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ORIGINAL ARTICLE

Calculated versus measured creatinine clearance for dosing methotrexate in the treatment of primary central nervous system lymphoma

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Abstract
Background High-dose methotrexate (HDMTX) ($\geq$3 g/m^2), the cornerstone of therapy for primary CNS lymphoma (PCNSL), is commonly dosed using a measured 24 h creatinine clearance (CrCl) every 2–4 weeks. Because these collections are cumbersome and at times unreliable, the use of a calculated CrCl was evaluated as a potential alternative.
Methods A retrospective analysis was performed on data from all 287 treatment cycles from the 25 patients with PCNSL who participated in a multi-center phase II clinical trial of HDMTX conducted by the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium.
Results The 25 patients had a median age of 61 years (range 32–75). Seventeen (68%) were men. The patients received a median of 14 (range 2–21) HDMTX treatments. For 256 of 287 treatments (89%), data were available to compare the measured and calculated (using the Cockcroft–Gault equation) CrCl. The average measured CrCl was 93 ml/min (95% CI, 89–96 ml/min), and the average calculated CrCl was 107 ml/min (95% CI, 102–112 ml/min). The Pearson correlation coefficient (r) was 0.49 ($P < 0.0001$) between the measured and calculated CrCl. The average MTX dose determined using measured CrCl was 14.1 g (95% CI, 13.6–14.5 g), and the average MTX dose determined using calculated CrCl was 14.7 g (95% CI, 14.2–15.1 g). MTX doses based on measured and calculated CrCl were significantly correlated ($r = 0.72$, $P < 0.0001$). Of the 256 HDMTX treatments evaluated, 158 (62%) had reliable 48 h serum MTX levels documented. Forty-seven levels (30%) were within target range (0.3–1 μmol/l), 99 levels (62%) were below target range (<0.3 μmol/l), 12 levels (8%) were in the range associated with mild toxicity range (>1–3 μmol/l), and no levels were in the range associated with severe toxicity (>3 μmol/l). Of these 158 treatments, the use of a calculated rather than measured CrCl would have yielded an identical MTX dose for 48 treatments (30%), a higher MTX dose for 62 treatments (40%), and a lower MTX dose for 48 treatments (30%). This distribution was not significantly different among the subsets of below target, within target range, and above target MTX levels ($P = 0.87$).
Conclusions In this cohort of patients with PCNSL, there is significant correlation between the calculated and measured CrCl. MTX doses determined using calculated and measured CrCl are not significantly different. For these patients, there is no clear association between the method of determining CrCl and serum MTX levels. As a result, calculated CrCl is a reasonable alternative to measured CrCl in this patient population and would avoid the inconvenience and potential inaccuracies associated with measured CrCl.

Keywords Primary central nervous system lymphoma · High-dose methotrexate · Calculated creatinine clearance · Cockcroft–Gault formula · Measured creatinine clearance · 24 h urine collection

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Abbreviations

PCNSL	Primary central nervous system lymphoma
HDMTX	High-dose methotrexate
MTX	Methotrexate
NABTT	New Approaches to Brain Tumor Therapy
CrCl	Creatinine clearance
Cr	Creatinine
ABW	Actual body weight
BSA	Body surface area
GFR	Glomerular filtration rate
^{99m}Tc-DTPA	Technetium-99m diethylenetriamine penta-acetic acid

Introduction

A high-dose methotrexate (HDMTX)-based regimen is now standard therapy for patients with primary central nervous system lymphoma (PCNSL) [18]. In a phase II clinical trial of MTX 8 g/m^2 as single-agent therapy, 52% of patients achieved a complete response, median progression free survival was 12.8 months, median overall survival was 55 months, and toxicity was modest [1]. However, HDMTX-based therapy is intensive, requiring a 4–5 day hospitalization for treatment cycles, which are administered every 14–28 days. To prevent MTX-associated complications—which can include myelosuppression, mucositis, and pulmonary, hepatic, and renal toxicity—patients require intravenous hydration, urine alkalinization, precisely timed doses of leucovorin rescue, and monitoring of daily serum MTX levels. Additionally, the MTX dose is typically based on a measured creatinine clearance (CrCl). Patients must therefore submit a 24 h urine collection prior to each treatment cycle. This process is cumbersome and often unreliable. Incomplete or misplaced collections can lead to treatment delays.

In contrast to the complexities of measured CrCl, a calculated CrCl can be determined using widely known formulae that rely on readily available information such as age, gender, weight, and serum creatinine. Currently, most chemotherapy regimens requiring a CrCl for dosing (typically those with drugs that are cleared by or toxic to the kidneys) use a calculated CrCl. Numerous clinical studies have specifically addressed this issue for a variety of malignancies and therapies [3, 5, 10, 14, 22, 25]. However, published studies of HDMTX for PCNSL have used only the measured CrCl for drug dosing [1, 9, 12]. To evaluate the use of a calculated CrCl in this population, we performed a retrospective study of 25 adult patients with PCNSL who received a total of 287 cycles of HDMTX in a phase II clinical trial [1]. By analyzing serum MTX levels, we also assessed the potential clinical impact of each method of determining CrCl.

Materials and methods

HDMTX phase II clinical trial

In a phase II clinical trial of single-agent HDMTX for PCNSL conducted by the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium, patients received induction HDMTX (8 g/m^2) every 14 days until achieving a complete response or a maximum of 8 cycles. If complete response was attained, two consolidation cycles of HDMTX were given every 14 days, followed by 11 maintenance cycles of HDMTX every 28 days. Patients were admitted to the hospital for each treatment cycle. Intravenous hydration and oral or intravenous sodium bicarbonate were administered to generate a urine output of more than 100 ml/h and a urine pH $\geq$ 7. MTX 8 g/m^2 was infused over 4 h, serum MTX levels were obtained every 24 h, and calcium leucovorin rescue was started 24 h after MTX infusion and continued until the MTX level was less than 0.10 μmol/l.

The administered MTX dose was determined using measured CrCl, for which patients submitted an outpatient 24 h urine collection prior to each treatment cycle. The MTX dose was reduced by the percentage reduction of the measured CrCl below 100. For example, a CrCl of 80 ml/min led to a 20% MTX dose reduction. Treatment was not administered if the measured CrCl was less than 50 ml/min.

Retrospective chart review

The Institutional Review Board of Johns Hopkins University approved this study. For each patient in the NABTT phase II clinical trial of HDMTX, the following data were obtained: age, gender, height, and total number of MTX cycles. For each treatment cycle, the following data were obtained: patient weight, serum creatinine concentration, 24 h urine volume, 24 h urine creatinine concentration, and 48 h serum MTX level.

As performed in the NABTT phase II clinical trial, the measured CrCl was determined from the 24 h urine collection as follows: CrCl (ml/min) = [urine Cr concentration (mg/dl) × urine volume (ml)]/[serum creatinine concentration (mg/dl) × time (1,440 min)]. This was then corrected to a body surface area (BSA) of 1.73 m^2 as follows: corrected CrCl = CrCl × (1.73 m^2/patient BSA). BSA was calculated using the Mosteller

method [17]. The calculated CrCl was determined using the Cockcroft–Gault formula: CrCl (ml/min) = [(140−age) × (weight)]/(serum creatinine concentration) × (72)] (×0.85 for women) [4]. Predicted total urine creatinine per kg body weight (an assessment of the completeness of a 24 h urine collection) was determined using the equation from the regression line of mean values in the Cockcroft–Gault study: [28–(0.2 × age)] (×0.85 for women) [4]. Forty-eight hour serum MTX levels were designated below target (≤0.3 μmol/l), within target range (>0.3–1 μmol/l), in the range associated with mild toxicity (>1–3 μmol/l), or in the range of severe toxicity (>3 μmol/l) based on the MTX elimination curve employed in the NABTT phase II HDMTX clinical trial [1, 19].

Statistical methods

Statistical analyses were conducted using SAS software, version 9.1 (SAS Institute, Cary, NC). Continuous variables were summarized by using mean ± standard deviation or mean and 95% confidence intervals. Categorical variables were illustrated by proportions along with estimated 95% confidence intervals using exact binomial distribution. The Pearson product-moment correlation coefficient was used to assess an association between continuous variables. Fisher's exact test was used to examine an association between categorical data. All statistical tests were two-sided and reported with exact *P*-values.

Results

All 25 patients in the NABTT phase II clinical trial were included in this analysis. They had a median age of 61 years (range 32–75 years). Seventeen patients (68%) were men. A total of 287 HDMTX cycles were administered. Patients received a median of 14 cycles (range 2–21 cycles). Other clinical characteristics are listed in Table 1.

For 256 of 287 treatment cycles (89%), sufficient data were available to compare measured and calculated CrCl. The mean measured CrCl was 93 ml/min (95% CI, 89–96 ml/min), and the mean calculated CrCl was 107 ml/min (95% CI, 102–112 ml/min). The Pearson correlation coefficient (*r*) was 0.49 ($P < 0.0001$) (Fig. 1). MTX doses based on measured and calculated CrCl had a Pearson correlation coefficient (*r*) of 0.72 ($P < 0.0001$) (Fig. 2). The average MTX doses using each method were not significantly different: 14.1 g (95% CI, 13.6–14.5 g) using measured CrCl versus 14.7 g (95% CI, 14.2–15.1 g) using calculated CrCl.

Table 1 Characteristics of the 25 patients who participated in a phase II clinical trial of HDMTX for PCNSL

Total patients	25
Median age (years)	61 (range 32–75)
Men	17 (68%)
Total MTX cycles administered	287
Median number of MTX cycles received	14 (range 2–21)
Average weight	88.8 ± 16.0 kg
Average body surface area (BSA)	2.1 ± 0.2 m^2
Average serum Cr	1.0 ± 0.3 mg/dl
Average measured CrCl	93 ± 30 ml/min
Average calculated CrCl	107 ± 43 ml/min
Average MTX dose using measured CrCl	14.1 ± 3.6 g
Average MTX dose using calculated CrCl	14.7 ± 3.8 g
Average 48h MTX level	0.40 ± 0.40 μmol/l

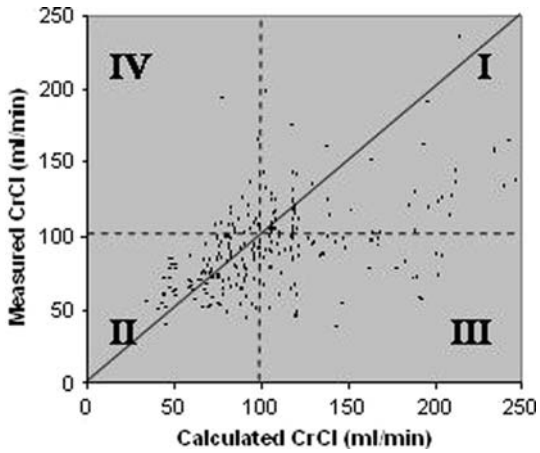

Fig. 1 Calculated versus measured CrCl for 256 cycles of HD-MTX. Pearson correlation coefficient (*r*) is 0.49 ($P < 0.0001$). MTX is dose-reduced for CrCl < 100 ml/min. In quadrant I ($N = 64$), both the measured and calculated CrCl are ≥100 ml/min, so neither method would lead to a dose reduction. In quadrant II ($N = 115$), both the measured and calculated CrCl are <100 ml/min and would require dose reduction. In quadrant III ($N = 56$), the measured CrCl is <100 ml/min, but the calculated CrCl is ≥100 ml/min, so only the measured CrCl would lead to a dose reduction. In quadrant IV ($N = 20$), the opposite situation occurs, and only the calculated CrCl leads to a dose reduction

Serum MTX levels were reviewed to assess the clinical impact of using calculated CrCl. Documented 48 h MTX levels were available for 158 of 256 treatment cycles (62%). The mean 48 h MTX level was 0.40 μmol/l. Ninety-nine levels (62%) were below target range (<0.3 μmol/l), 47 levels (30%) were in the target range (0.3–1 μmol/l), 12 levels (8%) were in the range associated with mild toxicity (>1–3 μmol/l), and no levels fell in the range of severe toxicity (>3 μmol/l). Treatment cycles were grouped according to whether the use of a

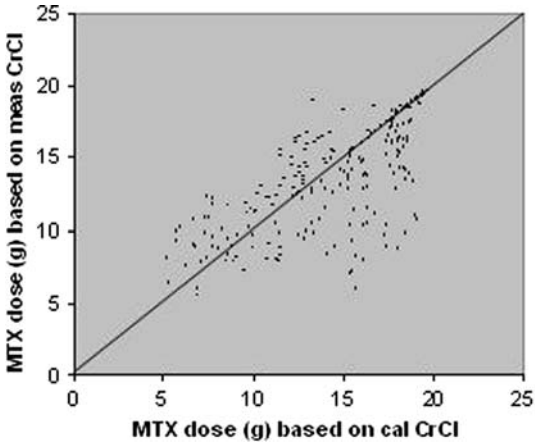

Fig. 2 MTX doses based on calculated versus measured CrCl for 256 cycles of HDMTX. Pearson correlation coefficient (r) is 0.72 ($P < 0.0001$)

calculated CrCl would have increased, decreased, or not changed the MTX dose administered that cycle (Fig. 3). Sixty-two cycles (40%) (with a mean 48 h MTX level of 0.36 μmol/l) would have had a higher MTX dose. Forty-eight cycles (30%) (with a mean 48 h MTX level of 0.47 μmol/l) would have had a lower MTX dose. Forty-eight cycles (30%) (with a mean 48 h MTX level of 0.30 μmol/l) would have had the same MTX dose. Among the subsets of MTX levels (below target, target, mild toxicity), the effect of calculated CrCl on MTX dosing was not significantly different ($P = 0.87$).

To determine the completeness of patients' 24 h urine collections, the 24 h total urine creatinine (per kg body weight) was determined for each treatment cycle (Fig. 4). This parameter is expected to remain relatively constant over time, regardless of renal function and urine volume, and serves as the underlying premise for calculated CrCl equations [4]. Data were available to perform this calculation for 247 of 256 treatment cycles (96%), representing 24 of 25 patients (96%). Of the 24 evaluable patients, only 2 (8%) had ≤20% variation in total urine creatinine among their urine collections over the course of treatment, the standard threshold used to deem consistent a patient's 24 h urine collections [4, 5, 25].

Discussion

Physicians have long sought to determine patients' renal function in an accurate yet convenient manner. Studies such as inulin or technetium-99 m diethylenetriamine penta-acetic acid (^{99m}Tc-DTPA) clearance have provided the most reliable means of determining glomerular filtration rate (GFR). However, these are costly and invasive tests, requiring the administration

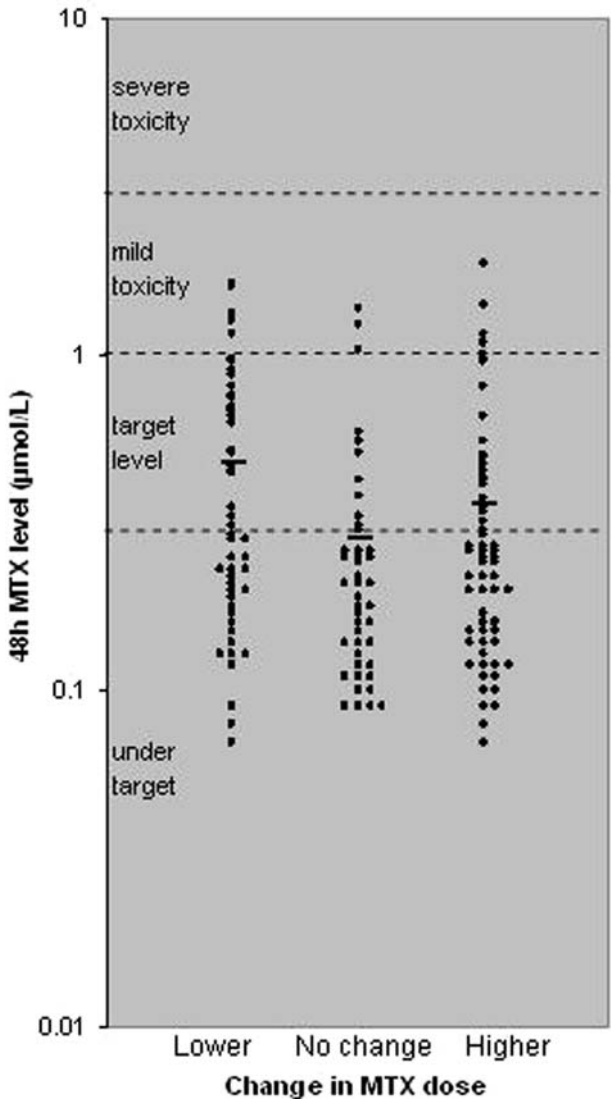

Fig. 3 One hundred and fifty-eight 48 h serum MTX levels from the phase II HDMTX trial. Levels are grouped according to how a calculated CrCl would affect MTX dosing

of exogenous substances, catheterization, and frequent blood draws. Thus, they are rarely used in everyday clinical practice. In their place, measured CrCl (based on a 24 h urine collection) and calculated CrCl (using equations incorporating readily available patient characteristics) have become the standard clinical GFR assessments. While measured CrCl has traditionally been considered the more reliable of these two methods, the required 24 h urine collections are cumbersome and inconvenient. Furthermore, when they are performed outside the context of an inpatient clinical research unit, difficulties in the timing and completeness of collection may render them inaccurate [20].

Despite the motivated patient population and close patient supervision characteristic of a clinical trial, only

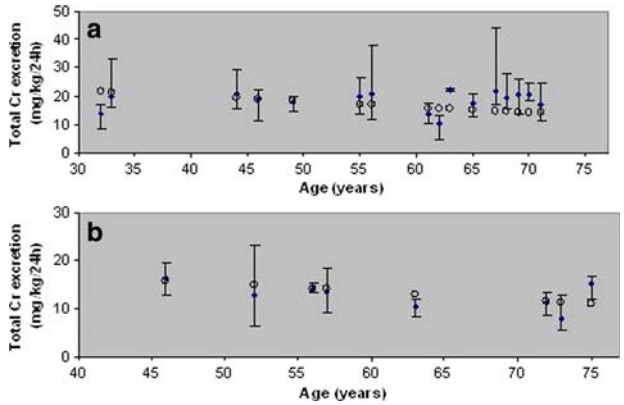

Fig. 4 Total Cr excretion per body weight (mg/kg) from 24 h urine collections for 16 men (**a**) and 8 women (**b**). *Filled circles* mean value for each patient. *Open circles* expected value for each patient based on gender and age (see text). *Error bars* denote the range of values for each patient over the course of treatment

8% of patients in this study had relatively constant total creatinine in their urine collections. As shown in Fig. 4, total daily creatinine excretion, a parameter expected to remain relatively constant over time for an individual patient (independent of urine volume and renal function), varied widely for most patients in this cohort. The effect of unreliable urine collections on the determination of CrCl can be seen in the following example. One patient in this study submitted a 24 h urine collection with a total creatinine excretion of 6.41 mg/kg before her fifth MTX cycle, and one with a total creatinine excretion of 16.18 mg/kg before her ninth cycle. These yield measured CrCl of 46 and 116 ml/min, respectively, a discrepancy which suggests highly unstable renal function. Yet for these treatment cycles she had identical serum creatinine values (0.7 mg/dl) and her weight varied by less than 1%. The patient's renal function may be more accurately represented by her calculated CrCl values for these treatment cycles (119 and 120 ml/min). Similar observations have led a number of authors to conclude that calculated CrCl is a superior means of determining renal function in actual clinical practice [16, 20, 23].

Over the past 30 years, the formula devised by Cockcroft and Gault [4] has become the most widely used means to calculate CrCl without a 24 h urine collection. The well-known equation has been evaluated in multiple clinical contexts. Within the field of oncology, in which multiple chemotherapeutic agents are either cleared by or toxic to the kidneys, a number of populations have been studied. The correlation between calculated and measured CrCl has been evaluated in women with gynecologic cancer receiving platinum-based chemotherapy [3, 14, 25], in children undergoing bone marrow transplant [11], and in patients with germ cell, bladder and head and neck cancers [5]. Calculated CrCl now replaces measured CrCl in almost all oncology settings. This is the first study to evaluate the correlation between measured and calculated CrCl in patients with PCNSL receiving HDMTX.

In this cohort of patients, there was a significant correlation between measured and calculated CrCl. There was also a significant correlation between the MTX doses determined from each method. However, because no gold-standard GFR assessment (eg, inulin or ^{99m}Tc-DTPA clearance) was performed in these patients, it is not possible to determine whether measured or calculated CrCl more closely represents true renal function in these patients. Given this limitation, a recent study of patients receiving the related drug pemetrexed, a renally cleared multi-target folate antagonist, may be instructive [15]. In that series, which included 47 patients (mean age 62 years, range 25–79 years) with normal and impaired renal function (CrCl as low as 19 ml/min), the Cockcroft–Gault formula was highly correlated with ^{99m}Tc-DTPA clearance ($r = 0.86$). As a result, the authors accepted calculated CrCl as equivalent to direct GFR measurement.

While numerous studies have compared measured and calculated CrCl, this is the first study to use serum drug levels to explore the clinical significance of each method. Such an analysis was possible because serum MTX levels are routinely obtained during the administration of HDMTX. They are drawn daily starting 24 h after MTX infusion and guide the administration of leucovorin rescue, the degree of urine alkalinization, and the duration of hospitalization. In this study, the 48 h MTX level was selected for analysis for the following reasons: 48 h levels tend to have less variation than 24 h levels; clinical MTX toxicity depends primarily on the duration of exposure to above-threshold concentrations rather than on peak concentration [2]; and studies of MTX toxicity generally employ the 48 h MTX level [24]. In our analysis, MTX levels not drawn at 48 h, while useful clinically when plotted on the expected MTX elimination curve, were not included.

HDMTX was administered safely, with only 12 of 158 cycles (8%) having levels in the range of mild toxicity, and no cycles with levels in the range of severe toxicity. This correlates with the clinical findings of the NABTT clinical trial, in which there were only 18 episodes of grade 3–4 toxicity after 287 treatment cycles [1]. In Fig. 3, MTX levels are grouped according to how the use of a calculated CrCl would affect MTX dosing. If calculated CrCl were used in place of measured

CrCl, the MTX dose would be higher in 40% of cycles, the same in 30% of cycles, and lower in 30% of cycles. This effect does not differ significantly among subsets of treatment cycles grouped according to MTX level (below target, target level, and mild toxicity) ($P = 0.87$). Along with the high correlation between MTX doses determined from measured and calculated CrCl, this suggests that using calculated CrCl to dose MTX is not likely to change the overall distribution of MTX levels.

Because this potentially toxic treatment regimen was well tolerated in the NABTT clinical trial, the possibility of increased toxicity with alternative dosing presents a valid concern. That is, could the use of calculated CrCl to dose MTX lead to MTX levels in the range of severe toxicity? As shown in Fig. 3, only 4 of 158 cycles (3%) have levels in the range of mild toxicity and would have higher MTX doses if calculated CrCl were used. Alternatively, using calculated CrCl might benefit the 39 cycles (25%) with levels in the below target range that would have higher MTX doses. However, the complex associations between renal function, MTX dose, and serum MTX levels limit such inferences. For instance, renal clearance, the primary component of MTX elimination, does not depend exclusively on filtration. As renal function worsens or MTX concentrations rise, renal tubular secretion of MTX increases [2], a capacity that is not reflected by GFR. This may in part explain why a study of children with acute lymphocytic leukemia found no association between CrCl and MTX levels [13]. In contrast, the association between MTX levels and clinical outcome appears clearer. Multiple studies have shown that serum MTX levels predict both therapeutic efficacy [6–8, 21] and toxicity [24].

This study represents the first evaluation of the use of calculated CrCl in individuals with PCNSL receiving HDMTX therapy. In this population, calculated and measured CrCl are significantly correlated. It cannot be determined from this study which CrCl method more closely represents true renal function. Importantly, data from this study suggests that outpatient 24 h urine collections, the basis for measured CrCl, are inconsistent in the vast majority of patients, even in the supervised setting of a clinical trial. Average MTX doses determined from calculated and measured CrCl are not significantly different, and the effect of using calculated CrCl to determine MTX doses is similar regardless of serum MTX level. Therefore, for these patients, there is no clear association between the method of determining CrCl and serum MTX levels. In conclusion, calculated CrCl appears to be a reasonable alternative to measured CrCl in this patient population and would avoid the inconvenience and potential inaccuracies associated with measured CrCl.

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