Methotrexate area under the curve is an important outcome predictor in patients with primary CNS lymphoma: A pharmacokinetic–pharmacodynamic analysis from the IELSG no. 20 trial

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**BACKGROUND:** This analysis was initiated to define the predictive value of the area under the curve of high-dose methotrexate (AUCHD-MTX) in patients with primary central nervous system lymphoma (PCNSL).

**PATIENTS AND METHODS:** We included 55 patients with PCNSL and available pharmacokinetic (PK) data from the International Extranodal Lymphoma Study Group (IELSG) no. 20 trial, randomised to HD-MTX (n = 30) or HD-MTX and high-dose cytarabine (HD-AraC) (n = 25). Individual AUCHD-MTX from population PK analysis was tested on drug toxicity and clinical outcome using multivariate logistic regression analysis and Cox hazards modelling.

**RESULTS:** AUCHD-MTX, the IELSG score and treatment group were significant predictors for treatment response (complete or partial) in the adjusted model. The AUCHD-MTX did not predict toxicity, with the exception of liver toxicity and neutropaenia. A high AUCHD-MTX was associated with better event-free survival (EFS) (P = 0.01) and overall survival (OAS) (P = 0.02). Both the AUCHD-MTX and the IELSG score were significant predictors of EFS and OAS in the adjusted model, with a hazard ratio of 0.82 and 0.73, respectively, per 100 μmol l⁻¹ h⁻¹ increase in AUCHD-MTX.

**CONCLUSIONS:** Individualised dosing of HD-MTX might have the potential to improve clinical outcome in patients with PCNSL, even when administered concurrently with HD-AraC. In the future, this could be carried out by using first-cycle PK modelling with determination of potential dose adaptations for later cycles using Bayesian analysis.

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Primary central nervous system lymphomas (PCNSLs) represent 4–6% of extranodal non-Hodgkin’s lymphomas, but their incidence in the general population is increasing (Ferreri et al, 2003a). High-dose methotrexate (HD-MTX) is a cornerstone of PCNSL treatment (Reni et al, 1997; Ferreri et al, 2002). Only recently, the International Extranodal Lymphoma Study Group (IELSG) concluded the first randomised study in immunocompetent patients with PCNSL (IELSG no. 20). A significant increase in complete remission rate and event-free survival (EFS) was found when adding high-dose cytarabine (HD-AraC) to HD-MTX (Ferreri et al, 2009). Accordingly, combined HD-MTX/HD-AraC should be seen as the new standard upfront treatment in PCNSL, as it is supported by the best level of evidence available in this disease (Ferreri et al, 2009). Treatment with HD-MTX is hampered by a highly variable pharmacokinetic (PK) behaviour, in part related to renal elimination and the potential for drug interactions (Evans and Christensen, 1985; Thyss et al, 1986; Ferrazzini et al, 1990; Reid et al, 1993; Ronchera et al, 1993; Takeda et al, 2002; Joerger et al, 2006). However, achieving a minimum area under the curve (AUC) of HD-MTX (AUCHD-MTX) might be important for clinical outcome in patients with PCNSL (Ferreri et al, 2004). In this study, we report a PK–pharmacodynamic (PKPD) analysis of HD-MTX in patients enrolled into the IELSG no. 20 trial, to define the
predictive value of AUChD-MTX and to identify clinical and thera-
peutic variables that could be manipulated to improve MTX effi-

cacy in patients with PCNSL.

MATERIALS AND METHODS
Patient population and treatment
We included 79 immunocompetent patients with PCNSL, rando-

mised to receive either HD-MTX alone (n = 40) or HD-MTX
with sequential HD-AraC (n = 39) from the IELSG no. 20 trial
(Ferreri et al, 2009). High-dose MTX was administered at 3.5 g m
–2 (0.5 g m
–2 in 15 min, followed by 3 g m
–2 as a 3 h infusion) on
day 1 in both arms, and HD-AraC was administered at 2 g m
–2 as a
1 h infusion every 12 h on days 2 and 3 in the combined treatment
arm. Radiotherapy was given after chemotherapy in 36 patients,
and at progression in 18 patients. Study design and inclusion
criteria have been published previously (Ferreri et al, 2009). The
determination of MTX serum levels was performed before and
immediately after the end of drug infusion, and repeated every
24 h until the MTX serum concentration fell under the threshold
concentration of 0.05 μmol l
–1. The concentration data of MTX
– collected at 0, 24, 48, 72 and 96 h from drug infusion – during the
first course of chemotherapy were considered for PK analysis.
Leucovorin rescue started 24 h after the start of HD-MTX infusion,
administered at a dose of 15 mg m
–2 intravenous push every 6 h
for 12 times or more until MTX serum levels were undetectable.
After 48 h from MTX infusion, leucovorin rescue was modified
according to MTX serum levels.

Population PK analysis
Population PK analysis was performed using the nonlinear
mixed-effects modelling program (NONMEM) version VI (double
precision, level 1.1) (Beal and Sheiner, 1998). First, a basic PK
model was developed for MTX concentration–time data. Model
selection was based on the minimum value of objective function,
the precision of parameter estimates and the fit of the model to the
data as approached by graphical plots. Inter-individual variability
was estimated using a proportional error model. Second, the
following covariates were tested for their relationship with CLMTX:
– patient gender, age, body-surface area (BSA), creatinine clearance
(CLCREA according to the Cockroft–Gault formula, assessed before
– chemotherapy (SD, PD) and responders (CR or PR). Analysis
of variance (ANOVA) was used to compare individual AUChD-MTX
with treatment-associated toxicity. To assess any potential
relationship between AUChD-MTX and clinical outcome, the former
was categorised into tertiles, with the higher tertile corresponding
to an AUC > 980 μmol l
–1 h and the lower tertile corresponding
to an AUC < 830 μmol l
–1 h. Both EFS and overall survival (OAS)
were calculated per AUChD-MTX category using survival analysis
and log-rank test, respectively. The following potential predictors
for chemotherapy response were studied using multivariate logistic
regression analysis: AUChD-MTX (tertiles), gender, categorical
IELSG prognostic score (Ferreri et al, 2003b) (0–1, 2–3, 4–5 points) and treatment group. The following potential
predictors for clinical outcome (EFS, OAS) were studied using
multivariate Cox hazards modelling: gender, IELSG score,
treatment group and AUChD-MTX. Both EFS and OAS curves were
calculated using the Kaplan–Meier method, and the log-rank
was used to detect potential differences per AUChD-MTX
category. A previously described threshold of AUChD-MTX ≥ 1100 μmol l
–1 h (Ferreri et al, 2004) was additionally analysed
on chemotherapy response and clinical outcome. All tests
of significance were two-sided; P < 0.05 was considered significant.
All statistical analyses were performed using STATA 10.1 software
(STATA Corp, College Station, TX, USA).

RESULTS
Patient population and data set
Patient characteristics have been described previously (Ferreri
et al, 2009). Out of the 79 patients, 55 had available PK data of
HD-MTX and were included into this analysis with the following
characteristics: median age 56 years, 32 female (58%) and 23 male
(42%); 30 patients were randomised to receive HD-MTX and
25 patients to combined HD-MTX/HD-AraC, with a median
IELSG-score of 2. Patient characteristics of the PKPD subgroup
and of the total population were not significantly different. After
chemotherapy, 7 HD-MTX and 18 HD-MTX/HD-AraC patients
achieved a CR (18 vs 46%; P = 0.006); 9 MTX and 9 MTX/AraC
patients achieved a PR, for an ORR of 40 and 69%, respectively
(P = 0.089). At a median follow-up of 30 months, 31 MTX and
23 MTX/AraC patients experienced failure (PD, relapse, death),
with a 3-year EFS of 21 and 38%, respectively (P = 0.01). In all,
12 MTX and 20 MTX/AraC patients are alive, with a 3-year OAS
of 32 and 46%, respectively (P = 0.07).

Population PK model
The MTX concentration–time data were best described by a linear
two-compartment model with first-order elimination from the
central compartment. The MTX clearance was 14.9 l h
–1 (relative
s.e. 9.95), with an inter-individual variability of 22.3% and a resi-
dual variability of 31.8%. Volume distribution was 71.9 l
(± 51.5), with an inter-individual variability of 30.1%. Inter-compartmental
clearance was 11.2 l h
–1 (± 5.2), with an inter-individual variability
of 35%. Two patients had a CLHD-MTX > 20 l h
–1, six patients
< 71 l h
–1. Median AUChD-MTX was 931 μmol l
–1 h (range 486–
1710 μmol l
–1 h). The AUChD-MTX was < 750 μmol l
–1 h in 11 out
of 55 cases with available PK data (20%), and > 1100 μmol l
–1 h in
due to the poor handling of the data. The maximum response recorded from treatment
was considered for activity analyses. Follow-up examinations
were conducted as reported previously (Ferreri et al, 2003a).

Toxicity and response assessment
Adverse events were separately assessed for each chemotherapy
course and graded according to the NCI-NCIC CTC version 3.0
(Trott et al, 2003). The worst toxicity per organ in 1000
per patient was considered for analysis. Treatment response was assessed on
contrast-enhanced brain MRI performed within 7 days before
chemotherapy and repeated after the second and fourth treatment
cycle and after WBRT. Response definition was based on changes
in tumour size of enhanced lesions on T1-weighted MRI, and
response definitions were objective response (OR; CR or PR).

Statistical analysis
Individual AUChD-MTX was compared between treatment groups,
patient gender and treatment response using Student’s t-test.
Patients were categorised into those having no response to
chemotherapy (SD, PD) and responders (CR or PR). Analysis
of variance (ANOVA) was used to compare individual AUChD-MTX
with treatment-associated toxicity. To assess any potential
relationship between AUChD-MTX and clinical outcome, the former
was categorised into tertiles, with the higher tertile corresponding
to an AUC > 980 μmol l
–1 h and the lower tertile corresponding
to an AUC < 830 μmol l
–1 h. Both EFS and overall survival (OAS)
were calculated per AUChD-MTX category using survival analysis
and log-rank test, respectively. The following potential predictors
for chemotherapy response were studied using multivariate logistic
regression analysis: AUChD-MTX (tertiles), gender, categorical
IELSG prognostic score (Ferreri et al, 2003b) (0–1, 2–3, 4–5 points) and treatment group. The following potential
predictors for clinical outcome (EFS, OAS) were studied using
multivariate Cox hazards modelling: gender, IELSG score,
treatment group and AUChD-MTX. Both EFS and OAS curves were
calculated using the Kaplan–Meier method, and the log-rank
was used to detect potential differences per AUChD-MTX
category. A previously described threshold of AUChD-MTX ≥ 1100 μmol l
–1 h (Ferreri et al, 2004) was additionally analysed
on chemotherapy response and clinical outcome. All tests
of significance were two-sided; P < 0.05 was considered significant.
All statistical analyses were performed using STATA 10.1 software
(STATA Corp, College Station, TX, USA).
The inclusion of patient age, BSA or concurrent administration of HD-AraC did not improve the model fit. The goodness-of-fit plots supported a good data fit of the final model (Figure 1).

**Statistical analysis**

The AUCHD-MTX tertiles are outlined across chemotherapy response and clinical outcome in Table 1. The AUCHD-MTX was not significantly different between treatment groups (902 μmol l⁻¹ h in the HD-MTX group, 965 μmol l⁻¹ h in the HD-MTX/HD-AraC group, P = 0.16). The AUCHD-MTX was significantly higher in the 29 responding patients compared with the 26 cases without chemotherapy response (1073 vs 867 μmol l⁻¹ h, P = 0.0001). Predictors of a favourable treatment response are outlined in Table 2. Patients with AUCHD-MTX > 1100 μmol l⁻¹ h had an odds ratio of 3.5 for having a favourable treatment response (P = 0.03). There was no significant relationship between AUCHD-MTX and toxicity, with the exception of liver dysfunction (AUCHD-MTX 1047 μmol l⁻¹ h in patients with any treatment-associated liver dysfunction vs 932 μmol l⁻¹ h in those without liver dysfunction, P = 0.02) and neutropaenia (AUCHD-MTX 1036 μmol l⁻¹ h in patients with grade 3 or 4 neutropaenia vs 914 μmol l⁻¹ h in those with no or grade 1 or 2 neutropaenia, P = 0.007). Patients with the highest AUCHD-MTX tertiles had a significantly better EFS and OAS as compared with patients in the lower two tertiles of AUCHD-MTX (Table 2 and Figure 2). The AUCHD-MTX > 1100 μmol l⁻¹ h was associated with a better EFS and OAS by the log-rank test (P = 0.023 and P = 0.056, respectively). Both the AUCHD-MTX and the IELSG score were significant predictors of EFS and OAS using multivariate Cox regression analysis (Table 3). When AUCHD-MTX > 1100 μmol l⁻¹ h was introduced into Cox regression analysis as a binary covariate, statistical significance was retained (HR = 0.51, P = 0.033 for EFS, HR = 0.50, P = 0.044 for OAS). No association was found between the volume of distribution, inter-compartmental clearance and any of the clinical end points.

**DISCUSSION**

This PKPD analysis of HD-MTX in patients from the IELSG no. 20 trial is of special value, as this is the first prospective, randomised trial in PCNSL with completed accrual (Ferreri et al, 2003a). This study shows that AUCHD-MTX is the most important and independent predictor of clinical outcome in this group of patients. This is an important issue considering the fact that the HD-MTX/HD-AraC combination is the new standard therapeutic approach to patients with PCNSL (Ferreri et al, 2009). Interestingly, this study showed that nearly 75% of patients did not achieve an AUCHD-MTX > 1100 μmol l⁻¹ h, which has been previously reported as an independent predictor for improved outcome.

![Figure 1](https://example.com/image1.png)

**Figure 1**  Goodness-of-fit plots of the final population pharmacokinetic model (all data log-transformed, drug concentration as μmol l⁻¹). Observed MTX concentrations vs model predictions (A) and vs individual Bayesian predictions (B).

| Covariate | AUCHD-MTX < 830 μmol l⁻¹ h | Pts (%) | OR (95% CI) | AUCHD-MTX 830–980 μmol l⁻¹ h | Pts (%) | OR (95% CI) | AUCHD-MTX > 980 μmol l⁻¹ h | Pts (%) | OR (95% CI) | P-value |
|-----------|-----------------------------|---------|-------------|-----------------------------|---------|-------------|-----------------------------|---------|-------------|---------|
| ORR       |                             |         |             |                             |         |             |                             |         |             |         |
| SD/PD     | 14 (54) OR 0.18 (0.05–0.61) | 10 (39) | 0.61 (0.19–1.89) | 2 (7) OR 16 (55) | 14.7 (2.93–74.4) | <0.001<sup>a</sup> |
| CR/PR     | 5 (17) OR 0.18 (0.05–0.61) | 8 (28) OR 0.61 (0.19–1.89) | 2 (7) OR 16 (55) | 14.7 (2.93–74.4) | <0.001<sup>a</sup> |
| Outcome   |                             |         |             |                             |         |             |                             |         |             |         |
| 3-Year EFS| 19 (34) OR 0.18 (0.05–0.61) | 18 (33) | 0.61 (0.19–1.89) | 2 (7) OR 16 (55) | 14.7 (2.93–74.4) | <0.001<sup>a</sup> |
| 3-Year OAS| 19 (34) OR 0.18 (0.05–0.61) | 18 (33) | 0.61 (0.19–1.89) | 2 (7) OR 16 (55) | 14.7 (2.93–74.4) | <0.001<sup>a</sup> |

Abbreviations: AUCHD-MTX = area under the curve of high-dose methotrexate; Pt = patient; OR = odds ratio; CI = confidence interval; ORR = objective response rate; SD = stable disease; PD = progressive disease; CR = complete response; PR = partial response; Ref = reference; EFS = event-free survival; OAS = overall survival.

<sup>a</sup>Analysis of variance.

<sup>b</sup>Log-rank test.
clinical outcome (Ferreri et al., 2004). The present results cannot be interpreted as a lack of benefit from combined HD-MTX/HD-AraC treatment, as not all patients had available PK data for HD-MTX, and combined HD-MTX/HD-AraC treatment was still a significant predictor for clinical outcome when AUCHD-MTX was dropped from the Cox model. It still indicates that inter-individual disparities in HD-MTX pharmacology have an important role in clinical outcome, and that optimising individual AUCHD-MTX is an important strategy for improving clinical outcome in PCNSL. Thus, the encouraging results of the IELSG no. 20 trial (Ferreri et al., 2003a) might be further improved by individualised MTX administration aimed to achieve a target AUCHD-MTX of 1000 μmol·h^-1·l^-1. This statement is also endorsed by the fact that there was no relevant impact of AUCHD-MTX on drug toxicity. The strengths of this study include a homogeneous patient population, the availability of detailed response, outcome and toxicity data in all patients, first-course PK data of MTX in most patients, as well as population PKPD analysis of HD-MTX time–concentration data. The main limitations of this study are that drug interactions between HD-MTX and HD-AraC could only indirectly be studied because no PK data of HD-AraC were available, and PK data of

| Covariate | OR | 95% CI | P-value |
|-----------|----|--------|---------|
| Patient gender | | | |
| Male | Ref | | |
| Female | 0.48 | 0.08–2.92 | 0.42 |
| IELSG risk score | | | |
| 0–1 | Ref | | |
| 2–3 | 0.05 | 0.005–0.44 | 0.007 |
| 4–5 | 0.03 | 0.002–0.48 | 0.01 |
| Treatment group | | | |
| HD-MTX | Ref | | |
| HD-MTX/HD-AraC | 9.33 | 1.33–65.53 | 0.02 |
| AUCHD-MTX (tertiles, μmol·h^-1·l^-1) | | | |
| <830 | Ref | | |
| 830–980 | 5.21 | 0.73–37.3 | 0.10 |
| >980 | 121.9 | 78.0–190.1 | 0.001 |

Table 2 Predictors for chemotherapy response (complete and partial remission) using multivariate regression modeling

| Abbreviations: OR = odds ratio; CI = confidence interval; IELSG = International Extranodal Lymphoma Study Group; HD-MTX = high-dose methotrexate; HD-AraC = high-dose cytarabine; AUC = area under the curve; Ref = reference. |

**Figure 2** Kaplan–Meier plots for event-free survival (A) and overall survival (B) grouped according to the highest AUCHD-MTX tertile (>980 μmol·h^-1·l^-1) and the lower two tertiles of AUCHD-MTX (<980 μmol·h^-1·l^-1).
HD-MTX from later courses were not available. However, the fact that tumour response was usually seen within the first two courses of chemotherapy (Ferreri et al, 2009) does suggest a strong correlation between first-course PK data and clinical outcome.

In a retrospective study (Ferreri et al, 2004), PCNSL patients treated with MTX-based chemotherapy and an AUH-MTX > 1100 μmolL⁻¹·h⁻¹ showed significantly better response and survival rates. In the IELSG no. 20 trial, only 22% of patients achieved this AUH-MTX, suggesting room for improving HD-MTX administration. Importantly, a suboptimal AUH-MTX was obtained equally in both treatment arms in the IELSG no. 20 trial. Therefore, the introduction of a personalised dose of HD-MTX, according to patient age, gender and CL_CREAP has the potential to significantly improve treatment activity in these patients, and should be investigated in future trials. According to the present observation, personalisation of the MTX administration schedule should not consider the concomitant use of HD-MTX/HD-AraC.

In conclusion, individualised dosing of HD-MTX might have the potential to improve clinical outcome in patients with PCNSL, even when administered concurrently with HD-AraC. In the future, this could be carried out by using first-cycle PK modelling with determination of potential dose adaptations for later cycles using Bayesian analysis.

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