



Risk factors for second-line dactinomycin failure after methotrexate treatment for low-risk gestational trophoblastic neoplasia: a retrospective study

YM Hoeijmakers,^a FCGJ Sweep,^b CAR Lok,^{c,d} PB Ottevanger^e

^a Department of Obstetrics and Gynaecology, Radboud University Medical Centre, Nijmegen, The Netherlands ^b Department of Laboratory Medicine, Radboud University Medical Centre, Nijmegen, the Netherlands ^c Department of Gynaecologic Oncology, Antoni van Leeuwenhoek, Amsterdam, the Netherlands ^d Cancer Institute Amsterdam, Amsterdam, the Netherlands ^e Department of Medical Oncology, Radboud University Medical Centre, Nijmegen, the Netherlands

Correspondence: YM Hoeijmakers, Department of Obstetrics and Gynaecology, Radboud University Medical Centre, PO Box 9101, 6500 HB Nijmegen, the Netherlands. Email: Y.Hoeijmakers@radboudumc.nl

Accepted 25 February 2020. Published Online 31 March 2020.

Objective To find risk factors for second-line dactinomycin failure in patients with low-risk gestational trophoblastic neoplasia (GTN).

Design Retrospective multicentre study.

Setting Tertiary reference centre.

Population Patients with low-risk GTN, treated with dactinomycin after methotrexate (MTX) failure.

Methods Retrospective analysis of 45 patients with low-risk GTN treated with dactinomycin after MTX failure, registered between 2006 and 2018.

Main outcome measures Treatment outcome and risk factors for second-line dactinomycin failure.

Results Thirty patients (66.7%) were cured and 15 patients (33.3%) required third-line therapy. Type of antecedent pregnancy and hCG levels pre-dactinomycin were risk factors for failure in univariate analysis (odds ratio [OR] 19.30, 95% CI 2.04–182.60, $P = 0.01$ and OR 2.77, 95% CI 1.18–6.50, $P = 0.02$, respectively). Level of hCG pre-dactinomycin remained a significant risk factor in multivariate analysis (OR 2.93, 95% CI 1.02–8.40, $P = 0.045$).

Complete remission (CR) was achieved in 83.3% of patients with pre-dactinomycin hCG levels <10 ng/ml, in 75% with hCG levels between 10 and 20 ng/ml, in 66.7% with hCG levels between 20 and 30 ng/ml, and in 50% with hCG levels between 30 and 40 ng/ml. No patients with hCG levels >40 ng/ml achieved CR. Patients with dactinomycin failure were treated surgically and/or with multi-chemotherapy; all except one achieved CR.

Conclusions Treatment with dactinomycin after MTX failure in patients with low-risk GTN resulted in CR in 66.7%. Chance of curative treatment with dactinomycin is strongly related to the hCG level.

Keywords Dactinomycin, gestational trophoblastic neoplasia, methotrexate, risk factors.

Tweetable abstract Chance of curative treatment with dactinomycin after MTX failure in GTN patients is strongly related to the level of hCG pre-dactinomycin.

Linked article This article is commented on by Y-J Tai, p. 1146 in this issue. To view this mini commentary visit <https://doi.org/10.1111/1471-0528.16229>.

Please cite this paper as: Hoeijmakers YM, Sweep FCGJ, Lok CAR, Ottevanger PB. Risk factors for second-line dactinomycin failure after methotrexate treatment for low-risk gestational trophoblastic neoplasia: a retrospective study. BJOG 2020;127:1139–1145.

Introduction

In post-molar gestational trophoblastic neoplasia (GTN), proliferating trophoblast tissue is still present after uterine curettage, resulting in a plateau or even an increase in human chorionic gonadotropin (hCG) serum concentration.¹ This occurs in 15% of complete molar pregnancies (CHM) and in 0.5–1% of partial molar pregnancies (PHM).^{2,3}

Post-molar GTN requires single-agent or multi-agent chemotherapy. The choice of treatment is based on the classification of GTN into low- or high-risk disease using the FIGO 2000 system.⁴ This scoring system predicts the potential for resistance to single-agent chemotherapy based on a combination of clinical and pathophysiological features of the disease. Patients with a FIGO score of ≤ 6 are low-risk and are treated with single-agent chemotherapy.

Patients with a score of ≥ 7 are considered high-risk and are treated with multi-agent chemotherapy. Usually, first-line treatment of patients with low-risk disease is methotrexate (MTX), whereas high-risk GTN patients are treated with etoposide, methotrexate, dactinomycin, cyclophosphamide and vincristine (EMA/CO) regimens.⁵⁻⁷

Although the FIGO scoring system has proven to be a valuable tool in predicting resistance to single-agent therapy, approximately 9–33% of patients treated with MTX for low-risk post-molar GTN require a change in chemotherapy due to resistance or toxic side effects.⁸⁻¹⁰ After MTX failure, patients can be treated with either dactinomycin or the EMA/CO regimen.^{1,6,7} Treatment with the EMA/CO regimen is associated with increased short- and long-term toxicity compared with treatment with single-agent regimens.⁹ As low-risk GTN has proven to be highly chemo-sensitive, with an overall survival of nearly 100%, one of the key aims is to reduce toxicity without jeopardising treatment outcome.⁹

Retrospective cohort studies showed that the chance of successful treatment with second-line dactinomycin for patients with MTX-resistant low-risk GTN, varies between 70 and 90%.^{9,11-13} However, these percentages were determined by using different treatment protocols and hCG level thresholds. Also, groups with a favourable prognosis were pre-selected based on low hCG levels before start of dactinomycin treatment. This makes comparisons of efficacy challenging. Consequently, it is unclear which patients will benefit from second-line therapy with dactinomycin and which will fail and should continue with EMA/CO after MTX failure. We therefore aimed to identify risk factors for second-line dactinomycin failure in an unselected patient group.

Material and methods

Patients

All patients treated with MTX between 2006 and 2018 for low-risk post-molar GTN were identified for this study. Selection was based on the Dutch clinical classification system. This system was in use until 2017. After 2017, the FIGO system was implemented nationally.¹⁴ We confirmed that all selected cases classified with the Dutch system as low-risk, were also low-risk with the FIGO 2000 system. We selected patients from the Dutch Central Registry for Hydatidiform Moles (DCRHM) and the Working party of Trophoblastic disease databases. These voluntary registries have been based at the Radboud University Medical Centre since 1977 and serve as an epidemiological database for all patients with GTD in the Netherlands. The local ethical committee of the Radboud University Medical Centre approved this study (reference number 2019-5767). There was no funding for this study. Patients were not involved in the development of this study.

All patients were initially treated for low-risk post-molar GTN with methotrexate 1 mg/kg on days 1, 3, 5 and 7, alternating with folinic acid 1 mg/kg on days 2, 4, 6 and 8. This course was repeated every 14 days until normalisation of the hCG levels occurred, followed by two or three consolidation courses. Patients were defined as MTX-resistant according to the Dutch guidelines, which is in line with the definition of the European Organization for the Treatment of Trophoblastic disease (EOTTD): plateauing of hCG levels for three consecutive weeks or when an increase in hCG levels for two consecutive weeks occurs.^{6,15} Disease relapse was defined as a rise in hCG levels after normalisation of hCG levels following completion of MTX treatment. Pre-dactinomycin serum hCG levels were usually measured within 1 week before start of dactinomycin therapy. Patients received dactinomycin according to standard of care: either the 5-day regimen (0.5 mg dactinomycin intravenously for 5 days repeated every 14 days until normalisation) or the pulsed schedule (1.25 mg/m² intravenously repeated every 2 weeks), both followed by two or three consolidation courses. When hCG levels were below 2 ng/ml, patients had achieved complete remission (CR). After CR, hCG levels were checked monthly for 1 year. Patients with either dactinomycin resistance or relapse after therapy were classified to the dactinomycin-failure group.

Measurement of hCG

All hCG measurements were performed using the in-house developed radioimmunoassay (RIA), based on polyclonal antibodies raised in rabbits.¹⁶ This assay has been utilised centrally since 1977 for all hCG measurements in sera sent to the DCRHM. It specifically detects intact hCG and its free beta-subunit and is calibrated with the third International Standard (IS) for Chorionic Gonadotropin (WHO, 75-537). Serum hCG concentrations of < 2 ng/ml are considered normal, representing the cut-off serum concentration at 95% specificity found in postmenopausal women.¹⁶

Statistical analysis

As data were not normally distributed, we used the Mann-Whitney *U*-test to compare baseline characteristics between the dactinomycin success and failure groups. We performed a univariate logistic regression analysis to identify risk factors for dactinomycin failure. Statistically significant univariate risk factors were then used in multivariate logistic regression analysis with backward step regression to identify multivariate risk factors associated with dactinomycin failure. To give a clear insight in chance of treatment success for individual patients, we divided the dactinomycin success and dactinomycin failure groups in equal categories based on the hCG level pre-dactinomycin: < 10 , 10–20, 20–30, 30–40 and > 40 ng/ml. We calculated predicted probabilities of treatment success per category using binary

logistic regression analysis. *P*-values of <0.05 were considered significant. Analysis was performed with IBM SPSS statistics, version 25 (IBM Corp., Armonk, NY, USA).

Results

Between 2006 and 2018, 51 patients treated with second-line dactinomycin were registered. Five patients who required a change in treatment due to MTX toxicity were excluded. They suffered from severe stomatitis or MTX-induced pneumonitis. One other patient was excluded because no follow-up data were available. In total, 45 patients were treated with second-line dactinomycin due to either MTX resistance ($n = 38$) or relapse after MTX treatment ($n = 7$) within the first year of follow up (Figure 1). No adverse effects were registered during or after treatment with dactinomycin. Thirty patients (66.7%) were cured after second-line dactinomycin therapy. The other 15 (33.3%) patients were either resistant to dactinomycin ($n = 11$) or had a relapse ($n = 4$) after dactinomycin therapy. These patients were treated with multi-chemotherapy and/or surgery. All but one patient achieved CR.

We compared baseline characteristics of the dactinomycin success and dactinomycin failure groups. Patients in the dactinomycin failure group had significantly more antecedent spontaneous miscarriages and term deliveries compared with the dactinomycin success group (Table 1). Human chorionic gonadotropin levels also differed between

both groups; patients in the dactinomycin failure group had a statistically significant higher hCG level before start of dactinomycin treatment than did patients in the dactinomycin success group (Table 1).

Also in univariate analysis, type of antecedent pregnancy and hCG level pre-dactinomycin treatment were risk factors for second-line dactinomycin failure (Table 2). Patients with a spontaneous miscarriage or term delivery prior to post-molar GTN had an odds ratio of 19.30 (95% CI 2.05–182.60, $P = 0.01$) to be dactinomycin-resistant. High hCG levels, usually measured within 1 week pre-dactinomycin treatment, were also associated with a higher odds ratio of 2.77 (95% CI 1.18–6.50, $P = 0.02$) of dactinomycin treatment failure. Other variables such as age at diagnosis, histology, treatment with second curettage, the presence of lung metastasis, hCG levels before start MTX, number of MTX or dactinomycin courses or relapse after MTX treatment were not found to be risk factors for second-line dactinomycin failure (Table 2). We performed multivariate analysis with the two variables associated with second-line dactinomycin failure in the univariate analysis. Only hCG pre-dactinomycin treatment remained a significant risk factor (OR 2.93, 95% CI 1.02–8.40, $P = 0.045$).

In the five categorised hCG level groups, hCG levels were missing in four patients with dactinomycin success and in four patients with dactinomycin treatment failure. Patients with an hCG level below 10 ng/ml achieved CR with dactinomycin in 83.3%. Patients with an hCG level between 10 and 20 ng/ml had a success rate of 75%, between 20 and 30 ng/ml a success rate of 66.7%, and between 30 and 40 ng/ml a success rate of 50%. No patients with hCG levels above 40 ng/ml achieved CR (Table 3).

The length of follow up for all patients cured with dactinomycin was 12 months. For the majority of patients with dactinomycin therapy failure requiring other (chemo)therapeutic treatment, the length of follow up after normalisation of hCG levels was 24 months. Two patients are still in their follow-up period. Patients cured by surgery after dactinomycin treatment had a follow-up period of 12 months. Four patients relapsed after normalisation of hCG. In one patient, the recurrence free survival is unknown. In the other three patients, relapse occurred at 2, 6 and 12 months after normalisation. The patients who relapsed after 2 and 12 months received multi-chemotherapy. The other patient, who relapsed after 6 months, eventually underwent a hysterectomy. Histology of the resected uterus showed progression from the initially diagnosed complete mole to a choriocarcinoma. All three patients were cured. Of the 11 dactinomycin-resistant patients, resistance was diagnosed after a maximum of 3.5 months (three dactinomycin courses) in nine patients. For two patients, the number of dactinomycin courses was unknown. Five patients had an hCG level of <20 ng/ml

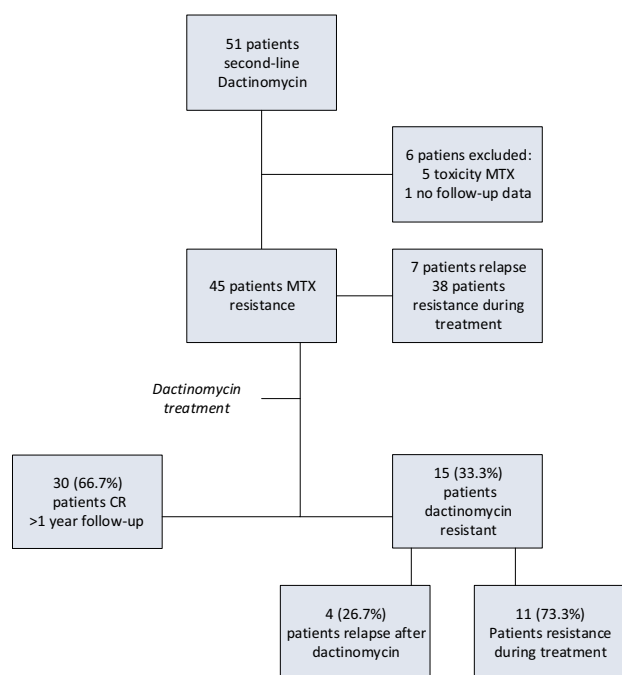


Figure 1. Study flow diagram.

Table 1. Baseline characteristics of the dactinomycin success group and the dactinomycin failure group

	Dactinomycin success (n = 30)	Dactinomycin failure (n = 15)	P-value
Age at time diagnosis (years), range	31.5 (17–51)	30 (18–38)	0.164
Antecedent pregnancy (number of patients, %)			
Molar pregnancy	29 (96.7%)	9 (60.0%)	0.002****
Spontaneous abortion	1 (3.3%)	4 (26.7%)	
Term delivery		2 (13.3%)	
Histology (number of patients, %)*			
Complete mole	22 (73.3%)	10 (66.7%)	0.635
Partial mole	4 (13.3%)	0	
Metastasis**	3 (10.0%)	2 (13.3%)	
Choriocarcinoma	0	2 (13.3%)	
Missing data	1 (3.3%)	1 (6.7%)	
Second uterine curettage	4 (13.3%)	4 (26.7%)	0.275
Hysterectomy pre-MTX treatment	1 (3.3%)	0	0.480
Serum hCG level (ng/ml) pre-MTX treatment	1513 (82–6100)	1138 (430–1830)	0.912
Serum hCG level (ng/ml) pre-dactinomycin treatment	12 (2.4–31.0)	59 (2.8–330)	0.022****
Lung metastasis (number of patients, %)**			
Yes	8 (26.7%)	5 (33.3%)	0.545
No	22 (73.3%)	9 (60.0%)	
Unknown		1 (6.7%)	

*Histology at time of diagnosis of disease (i.e. before start of MTX therapy).

**Histology was defined as a metastasis from a molar pregnancy, the location of the metastasis was not defined.

***Diagnosed during workup because of previous diagnosis with post-molar GTN.

****Significant at $P < 0.05$ level.

Table 2. Uni- and multivariate analysis for risk factors associated with second-line dactinomycin failure

Independent variables	Univariate analysis Odds (95% CI)	P-value	Multivariate analysis Odds (95% CI)	P-value
Age at diagnosis	0.91 (0.81–1.02)	0.101		
Histology ^a	3.47 (0.66–18.30)	0.143		
Antecedent pregnancy ^b	19.30 (2.05–182.60)	0.010*	12.50 (0.93–167.20)	0.057
Second curettage ^c	2.36 (0.50–11.19)	0.278		
Lung metastasis ^d	1.53 (0.39–5.95)	0.541		
Log-hCG before start MTX	1.10 (0.36–2.85)	0.982		
Number of MTX courses	0.82 (0.61–1.10)	0.185		
Relapse after MTX ^e	2.00 (0.37–10.75)	0.419		
Log-hCG before start ActD	2.77 (1.18–6.50)	0.020*	2.93 (1.023–8.40)	0.045*
Number of dactinomycin courses	0.83 (0.55–1.26)	0.382		

^aHydatidiform mole (complete or partial) versus choriocarcinoma/metastasis (reference: hydatidiform mole).

^bMiscarriage or term delivery versus molar pregnancy (reference: molar pregnancy).

^cNo second curettage versus second curettage (reference: second curettage).

^dNo lung metastasis versus lung metastasis (reference: no lung metastasis).

^eNo relapse after MTX versus relapse after normalization with MTX therapy (reference: no relapse).

*Significant at $P < 0.05$ level.

pre-dactinomycin. Two of these patients underwent a hysterectomy. Histology of the uterus showed progression from a complete mole to a choriocarcinoma in one patient,

and progression from a complete mole to a mixed choriocarcinoma and placental site trophoblastic tumour (PSTT) in the other patient. Of the six patients with hCG levels

Table 3. Second-line dactinomycin treatment success predicted probability divided in hCG level categories

hCG serum level	Dactinomycin-success patients	Dactinomycin-failure patients	Predicted probability
<10 ng/ml	15	3	0.833
10–20 ng/ml	6	2	0.750
20–30 ng/ml	4	2	0.667
30–40 ng/ml	1	11	0.500
>40 ng/ml	0	3	0.000

>20 ng/ml, four were treated with EMA/CO, with a maximum of five courses including two consolidation courses. All patients were cured after EMA/CO therapy. One of the remaining two patients received three courses of etoposide therapy followed by a hysterectomy; histology showed proliferating trophoblastic tissue. The other patient, initially diagnosed with a choriocarcinoma, received three courses of a regimen containing MTX, cyclophosphamide, dactinomycin and cisplatin, followed by three consolidation courses. Of the 15 dactinomycin failure patients, one patient succumbed to the disease after failing third-, fourth- and fifth-line chemotherapy. At initial diagnosis, the patient had a complete mole with no metastasis present. After relapsing post-MTX she developed lung metastasis and was treated with dactinomycin. After three dactinomycin courses, new lung metastasis was diagnosed; there were no metastases present at other sites. After first refusing third-line treatment, she continued with EMA/CO therapy, relapsed, and again had a long patient delay before start of fourth-line treatment with bleomycin, etoposide and cisplatin (BEP) chemotherapy. Afterwards, she underwent high-dose chemotherapy, followed by stem cell transplantation because of fourth-line treatment failure. Unfortunately, the patient died after stem cell transplantation due to progressive disease (Figure S1).

Discussion

Main findings

We identified risk factors for dactinomycin failure in an unselected group of patients, treated with second-line dactinomycin after MTX failure for low-risk GTN. In 66.7% of the patients, treatment with second-line dactinomycin resulted in a CR with a follow up of 1 year. Type of antecedent pregnancy and high hCG levels before start of dactinomycin therapy were risk factors for second-line dactinomycin therapy failure in univariate analysis. In multivariate analysis, hCG level pre-dactinomycin remained a significant risk factor for second-line dactinomycin failure.

We found treatment success percentages of 83.3% for patients with an hCG level of <10 ng/ml, 75% for patients with an hCG level between 10 and 20 ng/ml, 66.7% with an hCG level between 20 and 30 ng/ml, and 50% with an hCG level between 30 and 40 ng/ml. No patients with an hCG level >40 ng/ml were successfully treated with dactinomycin. So, risk of failure increases with an increase in pre-dactinomycin hCG levels.

Strengths and limitations

Our study is the first to analyse treatment outcome and risk factors for second-line dactinomycin failure in a group of patients where no selection was applied based on hCG levels pre-dactinomycin therapy. Therefore, we were able to analyse whether hCG level pre-dactinomycin is a predictor for treatment failure. We additionally determined pre-dactinomycin hCG cut-off levels. As hCG concentrations were quantified using the radioimmunoassay used by the Dutch national hCG reference centre, these absolute cut-off values cannot be readily applied in centres using other hCG assays. However, it proves that the level of hCG is related to outcome, and extra caution is warranted with higher hCG.

Because MTX-resistant low-risk post-molar GTN is rare, we are limited by a retrospective study design and a relatively small sample size. As we only had 15 events of dactinomycin failure, according to the rules of multivariate analysis we could include only two variables in this analysis, and therefore included the variables which were statistically significant in univariate analysis. We applied strict rules to determine the significance of these outcomes, and identified hCG levels measured pre-dactinomycin to be a significant risk factor. However, type of antecedent pregnancy may also be identified as a risk factor in a study with a larger sample size. Second-line dactinomycin treatment was given according to standard care; patients received either the 5-day or the pulsed regimen. Although there were differences in the cost-effectiveness of the regimens, studies showed no differences in treatment efficacy.^{13,17} We therefore did not subdivide patients treated with the 5-day regimen and those treated with the pulsed schedule. Because of the use of the Dutch classification system, the exact FIGO score was not known for all patients. Therefore, we were unable to analyse whether dactinomycin failure occurred more often in patients with FIGO stages 5 and 6. From the literature, it is known that this subgroup has a higher risk of becoming MTX-resistant.¹⁸ However, because 99% of the patients were eventually cured, starting with dactinomycin in patients with FIGO score 5–6 did not influence final outcome.

Interpretation

Multiple studies have reported on the effect of dactinomycin after MTX-treatment failure in patients with low-

risk GTN.^{9,11-13,19} However, those studies used a selected group of patients and included patients treated with second-line dactinomycin because of MTX toxicity.^{9,11-12,19} The percentage of successfully treated patients with second-line dactinomycin in our study is slightly lower compared with other studies.^{9,11-13,19} Most other studies suggested using a maximum hCG level measured before initiation of second-line therapy as a cut-off for treatment with either dactinomycin or EMA/CO after MTX failure. These levels were randomly chosen and hCG levels pre-dactinomycin could therefore not be identified as a risk factor in uni- or multivariate analysis.^{9,11,19} Because we did not select patients according to the level of hCG, patients with higher hCG levels pre-dactinomycin were included in our patient group. According to our results, these patients had a higher risk of dactinomycin failure compared with the patients included in the other studies. This also explains our slightly lower percentage of successfully treated patients. Because, except for one, all patients were eventually cured with multi-agent chemotherapy, the total of patients achieving CR was still close to 100%.

Low-risk GTN has proven to be highly chemo-sensitive, with an overall survival percentage of nearly 100%. Therefore, reduction of treatment toxicity and duration of treatment and follow up has become more important,⁹ especially as most patients affected by GTN are young, fertile women with a wish to conceive. According to the international guidelines, hCG levels should be followed monthly for 1 year in patients treated with second-line dactinomycin, and monthly for 2 years in patients treated with multi-agent chemotherapy (usually EMA/CO).¹ Multiple studies showed that multi-agent chemotherapy such as EMA/CO has an increased short- and long-term toxicity compared with dactinomycin.⁹ Moreover, patients treated with multi-agent regimens, particularly those containing higher cumulative levels of etoposide, have a higher chance of secondary malignancies including leukaemia, melanoma and breast and colon cancer.^{20,21} In addition, treatment with multi-agent chemotherapy increases the risk of an earlier menopause.^{21,22} According to our study, these risks could be prevented in two-thirds of the patients with low-risk post-molar GTN and MTX failure.

Theoretically, in patients with dactinomycin failure, the choice of treatment with dactinomycin instead of EMA/CO resulted in a delay in starting EMA/CO and a possible later hCG normalisation. For patients, this means lost time before a new pregnancy can be pursued. In our study, maximum treatment duration of second-line dactinomycin before switching to third-line treatment was 3.5 months, probably leading to an extension of total treatment duration. However, the added treatment duration of maximum 3.5 months seems limited, as it is advised that patients immediately treated with second-line EMA/CO are followed for 2 years

instead of 1 year when salvaged with second-line dactinomycin. In addition, in theory, when hCG levels decrease during dactinomycin treatment, fewer EMA/CO courses will be needed to achieve CR. Nevertheless, the risk of second-line dactinomycin failure with a possible increased treatment duration and longer exposure to toxic chemotherapy should be discussed with each individual patient eligible for this therapy. In particular, the risk of progression from the frequent initial diagnosis of molar pregnancy to a choriocarcinoma or even a PSTT or epithelioid trophoblastic tumor (ETT) should be taken into consideration when second-line dactinomycin fails. This is particularly the case for patients with a low pre-dactinomycin hCG level and thus a relative high chance of cure with second-line dactinomycin therapy.

Conclusion

This study indicates that hCG is a very useful marker to select patients with low-risk GTN for second-line treatment with dactinomycin. In total, 66.7% of 45 patients were successfully treated with second-line dactinomycin after MTX failure and were thus protected from the possible, more toxic multi-chemotherapy regimens with longer follow-up duration. Type of antecedent pregnancy was identified as a univariate risk factor. After multivariate analysis, high hCG levels pre-dactinomycin were identified as a risk factor for second-line dactinomycin failure. According to our cut-off levels, second-line dactinomycin chemotherapy is a good treatment option for patients with a serum hCG level of <20 ng/ml. For patients with serum hCG levels between 20 and 40 ng/ml, second-line dactinomycin should be considered as a treatment option. Above 40 ng/ml, the chance of failure is high and immediate treatment with EMA/CO should be considered. To implement our findings internationally, validation of our data and further studies are warranted to determine hCG serum level cut-offs quantified by other immunoassays.

Disclosure of interests

None declared. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

YMH, PBO and FCGJS were involved in the study design. YMH, PBO, FCGJS and CARL collected data for this study. YMH analysed the data and YMH, PBO, CARL and FCGJS interpreted the data. All authors were equally involved in writing, reviewing and editing the manuscript.

Details of ethical approval

This study was approved on 26 September 2019 by the local ethical committee of the Radboud University Medical Centre (reference number 2019-5767).

Funding

This study did not receive any specific grant from funding agencies in the public, commercial or non-for-profit sectors.

Acknowledgements

None.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Dactinomycin-failure patients. ■

References

- Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;6:vi39–50.
- Berkowitz RS, Goldstein DP. Clinical practice. Molar pregnancy. *N Engl J Med* 2009;360:1639–45.
- Ngan HY, Bender H, Benedet JL, Jones H, Montruccoli GC, Pecorelli S. Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. *Int J Gynaecol Obstet* 2003;83(Suppl 1):175–7.
- FIGO staging for gestational trophoblastic neoplasia 2000. FIGO Oncology Committee. *Int J Gynaecol Obstet* 2002;77:285–7.
- Froeling FE, Seckl MJ. Gestational trophoblastic tumours: an update for 2014. *Curr Oncol Rep* 2014;16:408.
- Mangili G, Lorusso D, Brown J, Pfisterer J, Massuger L, Vaughan M, et al. Trophoblastic disease review for diagnosis and management: a joint report from the International Society for the Study of Trophoblastic Disease, European Organisation for the Treatment of Trophoblastic Disease, and the Gynecologic Cancer InterGroup. *Int J Gynecol Cancer* 2014;24(9 Suppl 3):S109–116.
- Brown J, Naumann RW, Seckl MJ, Schink J. 15 years of progress in gestational trophoblastic disease: Scoring, standardization, and salvage. *Gynecol Oncol* 2017;144:200–7.
- van Trommel NE, Ngo Duc H, Massuger LF, Schijf CP, Sweep CG, Thomas CM. Early identification of persistent trophoblastic disease with serum hCG concentration ratios. *Int J Gynecol Cancer* 2008;18:318–23.
- McNeish IA, Strickland S, Holden L, Rustin GJ, Foskett M, Seckl MJ, et al. Low-risk persistent gestational trophoblastic disease: outcome after initial treatment with low-dose methotrexate and folinic acid from 1992 to 2000. *J Clin Oncol* 2002;20:1838–44.
- Matsui H, Suzuka K, Yamazawa K, Tanaka N, Mitsuhashi A, Seki K, et al. Relapse rate of patients with low-risk gestational trophoblastic tumor initially treated with single-agent chemotherapy. *Gynecol Oncol* 2005;96:616–20.
- Prouvot C, Golfier F, Massardier J, You B, Lotz JP, Patrier S, et al. Efficacy and safety of second-line 5-day dactinomycin in case of methotrexate failure for gestational trophoblastic neoplasia. *Int J Gynecol Cancer* 2018;28:1038–44.
- Lurain JR, Chapman-Davis E, Hoekstra AV, Schink JC. Actinomycin D for methotrexate-failed low-risk gestational trophoblastic neoplasia. *J Reprod Med* 2012;57:283–7.
- Covens A, Filiaci VL, Burger RA, Osborne R, Chen MD. Phase II trial of pulse dactinomycin as salvage therapy for failed low-risk gestational trophoblastic neoplasia: a Gynecologic Oncology Group study. *Cancer* 2006;107:1280–6.
- Eysbouts YK, Massuger L, Thomas C, Ottevanger P, Short D, Harvey R, et al. Dutch risk classification and FIGO 2000 for gestational trophoblastic neoplasia compared. *Int J Gynecol Cancer* 2016;26:1712–6.
- Hancock BW. Staging and classification of gestational trophoblastic disease. *Best Pract Res Clin Obstet Gynaecol* 2003;17:869–83.
- Thomas CM, Segers MF, Houx PC. Comparison of the analytical characteristics and clinical usefulness in tumour monitoring of fifteen hCG(-beta) immunoassay kits. *Ann Clin Biochem* 1985;22 (Pt 3):236–46.
- Mu X, Song L, Li Q, Yin R, Zhao X, Wang D. Comparison of pulsed actinomycin D and 5-day actinomycin D as first-line chemotherapy for low-risk gestational trophoblastic neoplasia. *Int J Gynaecol Obstet* 2018;143:225–31.
- Chapman-Davis E, Hoekstra AV, Rademaker AW, Schink JC, Lurain JR. Treatment of nonmetastatic and metastatic low-risk gestational trophoblastic neoplasia: factors associated with resistance to single-agent methotrexate chemotherapy. *Gynecol Oncol* 2012;125:572–5.
- Winter MC, Tidy JA, Hills A, Ireson J, Gillett S, Singh K, et al. Risk adapted single-agent dactinomycin or carboplatin for second-line treatment of methotrexate resistant low-risk gestational trophoblastic neoplasia. *Gynecol Oncol* 2016;143:565–70.
- Seckl MJ, RIGIHB, Newlands ES, Berkowitz RSCL, editors. *Late Toxicity after Therapy for Gestational Trophoblastic Tumours. Gestational Trophoblastic Disease*, 3rd edn. London: International Society for the Study of Trophoblastic Disease; 2003, pp. 470–84.
- Savage P, Cooke R, O'Nions J, Krell J, Kwan A, Camarata M, et al. Effects of single-agent and combination chemotherapy for gestational trophoblastic tumors on risks of second malignancy and early menopause. *J Clin Oncol* 2015;33:472–8.
- Newlands ES, Bower M, Holden L, Short D, Brock C, Rustin GJS, et al. The management of high-risk gestational trophoblastic tumours (GTT). *Int J Gynaecol Obstet* 1998;60(Suppl 1):S65–70.