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Flat-dose versus weight or body surface area-based methotrexate dosing in low-risk gestational trophoblastic neoplasia

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HIGHLIGHTS

- Methotrexate dose adjustment by BSA and weight did not influence chemotherapy response or disease relapse in low-risk GTN.
- BSA or weight was not associated with the number of methotrexate cycles required to achieve a complete treatment response.
- Flat-dose methotrexate (50 mg) within the 8-day MTX-FA regimen is supported in the treatment of low-risk GTN.

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ABSTRACT

Background. Single-agent methotrexate (MTX) is commonly used as first-line treatment for low-risk gestational trophoblastic neoplasia (LR-GTN), although no international consensus exists on the optimal treatment regimen to maximise complete hCG response (CR) and minimise relapse rates. Current regimens differ in the route of administration, dose scheduling, and use of flat-dose, body surface area (BSA)- or weight-based dosing. In the UK a methotrexate-folinic acid (MTX-FA) 8-day 50 mg intramuscular flat-dose regimen is used, with 15 mg oral folinic acid rescue. In LR-GTN patients, we aim to determine the effect of MTX dose adjustment by BSA and weight upon chemotherapy response and disease relapse.

Methods. Between January 1973 and August 2020, 935 LR-GTN patients treated with first-line MTX-FA were identified from a single UK specialist trophoblastic centre. Of these, 364 were included, of which 178 (49%) had a CR to first-line MTX-FA. Subgroup analyses were performed upon: (i) patients who changed chemotherapy due to MTX toxicity ($n = 33$); and (ii) patients with a FIGO score of 5–6 ($n = 85$). Logistic regression analysis explored the relationship between BSA or weight adjusted MTX dosing and: (i) CR to first-line chemotherapy; (ii) incidence of disease relapse. Linear regression analyses assessed the correlation of BSA and weight with the number of MTX-FA cycles required to achieve CR.

Results. In LR-GTN patients, BSA and weight adjusted MTX-FA dosing did not influence CR to first-line chemotherapy or the incidence of disease relapse. The number of MTX cycles required to achieve CR was not associated with BSA or weight. These findings were maintained in a subgroup analysis of FIGO 5–6 patients. The incidence of MTX toxicity was not influenced by BSA or weight.

Conclusions. In the treatment of LR-GTN, dose individualisation using BSA or weight is not required, and fixed dosing continues to be preferred as the UK standard.

Abbreviations: ALL, Acute lymphoblastic leukaemia; BSA, Body surface area; COVID-19, Coronovirus; CR, Complete hCG response; EMA/CO, Etoposide, methotrexate, dactinomycin, cyclophosphamide and vincristine; ESMO, European Society of Medical Oncology; GTN, Gestational Trophoblastic Neoplasia; FIGO, International Federation of Gynecology and Obstetrics; hCG, human chorionic gonadotrophin; HR-GTN, High-risk Gestational Trophoblastic Neoplasia; IM, Intramuscular; IQR, Interquartile range; IV, Intravenous; KS, Kolmogorov-Smirnov tests; LR, Logistic regression analysis; LR-GTN, Low-risk Gestational Trophoblastic Neoplasia; MTX, Methotrexate; MTX-FA, Methotrexate-folinic acid; SE, Standard error; STDC, Sheffield Trophoblastic Disease Centre; TR, Treatment resistance; UK, United Kingdom.

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1. Introduction

The International Federation of Gynaecology and Obstetrics scoring system (FIGO) is used worldwide to guide the primary treatment of patients diagnosed with gestational trophoblastic neoplasia (GTN). Using the sum of eight risk-factors, FIGO is designed to predict the risk of primary, single-agent chemotherapy resistance, stratifying patients into low- (score ⩽6) and high-risk groups (score ⩾7). In the United Kingdom (UK), low-risk (LR-GTN) patients are typically treated with first-line single-agent methotrexate (MTX) [1], employing a MTX-FA 8-day regimen, whilst high-risk (HR-GTN) patients receive first-line combination chemotherapy, usually with EMA/CO (etoposide, methotrexate, dactinomycin, cyclophosphamide and vincristine [1–3]). Despite FIGO classification, a third of patients treated for LR-GTN are resistant to first-line MTX-FA, increasing to four out of five of those scoring 5 or 6 [4,5].

In other malignancies (paediatric acute lymphoblastic leukaemia (ALL) and osteosarcoma), a relationship between serum MTX concentration and clinical response has been demonstrated [6,7]. Therefore, through dose-individualisation, pharmacokinetics could contribute to reducing MTX resistance. Indeed, it is widely accepted that chemotherapeutic drugs such as MTX, which have a narrow therapeutic index and variable inter-patient pharmacokinetics, should be individually dosed to maximise clinical effect, and minimise toxicity. Accepted dose adjustment techniques include serum drug levels or surrogate measures such as body surface area (BSA) [8,9]. BSA is correlated with blood volume, quantity of circulating plasma proteins, and urea clearance, which can influence the plasma level, and therefore the therapeutic effect and toxicity of drugs [10]. Of note, BSA based MTX dosing is already established in the management of ectopic pregnancy and in HR-GTN [10–13]. It is therefore feasible that in some LR-GTN patients, MTX resistance could be caused by subtherapeutic MTX delivery to the tumour itself. However, in much of Europe, including the UK., flat-dose MTX is standard practice in the treatment of LR-GTN [5,14].

The initial complete primary remission rate is an important endpoint because patients who develop resistance to first-line treatment need further treatment for cure; this could be further sequential single-agent chemotherapy, multi-agent chemotherapy or consideration of surgical options. Internationally, there has been a variety of MTX-FA regimens used reporting an approximate 57–90% primary remission rate in mainly retrospective, although some prospective, non-randomised studies. Randomised studies have reported MTX-FA primary remission rates of 48–88% [5]. Across all of these studies, the wide variability in the primary remission rates reflect differences in drug dosing, scheduling, and route of administration making comparison across these series difficult. MTX-FA regimens have used: (i) flat-dose, weight- or BSA-based dosing; (ii) intramuscular (IM), intravenous (IV) or oral administration; and (iii) five-day, eight-day or weekly scheduling. Guidelines developed by the European Society of Medical Oncology (ESMO) recommend flat-dose 50 mg IM MTX using an eight-day regimen, with 15 mg oral folinic acid rescue therapy (8-day MTX-FA). This is also the recommended practice in the UK, Germany, Austria and Switzerland [14–17]. In the United States, an eight-day weight adjusted dose of 1 mg/kg, or five-day 0.4 mg/kg/day regimen is administered IM or IV [18]. Meanwhile, Denmark [19] uses BSA-based regimens, whilst Spain employs either an 8 day or BSA-based regimen [16].

A prior Italian study revealed comparable rates of treatment resistance using weight-based versus flat-dose eight-day MTX regimens, yet the effect of BSA based dosing has not been evaluated [20]. Using a dataset of LR-GTN patients treated at the Sheffield Trophoblastic Disease Centre (STDC), this analysis explored the effect of BSA and weight upon: (i) complete response (CR) to single-agent MTX-FA; (ii) the incidence of disease relapse; (iii) the prediction of CR and disease relapse and; (iv) the number of MTX-FA cycles required to achieve a CR. An additional subgroup analysis was performed of patients at the highest risk of MTX-FA resistance; those scoring FIGO score 5 and 6.

2. Methods

2.1. Data collection

Patients were identified from the STDC registry between January 1973 and August 2020 and included if they had: (i) FIGO LR-GTN (score ⩽6); (ii) received first-line treatment with flat-dose 50 mg MTX dosing (8-day MTX-FA comprising 50 mg MTX IM on days 1, 3, 5, 7 with 15 mg oral folinic acid rescue 24 h after MTX on days 2, 4, 6, 8 repeated every 2 weeks. Treatment continued for 6 weeks following serum hCG normalisation); documentation of (iii) height and weight within three weeks of commencing MTX-FA; (iv) response to primary chemotherapy (treatment resistance (TR) versus complete response (CR)); (v) number of cycles of MTX-FA administered; and (vi) a follow-up period ⩾1 year after CR.

CR was defined as the normalisation of serum human chorionic gonadotrophin (hCG) levels for a minimum of 6 weeks on chemotherapy [21]. Treatment resistance was defined as a rise in ⩾2 serial hCG measurements over 4 weeks, or ⩾3 measurements with in inadequate fall (approximately 25%) in the same time frame [11]. Relapse after initial treatment was also recorded, defined by a rise in serum hCG after normalisation for ≥6 weeks, in the absence of confirmed pregnancy [21].

Patients were excluded if they had (i) changed treatment due to the coronavirus (COVID-19) pandemic; (ii) persistently raised hCG levels due to another cause; (iii) missing or incomplete records; (iv) FIGO score ⩾7; or (v) were not treated (Fig. 1).

All patients had previously given permission for anonymised clinical information to be held on the STDC registry, and therefore no further ethics committee approval was required.

2.2. Statistical analysis

BSA was calculated using the Mosteller formula: $\text{BSA}\ (\text{metres}^2) = \sqrt{\frac{\text{height (centimetres)} \times \text{weight (kg)}}{3600}}$ [22].

Logistic regression analysis (LR) explored the relationship between the variables BSA and weight, and primary outcome measures: (i) CR to first-line MTX-FA; and (ii) disease relapse. Wald's $\chi 2$ was calculated, using $\chi 2 = (\beta/(SE\,\beta))^2$ for each predictor, where β is the regression coefficient, and SE is standard error. *P*-values were generated using this value. Linear regression investigated whether BSA or weight adjusted MTX dosing influenced the number of cycles needed to achieve CR. R^2 was used to test goodness of fit of the model.

Data were tested for normality using the Shapiro-Wilk test. Kolmogorov-Smirnov tests (KS) were used to explore differences in BSA or weight between; (i) CR and TR to first-line single-agent MTX-FA; and (ii) relapse status. Analyses were performed using GraphPad Prism (version 9.1.1, San Diego, CA, USA).

3. Results

Of the 935 patients identified, 595 (64%) had a CR to first-line MTX-FA. Overall, 364 satisfied the inclusion criteria, with 571 patients being excluded largely due to incomplete height and weight data, with other reasons shown in Fig. 1. Of these 364 patients, 178 (49%) had CR to first-line single-agent MTX-FA, and 186 (51%) developedTR. (Fig. 1). Thirteen (4%) patients relapsed. Median follow up from the date of uterine evacuation was 188 months (IQR = 102–254 months).

The distribution of BSA (Fig. 2A) was comparable for patients with a CR (median 1.72, standard deviation (SD) 0.19) and TR (median 1.71, SD 0.21) (KS test, D = 0.07, $p = 0.76$) (Fig. 2B). The weight distribution (Fig. 2C) of CR (median 64.50 kg, SD 14.22) and TR patients (median 64.50 kg, SD 15.22) was also equivalent (KS test, D = 0.06, $p = 0.92$) (Fig. 2D).

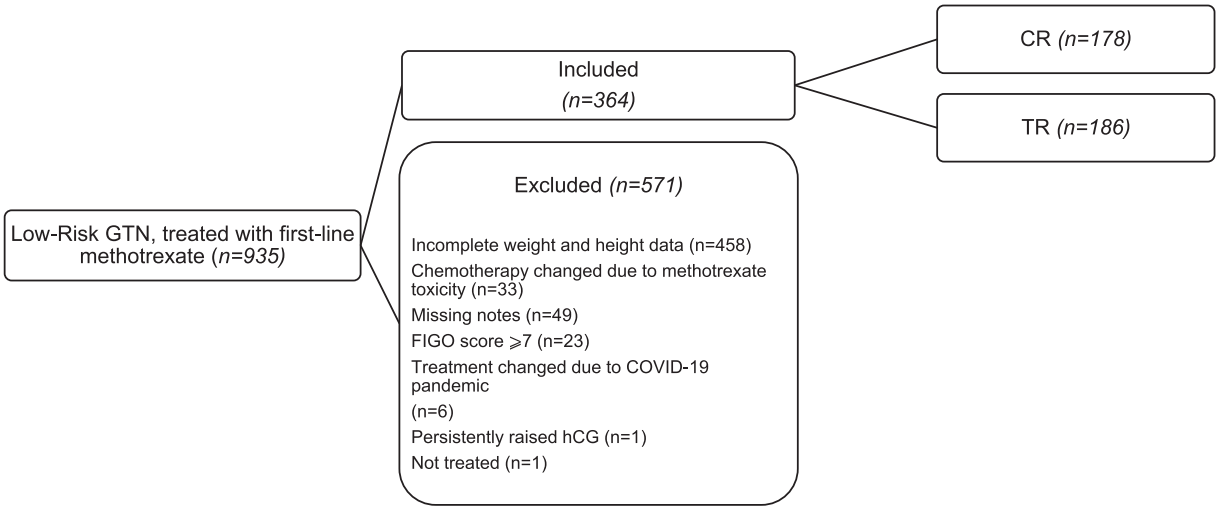

Fig. 1. CONSORT diagram demonstrating inclusion and exclusion criteria.
Key: COVID-19, coronavirus; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotrophin; n, number of patients; TR, treatment resistance.

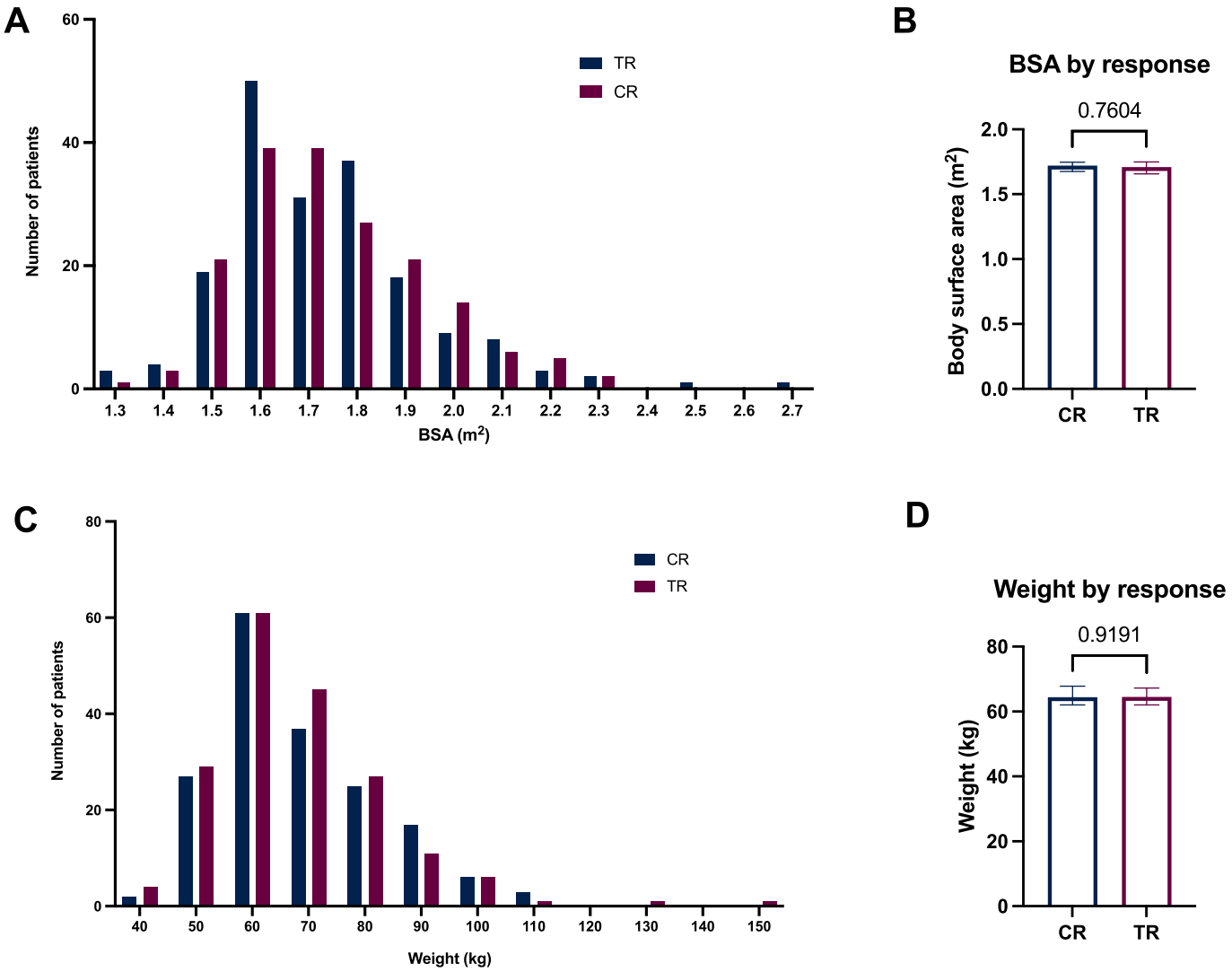

Fig. 2. The influence of body surface area and weight upon response to first-line single-agent methotrexate. A: The distribution of body surface area by methotrexate response. B: The distribution of weight by methotrexate response. C: Median body surface area according to methotrexate response. $n = 364$, Kolmogorov-Smirnov test, $D = 0.07$, $p = 0.76$. Error bars represent 95% confidence interval. D: Median weight according to methotrexate response. $n = 364$, Kolmogorov-Smirnov test, $D = 0.06$, $p = 0.92$. Error bars represent 95% confidence interval.
Key: BSA, body surface area; CR, complete response; kg, kilograms; m^2, metres squared; TR, treatment resistance.

Similarly, the distribution of BSA (Fig. 3A) was comparable for patients who relapsed (mean 1.76, SD 0.27) versus those who did not (mean 1.71, SD 0.20) (KS test D = 0.18, $p = 0.81$) (Fig. 3B). The weight distribution (Fig. 3C) of patients with relapse (mean 67.80 kg, SD 21.51) versus no relapse (mean 64.30 kg, SD 14.44) was also equivalent (KS test D = 0.13, $p = 0.99$) (Fig. 3D).

3.1. Regression analyses

Using logistic regression, BSA and weight did not predict CR (Fig. 4A) to first-line MTX-FA or relapse (Fig. 4B, Supplementary Table 1). Linear regression analysis revealed that BSA (Fig. 5A) and weight (Fig. 5B) did not influence the number of cycles required to achieve CR to first-line MTX-FA (Supplementary Table 2).

3.2. Subgroup analysis: MTX Toxicity

A total of 33 patients switched from MTX-FA therapy due to toxicity (3.5% dataset). The incidence of MTX-FA toxicity was not influenced by either BSA (KS test, D = 0.15, $p = 0.63$) or weight (KS test, D = 0.16, $p = 0.54$) (Supplementary Fig. 1).

3.3. Subgroup analysis: FIGO 5 and 6

In a subgroup analysis of patients with a FIGO score of 5 and 6 ($n = 85$), 27 patients (32%) had a CR to first-line-MTX-FA. The distribution of BSA (Supplementary Fig. 2A) was comparable for patients with a CR (median 1.74, standard deviation (SD) 0.21) and TR (median 1.74, SD 0.18) (KS test, D = 0.19, $p = 0.50$) (Supplementary Fig. 2B). The weight distribution (Supplementary Fig. 1C) of CR (median 68.00 kg, SD 15.61) and TR patients (median 66.15 kg, SD 12.22) was also equivalent (KS test, D = 0.16, $p = 0.74$) (Supplementary Fig. 2D).The incidence of relapse ($n = 3$) was not influenced by BSA (KS test, D = 0.77, $p = 0.07$) or weight (KS test, D = 0.76, p = 0.07) (Supplementary Fig. 3).

Using regression analysis, BSA and weight did not predict CR or relapse to first-line MTX-FA (Supplementary Fig. 4 and Supplementary Table 3). Furthermore, the number of cycles required to achieve CR to first-line MTX-FA was not influenced by BSA or weight (Supplementary Fig. 5 and Supplementary Table 4).

4. Discussion

In the treatment of LR-GTN, there is disparity regarding flat- versus BSA or weight-based MTX dosing. In this study, involving LR-GTN

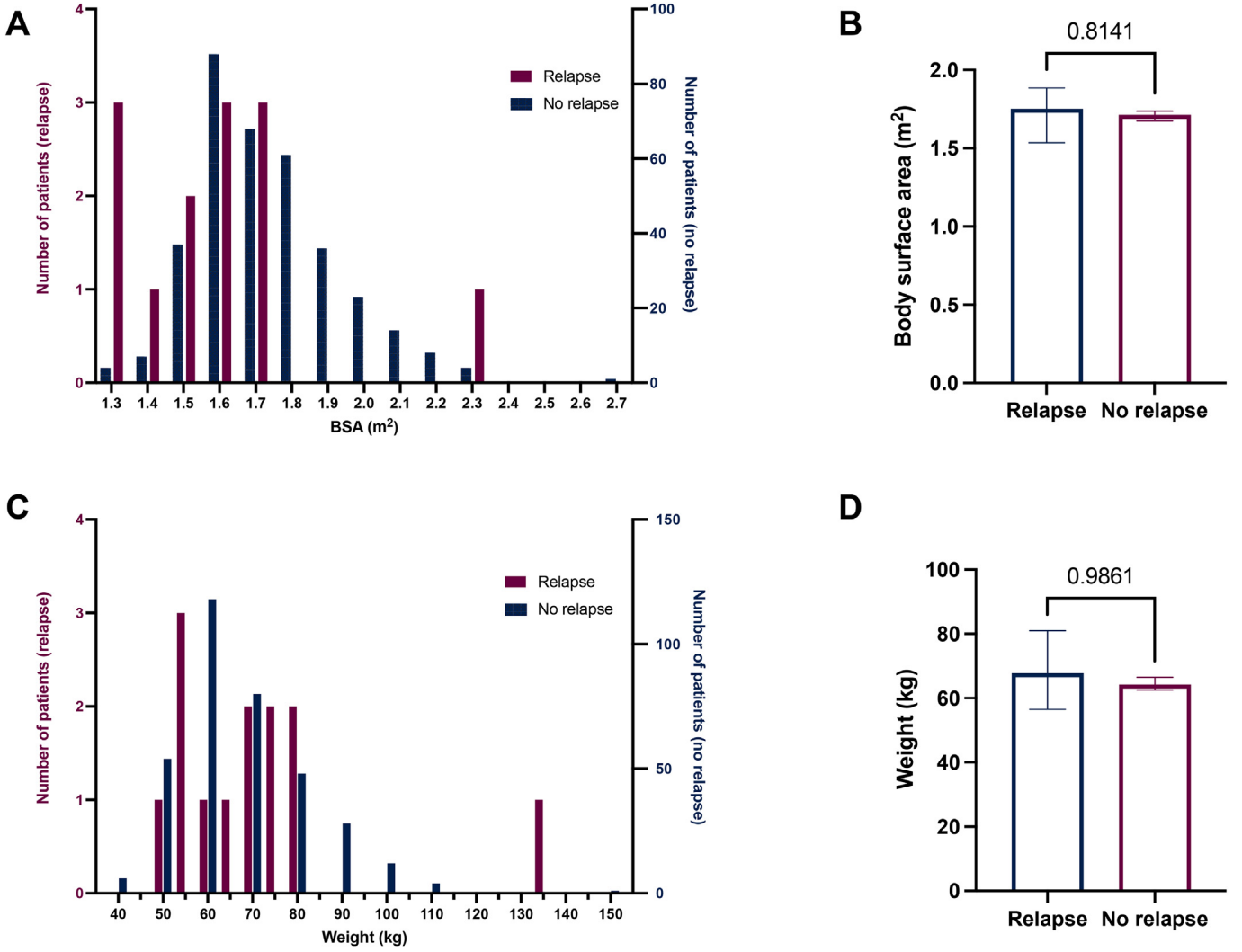

Fig. 3. The influence of body surface area and weight upon the incidence of disease relapse A: The distribution of body surface area by relapse status. B: The distribution of weight by relapse status. C: Median body surface area according to relapse status. $n = 364$, Kolmogorov-Smirnov test, D = 0.18, $p = 0.81$. Error bars represent 95% confidence interval. D: Median weight according to relapse status. $n = 364$, Kolmogorov-Smirnov test, D = 0.13, $p = 0.99$. Error bars represent 95% confidence interval.
Key: BSA, body surface area; CR, complete response; kg, kilograms; m^2, metres squared; TR, treatment resistance.

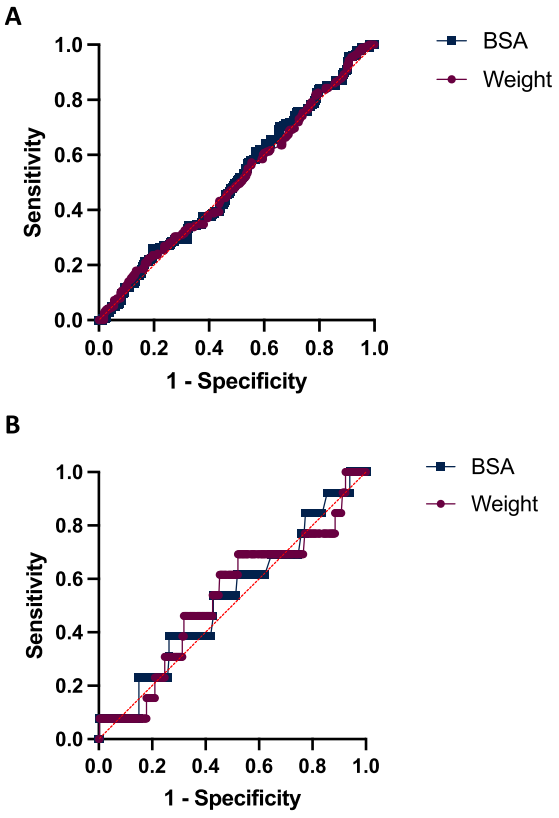

Fig. 4. Receiver operating characteristics curves demonstrating the role of body surface area and weight in predicting A: complete response to first-line single-agent methotrexate and B: disease relapse using logistic regression analysis (n = 364).
Key: BSA, body surface area; CR, complete response; ROC, receiver operating curve.

patients, there was no association between BSA or weight, and CR to first-line MTX-FA, or the number of cycles required to achieve CR. These findings were maintained within a subgroup analysis of patients with a FIGO score of 5 or 6. Furthermore, the incidence of MTX-FA toxicity was not influenced by either BSA or weight. Current UK practice, using flat-dose MTX-FA in the primary management of LR-GTN is therefore supported by these results.

In agreement with our findings, a previous multi-centre Italian study (MITO-9) revealed CR rates to be comparable between 8-day 50 mg flat-dose and weight-based 1 mg/kg/day MTX-FA regimens in LR-GTN patients [20]. Furthermore, CR rates to first-line single-agent MTX-FA were equivalent when comparing UK (8-day 50 mg flat-dose IM MTX) [23] and USA practice (8-day 1 mg/kg IM MTX) over a similar time period (72% and 78% respectively) [24]. Similarly, in a retrospective study of 300 patients treated with weight- or BSA-based chemotherapy dosing, similar levels of chemotherapy resistance were observed in patients with a BMI <25 kg/m^2 versus ≥25 kg/m^2. Within this study, the overall CR rate of 63.7% was comparable to our CR rate for all identified patients (64%). However, the study differed from ours by inclusion of multiple different MTX-FA regimens, as well as actinomycin D regimens, all of which used weight- or BSA-based dosing [25]. To our knowledge, previous literature has not evaluated the effect of BSA- or weight-based dosing upon patients with a FIGO score of 5–6, which represent a subgroup at higher risk of MTX-FA resistance. Despite the lower CR rate to MTX-FA in FIGO 5–6 patients ($n = 85$) compared to the whole FIGO ⩽6 cohort ($n = 364$) (32% versus 49% respectively), our study provides reassurance that flat-dose MTX-FA regimens are appropriate in this high-risk cohort.

There are no previously published studies evaluating the effect of BSA-based dosing on an 8-day regimen, so direct comparisons with our findings cannot be made. Across weekly BSA-based regimens, primary response rates range from 49 to 74%, with doses of 30-50 mg/m^2 [26,27]. However, consensus is that weekly regimens are generally less efficacious than 5- or 8-day regimens [5,24]. A dose of 20 mg/m^2 on a 5-day IM regimen had a remission rate of 69% amongst 42 patients treated between 1980 and 2002 [28].

Much of the high quality evidence for treatment of LR-GTN, including a Cochrane review of randomised control trials [29] and another meta-analysis of both randomised and non-randomised studies [30], have focused upon comparing various MTX-FA regimens to actinomycin-D. Limitations of the studies included underpowered studies, heterogeneity between included studies such as the different dosage regimens, definitions of persistence, different FIGO risk score thresholds, inclusion of patients with or without metastatic disease and choriocarcinoma, differing outcome measures and follow-up times. This renders comparisons across these studies challenging and difficult to interpret. In addition, evidence for BSA-based dosing is sparse, and the 8-day regimen with BSA-based dosing has not been evaluated.

Despite attempts to individualise dosing using BSA, there is considerable variability in plasma drug levels across many chemotherapeutic drugs [9]. Drug exposure of a target organ may be influenced by many factors which do not correlate with BSA or weight, including renal and liver function, the role of drug-metabolising enzymes and tumour resistance to the drug [10]. BSA-based dosing cannot account for these confounders upon treatment response, and may therefore be too indirect to

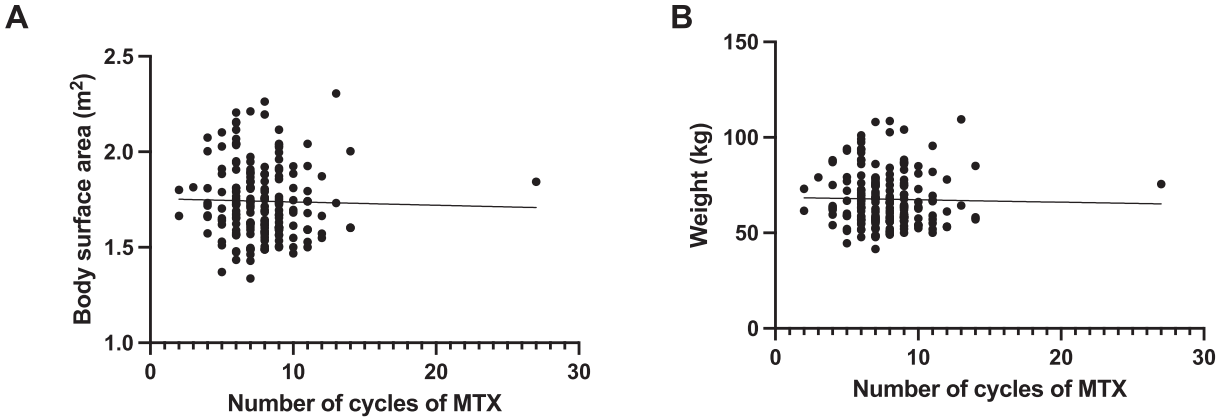

Fig. 5. The relationship between body surface area, weight and the number of methotrexate cycles required to achieve a complete treatment response using linear regression analysis. A: Body surface area. B: Weight. Linear regression output is plotted ($n = 178$).
Key: BSA, body surface area; CR, complete response; kg, kilograms; MTX, methotrexate.

confer meaningful clinical relevance. A future study directly measuring plasma drug levels in LR-GTN patients would help to account for this variability and further explore the role of BSA-based dosing. This technique has previously been proposed as a means of chemotherapeutic drug dosing [9].

The main limitation of our study involved the retrospective design, a common problem in GTN research. Sufficiently powered, prospective studies are difficult to design, due to the low incidence of GTN; indeed, the MITO study [20], one of the largest, multicentre studies in the field, was also retrospective. Despite using 47 years of data in our study, patient numbers were still low. This was compounded by the number of excluded patients due to incomplete or missing height and weight data, which likely arose due to the use of a flat-dose MTX-FA regimen, obviating the clinical need to collect or record such data. Incomplete and missing data affected a higher proportion of CR compared to TR patients, leading to inclusion bias. This also explained the lower-than-expected CR rates (49%) amongst the included cohort ($n = 364$), whilst the CR rate for all identified patients (64%, $n = 935$) was in keeping with previous literature [11,21,29–33]. Reassuringly, the FIGO scores of the included (median = 3, IQR 2–4) and excluded patients (median = 3, IQR 2–4) were comparable. Although this study involved a single centre, the results are internationally translatable to other centres which adopt the same 8-day 50 mg IM MTX/15 mg oral folinic acid regimen.

In conclusion, our study supports current UK practice using first-line flat-dose 50 mg MTX as the 8-day MTX-FA regimen in LR-GTN patients, when a fixed dose of folinic acid is used. Given these findings, height and weight do not need to be routinely measured prior to initiating low-risk chemotherapeutic treatment. Future studies could investigate the role of more accurate drug dosing using plasma derived MTX levels in predicting CR to first-line MTX-FA.

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Declaration of Competing Interest

MCW reports consulting fees from Easai, Pfizer, Gilead, Novartis, Genomic Health and Roche, personal fees and non-financial support from Lilly outside the submitted work. The remaining authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.11.025.

References

[1] M.J. Seckl, N.J. Sebire, R.S. Berkowitz, Gestational trophoblastic disease, Lancet 376 (9742) (2010) 717–729.
[2] J.R. Lurain, Treatment of metastatic gestational trophoblastic neoplasia, in: B.W. Hancock, M.J. Seckl, R.S. Berkowitz (Eds.), Gestational Trophoblastic Disease, 4th ed.ISSTD, 2015.
[3] J. Brown, R.W. Naumann, M.J. Seckl, J. Schink, 15 years of progress in gestational trophoblastic disease: scoring, standardization, and salvage, Gynecol. Oncol. 144 (1) (2017) 200–207, https://doi.org/10.1016/j.ygyno.2016.08.330.
[4] V.L. Parker, A.A. Pacey, J.E. Palmer, J.A. Tidy, M.C. Winter, B.W. Hancock, Classification systems in gestational trophoblastic neoplasia - sentiment or evidenced based? Cancer Treat. Rev. 56 (2017) 47–57.
[5] M.C. Winter, Treatment of low-risk gestational trophoblastic neoplasia, Best Prac. Res. Clin. Obstet. Gynaecol. 74 (2021 Jul) 67–80.
[6] N. Graf, K. Winkler, M. Betlemovic, N. Fuchs, U. Bode, Methotrexate pharmacokinetics and prognosis in osteosarcoma, J. Clin. Oncol. 12 (7) (1994) 1443–1451.
[7] W.E. Evans, W.R. Crom, M. Abromowitch, R. Dodge, A.T. Look, W.P. Bowman, et al., Clinical pharmacodynamics of high-dose methotrexate in acute lymphocytic leukemia. Identification of a relation between concentration and effect, N. Engl. J. Med. 314 (8) (1986) 471–477.
[8] P.R. Przekop, H. Tulgan, A.A. Przekop, M. Glantz, Adverse drug reaction to methotrexate: Pharmacogenetic origin, J. Am. Osteopath. Assoc. 106 (12) (2006) 706–707.
[9] P. Canal, E. Chatelut, S. Guichard, Practical treatment guide for dose individualisation in cancer chemotherapy, Drugs. 56 (6) (1998) 1019–1038.
[10] S.A. Kaestner, G.J. Sewell, Chemotherapy dosing part I: scientific basis for current practice and use of body surface area, Clin. Oncol. 19 (1) (2007) 23–37.
[11] M.C. Winter, J.A. Tidy, A. Hills, J. Ireson, S. Gillett, K. Singh, et al., Risk adapted single-agent dactinomycin or carboplatin for second-line treatment of methotrexate resistant low-risk gestational trophoblastic neoplasia, Gynecol. Oncol. 143 (3) (2016) 565–570.
[12] RCOG, Diagnosis and Management of Ectopic Pregnancy Guideline number 21, BJOG Int. J. Obstet. Gynaecol. 123 (13) (2016) e15–e55.
[13] S.D. Pan, L.L. Zhu, M. Chen, P. Xia, Q. Zhou, Weight-based dosing in medication use: what should we know? Patient Prefer. Adherence. 10 (2016) 549–560.
[14] J. Tidy, M. Winter, K. Singh, J. Ireson, S. Gillet, A. Hills, Gestational Trophoblastic Neoplasia: a Guide To Management At Weston Park Hospital [Internet], Sheffield Teaching Hopsitals Foundation Trust (STHFT), 2019, Available from https://stdc.group.shef.ac.uk/resources/5_4_1_GestationlTrophoblasticNeoplasiaGuidetoManagement.pdf.
[15] M.J. Seckl, N.J. Sebire, R.A. Fisher, F. Golfier, L. Massuger, C. Sessa, Gestational trophoblastic disease: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 24 Suppl 6 (2013) ei39–50.
[16] A. Santaballa, Y. García, A. Herrero, N. Laínez, J. Fuentes, A. De Juan, et al., SEOM clinical guidelines in gestational trophoblastic disease (2017), Clin. Transl. Oncol. 20 (2018) 38–46.
[17] C. Tempfer, L.C. Horn, S. Ackermann, M.W. Beckmann, R. Dittrich, J. Einenkel, et al., Gestational and non-gestational trophoblastic DiseaseGuideline of the DGGG, OEGGG and SGGG (S2k level, AWMF registry no. 032/049, December 2015), Geburtshilfe Frauenheilkd. 76 (2) (2016) 134–144.
[18] N.R. Abu-Rustum, C.M. Yashar, S. Bean, K. Bradley, S.M. Campos, H. Sook Chon, et al., Gestational trophoblastic neoplasia, version 2. 2019, NCCN clinical practice guidelines in oncology, JNCCN J. Natl. Compr. Cancer Netw. 17 (11) (2019) 1374–1391.
[19] I. Niemann, L.O. Vejerslev, L. Frøding, J. Blaakær, L.L. eth Maroun, E.S. tæhr Hansen, et al., Gestational trophoblastic diseases - clinical guidelines for diagnosis, treatment, follow-up, and counselling, Dan. Med. J. 62 (11) (2015), A5082.
[20] G. Mangili, R. Cioffi, S. Danese, L. Frigerio, G. Ferrandina, G. Cormio, et al., Does methotrexate (MTX) dosing in a 8-day MTX/FA regimen for the treatment of low-risk gestational trophoblastic neoplasia affect outcomes? The MITO-9 study, Gynecol. Oncol. 151 (3) (2018) 449–452.
[21] I.A. McNeish, S. Strickland, L. Holden, G.J.S. Rustin, M. Foskett, M.J. Seckl, 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. 20 (7) (2002) 1838–1844.
[22] R. Mosteller, Simplified calculation of body-surface area, N. Engl. J. Med. 317 (17) (1987) 1098.
[23] F. Khan, J. Everard, S. Ahmed, R.E. Coleman, M. Aitken, B.W. Hancock, Low-risk persistent gestational trophoblastic disease treated with low-dose methotrexate: efficacy, acute and long-term effects, Br. J. Cancer 89 (12) (2003) 2197–2201.
[24] J.R. Lurain, Gestational trophoblastic disease II: classification and management of gestational trophoblastic neoplasia, Am. J. Obstet. Gynecol. 204 (1) (2011) 11–18.
[25] I. Maestá, N.S. Horowitz, D.P. Goldstein, M.R. Bernstein, L.A.C. Ramírez, J. Moulder, et al., Response to chemotherapy in overweight/obese patients with low-risk gestational trophoblastic neoplasia, Int. J. Gynecol. Cancer 25 (4) (2015 May) 734–740.
[26] W.D. Kang, H.S. Choi, S.M. Kim, Weekly methotrexate (50mg/m(2)) without dose escalation as a primary regimen for low-risk gestational trophoblastic neoplasia, Gynecol. Oncol. 117 (3) (2010 Jun) 477–480.
[27] N.C. Gleeson, M.A. Finan, J.V. Fiorica, W.S. Robert, M.S. Hoffman, J. Wilson, Nonmetastatic gestational trophoblastic disease. Weekly methotrexate compared with 8-day methotrexate-folinic acid, Eur. J. Gynaecol. Oncol. 14 (6) (1993) 461–465 1993/01/01 ed.
[28] R.A. Abrão, J.M. de Andrade, D.G. Tiezzi, H.R.C. Marana, F.J.C. dos Reis, W.S. Clagnan, Treatment for low-risk gestational trophoblastic disease: comparison of single-agent methotrexate, dactinomycin and combination regimens, Gynecol. Oncol. 108 (1) (2008) 149–153.
[29] T.A. Lawrie, M. Alazzam, J. Tidy, B.W. Hancock, R. Osborne, First-line chemotherapy in low-risk gestational trophoblastic neoplasia, Cochrane Database Syst. Rev. 2016 (6) (2016), CD007102.
[30] J. Hao, W. Zhou, M. Zhang, H. Yu, T. Zhang, R. An, et al., Direct comparisons of efficacy and safety between actinomycin-D and methotrexate in women with low-risk gestational trophoblastic neoplasia: a meta-analysis of randomized and high-quality non-randomized studies, BMC Cancer 21 (1) (2021 Dec) 1122.
[31] W.B. Growdon, A.J. Wolfberg, D.P. Goldstein, C.M. Feltmate, M.E. Chinchilla, E.S. Lieberman, et al., Evaluating methotrexate treatment in patients with low-risk postmolar gestational trophoblastic neoplasia, Gynecol. Oncol. 112 (2) (2009 Feb) 353–7.
[32] A. Sita-Lumsden, D. Short, I. Lindsay, N.J. Sebire, D. Adjogatse, M.J. Seckl, et al., Treatment outcomes for 618 women with gestational trophoblastic tumours following a

molar pregnancy at the Charing Cross Hospital, 2000–2009, Br. J. Cancer 107 (11) (2012 Nov 20) 1810–1814.
[33] R.J. Osborne, V. Filiaci, J.C. Schink, R.S. Mannel, A. Alvarez Secord, J.L. Kelley, et al., Phase III trial of weekly methotrexate or pulsed dactinomycin for low-risk gestational trophoblastic neoplasia: a gynecologic oncology group study. Journal of clinical oncology, Off. J. Am. Soc. Clin. Oncol. 29 (7) (2011 Mar 1) 825–831.

Glossary

Gestational trophoblastic neoplasia – an umbrella term for multiple types of invasive tumour, arising from placental tissue, which typically occur after a molar pregnancy.