² IV push followed by 200 mg/m² IV over 12 h day 1), Act-D (0.5 mg IV days 1 & 2), leucovorin (15 mg PO every 12 h for 4 doses, days 2 & 3), cyclophosphamide (600 mg/m² IV day 8), and vincristine (1.0 mg/m² IV day 8) [12]. EMA/CO administration requires inpatient hospitalization, centralized intravenous access and possible travel to a tertiary care center. Exposure to these costs may be avoided when utilizing superior primary therapy.

Based on small, prior randomized controlled trials including commonly used 5- and 8-day MTX regimens, GOG 0275 is currently enrolling patients and has been designed to answer these questions by prospectively comparing the 8-day MTX regimen, the 5-day MTX regimen, and pulsed Act-D, using updated WHO reporting [1] and prospectively collected QOL information [13]. However, GOG 0275 has been slow to accrue patients, and many providers persist in using MTX based regimens. Act-D is more costly per dose, has more reported alopecia, mucositis, hematologic toxicity, and in some centers requires centralized access [10].

In light of the discrepancy between evidence and practice, the purpose of our study is to assess the cost-effectiveness of GOG 0174 Act-D and MTX regimens for the treatment of

low risk gestational trophoblastic neoplasia (GTN) with a revised WHO score of 0–6, and modeled 5-day and 8-day IM MTX regimens separately using data from smaller studies using these regimens [8,9].

2. Methods

A decision-analysis model was constructed using TreeAge Pro software (TreeAge Software Inc., Williamstown, MA) (Fig. 1A) to evaluate the results of a phase III randomized controlled trial conducted by the GOG comparing weekly methotrexate (MTX) versus pulsed dactinomycin (Act-D) for low-risk GTN (GOG trial 0174). A separate exploratory model was also constructed to include common 5-day and 8-day MTX regimens used for low-risk GTN but not evaluated in this collaborative group trial (Fig. 1B). Both of these regimens are arms in the on-going GOG 0275 (NCT01535053) and are being compared to the pulsed dactinomycin regimen [13].

Costs incurred for treatment were applied to each arm in the model with the overall cost calculation of chemotherapy based on the average number of chemotherapy cycles used in each arm from the trial. Rates of cross-over to alternative single agent treatment were applied based on published trial data. Finally, requirement of multi-agent chemotherapy was modeled based on failure rates of cross-over single agent therapy. Rates of cure, cross-over to alternative single-agent, and requirement of multi-agent chemotherapy are included in Table 1. Effectiveness was measured as cost per avoidance of first line treatment failure using an incremental cost effectiveness ratio (ICER). A secondary analysis defined effectiveness as cost per avoidance of multi-agent chemotherapy. ICER is a numerical value comparing two regimens and indicating how much it would cost to gain a unit in effectiveness. Quality of life was assumed to be perfect (utility score = 1) for each regimen since it was not evaluated in the trial. Sensitivity analyses were performed to account for uncertainties in assumptions and inputs. A sensitivity analysis tests the model's validity over a range of possible values of a clinical variable in an effort to identify values at which these changes would modify the outcome of the model. When estimates for certain outcome variables contain uncertainties, a sensitivity analysis helps validate the model's results and clarify the strength of any interpretation.

2.1. Costs

Costs for each arm were in 2014 US dollars and were obtained through publicly available databases (Table 2). When necessary, costs were adjusted for inflation to 2014 US dollars using the medical component of the Consumer Price Index [14]; publicly accessible inflation data tables. Publicly available Medicare reimbursement data [15] was used to determine drug costs incurred for each arm and were calculated for a 70 kg hypothetical woman, BSA 1.76, and included costs of administration, pre-medications, outpatient physician visit, peripherally inserted central catheter (PICC), and the cost of the chemotherapeutic agent estimated from 2014 CPT and J codes. Inpatient costs were obtained using International Classification of Diseases, Ninth Revision (ICD-9) codes to search the 2012 national database of the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project Nationwide Inpatient Sample [16], for mean costs of hospitalization.

2.2. Sensitivity analysis

One-way sensitivity analyses were performed by varying treatment costs, rates of cure, and QOL-related utility scores. Specifically, costs and rates were varied between 50 and 200% of the base case estimates. QOL was not included in the base case analysis since it was not evaluated prospectively. However, in sensitivity analysis, QOL was varied by decreasing the QOL utility score as a percentage of perfect QOL (1.0 being perfect QOL with fraction of 1.0 indicating decreased QOL, i.e. 0.75 being a fraction of perfect QOL).

3. Results

3.1. Base case

Act-D was the most expensive treatment with an average cost of \$18,505 vs. \$8,950 for weekly MTX (Table 2). The 17% improvement in cure with Act-D was associated with an ICER of \$56,215 per avoidance of 1st line treatment failure. During sensitivity analysis the ICER dramatically increased with small decreases in Act-D QOL utility score (Fig. 2). When effectiveness was defined as avoidance of multi-agent chemotherapy, weekly MTX dominated Act-D (both more effective and less expensive). There was a 5.6% requirement of multi-agent chemotherapy with weekly methotrexate versus 6.5% in the Act-D group.

3.2. Exploratory model

The 8-day MTX arm was the least expensive treatment compared to 5-day MTX, weekly MTX, and Act-D (\$6957 versus \$7701 versus \$8950 versus \$18,505) (Table 2). 8-day MTX was also the most effective treatment, thereby dominating the other regimens, being both less costly and more effective to avoid 1st line treatment failure. 5-day MTX was also more effective than either weekly MTX or Act-D.

4. Conclusions

Pulsed Act-D is more effective but more costly than weekly MTX with an ICER of \$56,215 per avoidance of first line treatment failure. However, small decreases in QOL with Act-D cause dramatic increases in the ICER. The currently enrolling clinical trial GOG 0275, unlike GOG 0174, prospectively collects quality of life data; however it is unclear when the results of this trial will become available. The limited toxicity data collected on Act-D, associating its use with alopecia, nausea and vomiting, suggests it is a reasonable assumption that QOL scores will drop compared to MTX regimens.

A major criticism of GOG 0174 was the protocol's utilization of a *weekly* MTX regimen as a treatment arm since alternative regimens for low risk GTN are much more frequently used. For this reason, included in our exploratory analysis were two other well-known MTX treatment regimens. A 5-day IM MTX regimen, first described by Soper et al. in 1994 [4,5] involves giving the patient 0.4 mg/kg (maximum 25 mg IV) IV or IM daily $\times$ 5 days. This is recycled every fourteen days until the β -hCG is normal for three weeks. It is easily administered to patients in an outpatient setting and requires no permanent or temporary central venous access. The efficacy of this regimen compared to biweekly pulsed Act-D 1.25 mg/m² was assessed by a single center randomized trial of 75 patients by Mousavi et al. [8]

In this trial the success rate of biweekly pulsed Act-D was 90%, while the success rate of the 5 day MTX regimen was 68%. All of the patients in the Act-D group who failed first line therapy (10%) responded to second line methotrexate, two of the patients in the 5 day MTX group required EMA-CO after failing 2nd line therapy in addition to first line therapy. This difference, (0% vs. 8%) did not reach statistical significance. However, Act-D patients required statistically significantly more chemotherapy courses than the MTX patients to achieve remission (5.3 vs. 3.1, $p = 0.01$).

The 2nd alternative regimen, the Charing Cross or Modified Bagshawe regimen, is an eight-day regimen where 1 mg/kg of MTX is given days two, four, six, and eight with folinic acid rescue, and then is repeated every 14–16 days [6,7]. This regimen's success rate has been reported as high as 73.6% [9], but has not been compared head to head with pulsed biweekly Act-D in a randomized control trial. Rather, the eight-day MTX regimen was compared to a 5-day Act-D regimen (10 mcg/kg D1–5) in a small single-center randomized control trial [9]. There are a multitude of other published first line therapies, all similarly effective with varying side effects, often lacking control groups or adequate reporting of clinical characteristics [10].

In our exploratory model, both 5- and 8-day MTX were assumed to have greater effectiveness than the weekly MTX utilized in GOG 0174. Their superior efficacy combined with the significantly lower cost associated with these alternative regimens meant that 5-day and 8-day MTX dominated both GOG 0174 treatment arms in our cost analysis. While our analysis is supportive of 5-day and 8-day alternative regimens, our use of arms from different randomized trials for comparison has inherent bias. There are limitations to using historic phase II data and earlier randomized controlled trials for two reasons. FIGO and WHO score reporting has been revised since the phase II data was published [17]. In addition, previous publications did not report the proportions of patients enrolled in small RCTs or phase II trials that had high-range low-risk WHO scores (5–6). At least in small RCTs it is assumed that randomization would equally distribute those patients among treatment arms, but the lack of reporting makes this impossible to verify [8]. It is possible that quoted 5-day and 8-day regimen effectiveness data in all of our cited sources is more a reflection of the WHO risk scores included in the cohort of patient's studied rather than the relative effectiveness of the regimen itself. This is a question that GOG 0275 has been designed to answer, and the recent Cochrane meta-analysis also tries to address but does so incompletely given the data available [10].

Use of first line complete response as the primary outcome for evaluation of treatment of low risk GTN, (a disease that has a nearly 100% eventual cure rate [11]) may be an inappropriate metric. Redefining failure of therapy from the lack of a complete response to first line therapy, to the need for multi-agent chemotherapy, creates better evidence for clinicians and patients who need to make real-life decisions. Multiagent chemotherapy for low-risk GTD increases health care costs, side effects, and at-least temporarily disables the patient in question. While not included in our model, additional personal costs to the patient can also include loss in wages, travel to a special center, and need for child or relative care.

Our model may help explain why the use of Act-D has been met with muted enthusiasm in community practice despite several trials supporting its use as first line therapy for low-risk GTN, including a Cochrane meta-analysis. Shah et al., published a cost-analysis that supports use of the 8-day MTX/folinic acid regimen [18]. The 8-day MTX regimen may be slightly more cumbersome to administer to outpatients due to potential restraints related to availability of needed services on weekends. Given that there is randomized control trial data available comparing Act-D to 5 and 8-day MTX regimens, our model adds important additional information to the dialogue surrounding this question. The model translates provider hesitation toward use of biweekly pulsed Act-D as first line therapy for low risk GTN, into agreed upon health-care metrics. GOG 0275 with its standardized reporting and appropriate power is designed to minimize bias and help settle the question of the optimal first line therapy. Unfortunately, this trial's ability to answer this question in a timely fashion may be undermined secondary to slow accrual. Although our analysis uses the imperfect data that is available, its value lies in its immediate ability to deliver practical information to clinicians regarding costs and effectiveness for low risk GTN treatment.

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HIGHLIGHTS

- Use of Act-D over MTX had an incremental cost effectiveness ratio (ICER) of \$56,215.
- With sensitivity analysis any toxicity associated with Act-D inflated the ICER.
- If goal is avoidance of multi-agent chemotherapy, any MTX regimen outperformed Act-D.

Fig. 1.

Decision tree models with TreeAge Pro software. 1A: Act-D vs. MTX base case analysis using GOG 0174 [2] format and outcome data. 1B: Exploratory model combining GOG0174 [2], and data from Mousavi et al. [8] for 5-day MTX outcomes, and Lertkahchonok et al. for 8-day MTX outcomes [9]. Assumption is that all patients that fail first line single agent therapy will cross over to different single agent prior to starting multi-agent chemotherapy.

Fig. 2.

Sensitivity analysis for QOL. In our base case model, QOL equivalence of weekly MTX and Act-D was assumed since no QOL data was collected prospectively in GOG0174 (utility score = 1). However if utility score was varied on sensitivity analysis, small decreases in QOL (utility score < 1) with Act-D in compared to weekly MTX resulted in huge cost increases. However with lack of prospectively collected patient data this cannot be assumed for our main analysis.

Table 1

Data used for decision tree models on effectiveness used for decision tree models with outcome, single agent cross-over, total number of cycles, and multi-agent chemotherapy usage rates derived from GOG0174 [2], Mousavi et al. [8] for 5-day MTX outcomes, and Lertkahchonok et al. [9] for 8-day MTX outcomes. Cost per cycle derived from publically available data bases.

	Pulsed dactinomycin	Weekly methotrexate	5-day methotrexate	8-day methotrexate
Cure	70%	53%	68%	74%
Cross-over	30%	47%	32%	27%
Multi-agent chemotherapy	7.2% overall (27% non-responders)	6.3% overall; (15% non-responders)	8%	0%
Regimen	Average number of cycles		Cost per cycle (\$ US dollars)	
Pulsed dactinomycin	4		\$4000	
Weekly methotrexate	8		\$155	
5-day methotrexate	3		\$454	
8-day methotrexate	4		\$683	
Multi-agent chemotherapy	3		\$9776	

Table 2

Total costs per regimen, (based on average amount of chemotherapy cycles, costs of cross-over to an alternate regimen, and need for multi-agent chemotherapy, as well as costs related to administration, physician visits, and hospitalizations) and first line effectiveness per regimen. ICER = incremental cost effectiveness ratio. On base case analysis Act-D had an incremental cost effectiveness ratio of \$56,215. Given the relative historic effectiveness of 8-day MTX (74%) compared to pulsed Act-D (70%), and it being significantly cheaper per regimen, it dominated all exploratory model analysis in both cost and effectiveness.

Regimen	Average cost per regimen	Complete response	ICER
Base case model			
Pulsed dactinomycin	\$18,505	70%	\$56,215
Weekly methotrexate	\$8950	53%	
Exploratory model			
Pulsed dactinomycin	\$18,505	70%	
Weekly methotrexate	\$8950	53%	
5-day methotrexate	\$7701	68%	
8-day methotrexate	\$6957	74%	Dominated