Area under the curve of methotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas

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Although high-dose methotrexate (HD-MTX) is the most effective drug against primary CNS lymphomas (PCNSL), outcome-determining variables related to its administration schedule have not been defined. The impact on toxicity and outcome of the area under the curve (AUCMTX), dose intensity (DIMTX) and infusion rate (IRMTX), as well as the plasmatic creatinine clearance (CLcrea) was investigated in a retrospective series of 45 PCNSL patients treated with three different HD-MTX-based combinations. Anticonvulsants were administered in 31 pts (69%). Age > 60 years, anticonvulsant therapy, slow IRMTX (<800 mg m⁻² h⁻¹), and reduced DMTX (<1000 mg m⁻² wk⁻¹) were significantly correlated with low AUCMTX values. Seven patients (16%) experienced severe toxicity, which was independently associated with slow CLcrea. A total of 18 (40%) patients achieved complete remission after chemotherapy, which was independently associated with slow CLcrea. In all, 22 patients were alive at a median follow-up of 31 months, with a 3-year OS of 40±9%; slow CLcrea and AUCMTX >1100 µmol h⁻¹ were independently associated with a better survival. Slow CLcrea and high AUCMTX are favourable outcome-determining factors in PCNSL, while slow CLcrea is significantly related to higher toxicity. AUCMTX significantly correlates with age, anticonvulsant therapy, IRMTX, and DIMTX. These findings, which seem to support the choice of an MTX dose ≥3 g m⁻² in a 4–6-h infusion, every 3–4 weeks, deserve to be assessed prospectively in future trials. MTX dose adjustments in patients with fast CLcrea should be investigated.

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PATIENTS AND METHODS

Study population
A questionnaire requesting epidemiological, clinical, histopathological, therapeutic, and survival data of immunocompetent patients with PCNSL treated with HD-MTX-based primary chemotherapy.
considering the capacity of some of these drugs to interfere with MTX metabolism (Jacobs et al., 1976). This study conformed to the tenets of the Declaration of Helsinki and all the patients accessioned provided signed informed consent to the treatment. This consent extended to the use of biological, histopathological, radiological, biochemical, and clinical data for scientific purposes.

**MTX variables**

\(\text{CL}_{\text{crea}}\) value, determined before the start of chemotherapy, was obtained by the formula of Cockcroft and Gault (1976):

\[
\text{CL}_{\text{crea}} \text{ (ml min}^{-1} \text{)} = \frac{(140 – \text{age}) \times \text{body weight}}{\text{creatinine serum level} \times 72}
\]

\(\text{CL}_{\text{crea}}\) value in females was considered as 85% of the value for males.

The MTX variables investigated were AUC\(_{\text{MTX}}\), DI\(_{\text{MTX}}\), and IR\(_{\text{MTX}}\). The individual AUC\(_{\text{MTX}}\) (\(\mu\)mol h\(^{-1}\)) related to the first course of chemotherapy was determined according to a one-compartment model by using the statistical population pharmacokinetic program P-PHARM-Version 3 (InnaPhase, 77420 Champs-sur-Marne, France), considering MTX dosage and serum levels at 0, 24, 48, and 72 h after drug infusion for calculation. DI\(_{\text{MTX}}\) expressed as mg m\(^{-2}\) wk\(^{-1}\), was calculated by the Hryniuk method (Hryniuk and Goodyear, 1990). This was a ratio between the total dose of MTX administered (mg m\(^{-2}\)) and the treatment duration expressed in days divided by 7. Treatment duration was calculated from the first day of the first course to the 22nd or 29th day of the last course (respectively for regimens administered every 3 or 4 weeks) (Hryniuk and Goodyear, 1990). The IR\(_{\text{MTX}}\) expressed as mg m\(^{-2}\) h\(^{-1}\), was defined as the MTX dose (mg m\(^{-2}\)) administered per hour during the first chemotherapy course.

**Statistical considerations**

Correlations between AUC\(_{\text{MTX}}\) and the other variables were analysed by the Spearman test. The impact of studied variables on severe toxicity and complete response rate was analysed by logistic regression. Severe toxicity was defined by the onset of one of two major events: toxic death or interruption of chemotherapy due to toxicity. Complete response was defined as the disappearance of all evidence of lymphoma.

\(\text{CL}_{\text{crea}}\), AUC\(_{\text{MTX}}\), DI\(_{\text{MTX}}\), and IR\(_{\text{MTX}}\) were firstly analysed as continuous variables; then, quartiles values were applied as cutoff to differentiate the risk groups (categorical variables): lower quartile for \(\text{CL}_{\text{crea}}\) (85 ml min\(^{-1}\)) and upper quartile for DI\(_{\text{MTX}}\) (1000 mg m\(^{-2}\) wk\(^{-1}\)), for AUC\(_{\text{MTX}}\) (1100 \(\mu\)mol h\(^{-1}\)), and for IR\(_{\text{MTX}}\) (800 mg m\(^{-2}\) h\(^{-1}\)).

Survival curves were generated by the Kaplan–Meier method. The overall survival (OS) was calculated from diagnosis to the date of death or the last date of follow-up. Impact on survival of clinical and therapeutic variables was evaluated through the log-rank test.

**RESULTS**

**Study group**

The study group consisted of 45 patients treated between 1995 and 2001 (Calderoni and Aebi 2002; Pasini et al., 2002; Ferreri et al., 2002a). Patients’ characteristics and extent of disease at diagnosis are summarised in Table 1. Chemotherapy regimens and MTX administration schedules are reported in Table 2. All patients were treated with adequate pre-MTX hydration, urinary alkalinisation, and escalated leucovorin dosages according to MTX serum levels. Dehydration, aciduria, renal or cardiac dysfunction, pleural effusion, or gastrointestinal tract obstruction were excluded before commencing treatment in all cases. Post-chemotherapy RT, which

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**Table 1** Patients’ characteristics and extension of disease at diagnosis

| Entire series                           |   |
|----------------------------------------|---|
| No.                                    | 45|
| Median age (range)                     | (54 – 76) |
| >70 years                              | 2 (4%)|
| Males                                  | 29 (64%)|
| Performance status (ECOG score)        |   |
| 0–1                                    | 19 (42%)|
| 2                                      | 13 (29%)|
| 3                                      | 11 (24%)|
| 4                                      | 2 (4%)|
| Prior cancer*                          | 2 (4%)|
| Histotype (REAL/WHO Classification)    |   |
| Diffuse large B-cell lymphoma          | 42 (93%)|
| Anaplastic large-cell Ki1 lymphoma     | 1 (2%)|
| Unclassified                           | 2 (4%)|
| High LDH serum level<sup>6</sup>        | 13/38 (34%)|
| Intracranial disease<sup>6</sup>       | 1/30 (3%)|
| Positive CSF cytology examination<sup>6</sup> | 2/77 (7%)|
| Elevated CSF protein levels<sup>7</sup>| 13/19 (68%)|
| Multiple lesions<sup>8</sup>           | 25/45 (56%)|
| Involvement of deep structures<sup>9,10</sup> | 25/44 (57%)|

<sup>6</sup>CSF = cerebrospinal fluid. <sup>7</sup>Prior cancers: renal cell carcinoma and Waldenstrom's macroglobulinaemia. <sup>8</sup>Ratio between the number of positive cases and the number of assessed patients. <sup>9</sup>The cutoff to define normal CSF protein levels was 45 mg dl\(^{-1}\) in patients <60 years and 60 mg dl\(^{-1}\) in patients >60 years. <sup>10</sup>Deep structures of the brain: basal ganglia, corpus callosum, brain stem, and cerebellum. ECOG = Eastern Cooperative Oncology Group; LDH = Lactic Dehydrogenase; REAL = Reversed European American lymphoma.

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**Table 2** Chemotherapy regimens

| Regimen                  | No. of patients | MTX dose (mg m\(^{-2}\)) | MTX infusion (h) | MTX dose day | Other drugs | i.t. CHT | Planned no. of courses | Courses every weeks |
|--------------------------|-----------------|--------------------------|------------------|--------------|-------------|---------|------------------------|--------------------|
| MTX alone (Calderoni and Aebi, 2002) | 10              | 1000–3000                | 8000             | 4           |             | Yes/No  | 2–3                    | 4                  |
| MATILDE (Ferreri et al., 2002a) | 11              | 3500                     | 3                | 1 and 7     |             |         |                        |                    |
| MTX+AraC (Pasini et al., 2002) | 24              | 1000–2000<sup>b</sup>    | 24               |             | AraC 2 g m\(^{-2}\) × 2 d 2 | No      | 3                     | 3                  |
|                          |                 |                          |                  |             | IDA 15 mg m\(^{-2}\) × d 1 |         |                        |                    |
|                          |                 |                          |                  |             | TTP 25 mg m\(^{-2}\) × 3 |         |                        |                    |
|                          |                 |                          |                  |             | AraC 2 g m\(^{-2}\) × 2 d 3 | no      | 3                     | 3                  |

<sup>b</sup>MTX = methotrexate; l.t. CHT = intrathecal chemotherapy; AraC = cytarabine; IDA = idarubicin; TTP = thiopeta. Infusion preceded by an initial MTX bolus. *Four patients received 3500–8000 mg m\(^{-2}\) in 24-h infusion. DI\(_{\text{MTX}}\) (mean ± s.d.) of the used chemotherapy regimens were 1638 ± 1642, 844 ± 180, and 780 ± 1080 mg m\(^{-2}\) week\(^{-1}\) (\(P<0.01\)), respectively, for HD-MTX alone, MATILDE, and MTX+AraC combination.
consisted of whole-brain irradiation, followed or not followed by a tumour-bed boost, was planned in all cases, but it was in fact performed as part of the first-line therapy in 31 patients, with median brain and tumour-bed doses of 36 ± 5 and 42 ± 9 Gy, and as part of salvage therapy in six cases. Anticonvulsants were administered in 31 patients (69%), and consisted of phenobarbital (100 – 150 mg d⁻¹) in 27 cases, hydantoin (100 – 300 mg d⁻¹) in two cases and carbamazepine (400 – 800 mg d⁻¹) in two cases.

**MTX parameters**

The mean value ± s.d. of CLc rea was 119 ± 57 ml min⁻¹. The mean value ± s.d. of AUCMTX was 731 ± 525 μmol h⁻¹. Patients ≤ 60 years old displayed a faster CLc rea (mean ± s.d.: 118 ± 38 vs 94 ± 28 ml min⁻¹; P = 0.01), and a higher AUCMTX (846 ± 562 vs 502 ± 359 μmol h⁻¹; P = 0.02) with respect to patients > 60. According to the PS, patients with an ECOG score of 0 – 2 displayed a CLc rea (100 ± 28 vs 112 ± 35 ml min⁻¹; P = 0.17) and a similar AUCMTX (1397 ± 1208 vs 1238 ± 836 μmol h⁻¹; P = 0.53) with respect to patients with a PS of 0 – 2. The mean value ± s.d. of DLMTX was 992 ± 1140 mg m⁻² week⁻¹. Seven patients (16%) received only one course of chemotherapy (severe toxicity in five, no response in two), 16 (36%) received two, 14 (31%) received three, and eight (18%) received more than three courses. No difference in the used MTX dose according to age or PS was observed; the proportion of patients ≤ 60 years old and > 60 treated with a dose > 3 g m⁻² was similar (47 vs 47%; P = 0.99); 53% of patients with PS 0 – 2 and 31% of patients with PS 3 – 4 received an MTX dose > 3 g m⁻² (P = 0.19). No cases of reduction of more than 25% of the MTX dose in further courses with respect to the planned dose were observed. The MTX dose of the further courses was increased by more than 25% with respect to the MTX dose of the first course in three (7%) cases. The mean value ± s.d. of IRMTX during the first chemotherapy course was 475 ± 423 mg m⁻² h⁻¹. This parameter remained unmodified during further courses in all cases.

**AUCMTX-determining variables**

Variables significantly correlated with the AUCMTX are reported in Table 3. Anticonvulsant use and age correlated inversely with AUCMTX, while a direct correlation between AUCMTX and IRMTX and DLMTX was observed. No correlation with sex, performance status (PS), and CLc rea was observed. Patients treated with MATILde chemotherapy regimen achieved significantly higher AUCMTX values.

**Severe toxicity**

The predictive value of MTX variables on severe toxicity was analysed considering toxic death (n = 2) and interruption of chemotherapy due to toxicity (n = 5) as events. Severe toxicity consisted of pulmonary thromboembolism in two cases (lethal in both), sepsis in two, acute renal failure in one, and persistent grade IV thrombocytopenia in two. These events were observed during the first two courses of chemotherapy. As reported in Table 4, CLc rea was independently associated with severe toxicity; a significantly higher toxicity rate was observed in patients with a CLc rea ≤ 85 ml min⁻¹. Importantly, a DLMTX > 1000 mg m⁻²/week, and an AUCMTX > 1100 μmol h⁻¹ were not related to a higher toxicity.

**Objective response**

After primary chemotherapy, 18 patients (40%) achieved a complete remission and 16 (36%) a partial response (overall response rate = 76%); four patients (9%) had stable disease, five (11%) experienced progressive disease, and two (4%) died of toxicity. As reported in Table 4, a slow CLc rea (≤ 85 ml min⁻¹) was significantly and independently associated with a higher complete remission rate.

**Overall survival**

A total of 26 patients experienced failure: early progression of the disease in nine cases, relapse after initial response (complete and partial) in 15 and toxic death in two cases, with a 2-year failure-free survival of 50 ± 8%. In all, 22 patients are alive (19 NED) at a median follow-up of 31 months (range 4 – 72 months), with a 3-year OS of 40 ± 9%. The cause of death was lymphoma in 20 cases, acute toxicity in two, and unrelated disorder in one.

Univariate analyses showed that patients with a slow CLc rea (≤ 85 ml min⁻¹) survived longer than patients with a fast CLc rea (> 85 ml min⁻¹), with 3-year OS values of 88 ± 13 and 25 ± 9% (P = 0.0005), respectively (Figure 1). Patients treated with an AUCMTX > 1100 μmol h⁻¹ survived significantly longer than patients treated with lower levels (3-year OS: 78 ± 12 vs 32 ± 9%; P = 0.05) (Figure 2). The use of anticonvulsants and IRMTX was not associated with survival, and no significant difference in the efficacy of the used chemotherapy regimens was observed. Multivariate analysis (Table 5) confirmed the independent prognostic value of CLc rea and AUCMTX.

**DISCUSSION**

The present study focused on the impact on toxicity and outcomes of CLc rea, AUCMTX, DLMTX, and IRMTX in a multicentre retrospective series of 45 immunocompetent patients with PCNSL. This series is representative of PCNSL patients currently treated with HD-MTX-based chemotherapy, since it displays similar median age, PS distribution, histotypes, and oacular and meningeal infiltration rates with respect to more comprehensive unselected
A retrospective series (Ferreri et al., 2002b), and to the largest published prospective trials (O’Brien et al., 2000; Deangelis et al., 2002). A clear relationship between the studied variables and therapeutic outcome is difficult to establish, considering the multitude of other factors, such as protein binding, membrane transport, dihydrofolate reductase levels, tissue distribution, or concurrent drugs, which may also influence the efficacy of MTX. Nevertheless, as has been reported for other malignancies (Evans et al., 1986; Graf et al., 1994; Delepine et al., 1995; Bacci et al., 1998), the characterisation of the MTX variables investigated could be useful to identify different risk groups and to define the optimal administration schedule of this drug in PCNSL patients.

HD-MTX is the most effective drug against PCNSL; any regimen without this drug is associated with outcomes which are no better than with RT alone (Schultz et al., 1996; O’Neill et al., 1999; Mead et al., 2000). When used as primary treatment, alone or combined

Table 4  Logistic regression: variables correlated to severe toxicity (n = 7) and complete remission rate (n = 18) after primary chemotherapy

| Variables          | Subgroups | No. | Severe toxicity | P     | Complete response | P     |
|--------------------|-----------|-----|-----------------|-------|-------------------|-------|
| Age                | ≤ 60 years| 30  | 3 (10%)         | 0.28  | 11 (37%)          | 0.26  |
|                    | > 60 years| 15  | 4 (27%)         | 0.28  | 7 (46%)           | 0.26  |
| PS                 | 0–1       | 16  | 2 (13%)         | 0.14  | 10 (62%)          | 0.19  |
|                    | 2–4       | 29  | 5 (17%)         | 0.14  | 8 (28%)           | 0.19  |
| Anticonvulsants    | No        | 14  | 1 (7%)          | 0.97  | 6 (43%)           | 0.51  |
|                    | Yes       | 31  | 6 (19%)         | 0.97  | 12 (39%)          | 0.51  |
| IR_{MTX} (mg m⁻² h⁻¹) | ≤ 800     | 33  | 4 (12%)         | 0.11  | 15 (45%)          | 0.49  |
|                    | > 800     | 12  | 3 (33%)         | 0.11  | 3 (25%)           | 0.49  |
| DL_{MTX} (mg m⁻² week⁻¹) | ≤ 1000    | 33  | 6 (18%)         | 0.48  | 14 (42%)          | 0.52  |
|                    | > 1000    | 12  | 1 (8%)          | 0.48  | 4 (33%)           | 0.52  |
| CL_{crea} (ml/min⁻¹) | ≤ 85      | 12  | 4 (33%)         | 0.05  | 8 (67%)           | 0.02  |
|                    | > 85      | 33  | 3 (9%)          | 0.05  | 10 (30%)          | 0.02  |
| AUC_{MTX} (µmol h⁻¹) | ≤ 1100    | 34  | 6 (17%)         | 0.45  | 14 (41%)          | 0.95  |
|                    | > 1100    | 11  | 1 (9%)          | 0.45  | 4 (36%)           | 0.95  |
| Chemotherapy regimen | HD-MTX     | 10  | 0 (0%)          | 0.45  | 2 (20%)           | 0.45  |
|                    | MATILde   | 11  | 3 (27%)         | 0.45  | 3 (27%)           | 0.45  |
|                    | MTX+AraC  | 24  | 4 (17%)         | 0.25  | 13 (54%)          | 0.25  |

HD-MTX = high-dose methotrexate. *The incidence of severe complications was significantly higher in patients with a PS > 2 with respect to the others (41 vs 9%, P = 0.002). An additional logit analysis with patients grouped according to PS ≤ 2 vs > 2 confirmed the independent association between toxicity and CL_{crea}.

Figure 1  OS curves for patients grouped according to the CL_{crea}. Patients with a slow CL_{crea} (≤ 85 ml/min⁻¹; dotted line) showed a better OS with respect to patients with a fast CL_{crea} (> 85 ml/min⁻¹; continued line).

Figure 2  OS curves for patients grouped according to the AUC_{MTX}. Patients treated with an AUC_{MTX} > 1100 µmol h⁻¹ (continued line) showed a significantly better survival with respect to those treated with an AUC_{MTX} ≤ 1100 µmol h⁻¹ (dotted line).
with other drugs, followed or not followed by RT, HD-MTX produces a response rate of 70–80%, with a 2-year OS of 60–70% (Ferreri et al., 2000). The survival benefit of the addition of other drugs to HD-MTX is matter of debate, considering that not only do randomised trials comparing mono-chemotherapy with HD-MTX and poly-chemotherapy not exist, but also that the activity of these drugs has not been assessed as a single drug in prospective trials. Thus, HD-MTX remains a crucial drug against PCNSL, being an irreplaceable component of primary chemotherapy. Nevertheless, the prognostic role of the AUCMTX and DI MTX as well as the optimal MTX dose, IR and dose timing of this drug have not been clearly defined in PCNSL. A single study comparing some MTX parameters in PCNSL patients treated with blood–brain barrier disruption or with systemic chemotherapy has been reported (Zylber-Katz et al., 2000), but their impact on outcome has not been analysed. Conversely, the prognostic role of MTX pharmacokinetics has been reported in other malignancies in which this drug plays a critical role, such as acute leukaemia (Evans et al., 1986) and osteosarcoma (Graf et al., 1994; Delepine et al., 1995; Bacci et al., 1998). Patients with acute leukaemia have been grouped according to a slow, medium or fast CLMTX, obtaining an inverse association with outcome (Evans et al., 1986). A significant correlation between a faster CL MTX and lower serum and cerebrospinal fluid (CSF) MTX concentrations has also been documented, suggesting an insufficient treatment both of the brain and meninges, and a greater risk of CNS relapse in this subgroup of leukaemia patients (Evans et al., 1983). Likewise, a significant survival effect of serum peak concentration of MTX has been reported in osteosarcoma (Graf et al., 1994).

Our study suggests that CLcria and AUCMTX are independent predictors of MTX efficacy in PCNSL patients also. A CLcria \leq 85 \text{ ml/min}^{-1} was associated with a higher complete remission rate and better survival, which was independent of age, PS, DI MTX, IRMTX and other therapeutic variables. Patients treated with an AUCMTX > 1100 \text{ μmol h}^{-1} showed a significantly better survival with respect to those treated with lower AUCMTX levels. CLcria is defined based upon CLcria decreased CLcria represents decreased CLcria which for a given dose would produce an increased AUCMTX. However, in the present series, CLcria and AUCMTX are two independent variables, which is explained by the heterogeneity in MTX dose, DI MTX and IRMTX, as well as by differences in the MTX metabolism, according to the drug infusion duration (see below). A strongly inverse correlation between CLcria and AUCMTX could be observed, for example, in a prospective trial, where the used MTX dose and schedule is the same for the entire series. Considering that AUCMTX is significantly correlated, among others, with DI MTX, IRMTX and anticonvulsant therapy, changes in these parameters could lead to significant changes in AUCMTX and efficacy. Importantly, as reported in Table 4, a higher AUCMTX was not associated with a higher incidence of severe toxicity (9 vs 17%, \( P = 0.45 \)). The single case of severe toxicity in the group of patients treated with an AUCMTX > 1100 \text{ μmol h}^{-1} consisted of nonlethal persistent thrombocytopenia, without bleeding complications in a patient with a CLcria of 186 ml min\(^{-1}\). On the other hand, four of the five cases of severe renal and haematological toxicity were observed in patients with slow CLcria. A close follow-up with haematologic profile and renal function assessment appears advisable in this subgroup of patients.

Premature CLcria assessment could also be useful to identify groups of PCNSL patients with different MTX efficacy, and the use of higher doses in patients with a fast CLcria should be critically considered. The choice of the MTX dose is a relevant issue in PCNSL, especially because of the high interpatient and intrapatient variability. Improvement of therapeutic strategies was not associated with survival or toxicity. However, the significant association between a DI MTX > 1000 mg m^{-2} week^{-1} and higher AUCMTX levels seems to suggest that, when administered every 3–4 weeks, a MTX dose \( \geq 3000 \text{ mg m}^{-2} \) could produce better results than lower doses. This also seems to be supported by the MSKCC and RTOG experience (Deangelis et al., 1992, 2002). In a previous trial (Deangelis et al., 1992), MTX administered at a dose of 1 g m^{-2} produced an overall response rate of 64% and a 5-year OS of 28%, while, in a recently reported trial (Deangelis et al., 2002), the use of a 3.5-g m^{-2} MTX dose produced an overall response rate of 90% and a 5-year OS of 50%. Analysed together, these data suggest that a higher amount of MTX administered in a single dose increases drug exposure and activity. Moreover, as previously reported (Ferreri et al., 1997), this strategy seems to lead to a higher diffusion of the drug across the blood–brain barrier and increased drug concentrations in the CSF, with a potential positive impact on efficacy against PCNSL. From the present analysis, no significant association between IRMTX and survival was observed. This could be due to the strong correlation observed between this parameter and AUCMTX. The identification of the best IRMTX in PCNSL needs further studies. In the meantime, an IRMTX of > 800 mg m^{-2} h^{-1} appears advisable, since it is associated with higher AUCMTX and does not display significantly higher toxicity in comparison to slower rates. Anticonvulsants are commonly used in PCNSL patients presenting seizures. These drugs interact with hepatic aldehyde oxidase, which constitutes a major mechanism for MTX degrada-

| Variables | Subgroups | Odds ratio (CI 95%) | \( P \) |
|-----------|-----------|-------------------|-------|
| Age       | Continuous variable | 1.06 (1.01 – 1.11) | 0.04  |
| PS        | 0/2      | 2.55 (1.92 – 7.02) | 0.05  |
| Anticonvulsant | No/Yes   | 1.46 (0.28 – 7.53) | 0.65  |
| IRMTX     | 0/2      | 0.51 (0.11 – 2.49) | 0.41  |
| DI MTX    | <800     | 3.38 (0.53 – 4.98) | 0.21  |
| CLcria    | >1000    | 6.01 (3.04 – 9.77) | 0.005 |
| AUCMTX    | <1100    | 3.38 (0.53 – 4.98) | 0.21  |
| Cytarabine | No/Yes   | 1.36 (0.49 – 4.11) | 0.78  |

\*Similar results were obtained when analysis was performed according to the chemotherapy regimen.
dose adjustments are needed when anticonvulsants are contempo-
larly used should be better explored.

To identify new active drugs and combinations remains the most important strategy to improve therapeutic results in PCNSL patients, and any effort to define the best administration schedule for HD-MTX should be encouraged. With certain limitations due to their retrospective nature, our data seem to suggest that slow CL_crea and high AUC_MTX are independently associated with better outcome in PCNSL patients. Comprehen-
sively, these interesting findings deserve to be assessed in
prospective trials. In the meantime, a MTX dose \( \geq 3000 \text{ mg m}^{-2} \)
administered in a 4- or 6-h infusion, every 3–4 weeks, appears an advisory schedule to adopt in clinical practice. The need to increase the MTX dose to ensure adequate exposure, such as higher AUC_MTX values, in patients with a fast CL_crea should be critically considered.

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