High-dose methotrexate toxicity in elderly patients with primary central nervous system lymphoma

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Background: The dose of high-dose methotrexate (HDMTX) in elderly patients often has to be reduced, resulting in a loss of treatment efficacy. We evaluated HDMTX-related toxicity with special regard to age distribution in patients with primary central nervous system lymphoma (PCNSL) in a phase IV multicenter trial.

Patients and methods: One hundred and fifty-four patients (median age 61 years; 89 patients >60 years old, 21 patients >70 years old) received 619 HDMTX cycles. Toxicity was evaluated prospectively using the WHO classification. Unless a reduced dose was required after calculating a decreased glomerular filtration rate (GFR), the patients received 4 g/m² HDMTX followed by leucovorin rescue.

Results: Toxicity was generally mild with toxicities of WHO grade ≥3 usually <10%. The differences in the incidence and severity of toxicity were not statistically significant between patients >60 years and ≤60 years old. The same was true for therapy termination owing to MTX toxicity and for delayed serum MTX clearance. Dose reduction significantly differed between patients ≤60 years and those >60 years old (18% versus 44%; P = 0.001).

Conclusions: HDMTX is a safe treatment for PCNSL patients regardless of age, with adherence to dose reduction determined by calculating the GFR before each treatment cycle.

Key words: elderly, glomerular filtration rate, methotrexate, toxicity

Introduction

Primary central nervous system lymphoma (PCNSL) is defined as a non-Hodgkin’s lymphoma that arises within and at the time of diagnosis is confined to, the central nervous system [1]. Most cases of PCNSL occur in elderly patients, the median age at diagnosis in immunocompetent patients being ~55 years old [1]. Age >60 years is associated with a poor prognosis [2]. The prognosis of PCNSL was markedly enhanced by the addition of high-dose methotrexate (HDMTX) to whole-brain irradiation (WBI), while chemotherapy protocols effective in extracerebral lymphoma did not improve survival compared with WBI alone [3,4]. Cerebrospinal fluid (CSF) permeation by MTX is dose-dependent, i.e. the percentage of courses with cytostatic CSF levels varies from 0% to 100% with doses between 0.5 and 6 g/m² [5–7]. HDMTX is also used to treat other malignancies such as acute lymphoblastic leukemia and osteosarcoma, but since these diseases usually affect younger people, few data are available on toxicity in older patients. This patient population is particularly at high risk for acute toxicity such as impaired renal and hepatic function. Thus, the MTX dose is often primarily reduced in elderly patients, resulting in a reduced treatment efficacy and a less favorable outcome in this population with an already poor prognosis [2].

In an ongoing prospective multicenter study in PCNSL patients, we evaluated the incidence and severity of HDMTX-related toxicity with special regard to age distribution.

Patients and methods

Patients

All patients were included in a multicenter phase IV study to evaluate the role of adjuvant WBI in the primary treatment of PCNSL (German Primary CNS Lymphoma Study Group 1) (Figure 1). Initial treatment consisted of HDMTX in all patients. Ethics committee approval was obtained for this study. Patients were then randomized according to remission status. Those with complete remission (CR) either received immediate WBI,
or WBI was deferred until relapse. Patients without CR were randomized to either receive immediate WBI or cytarabine. Inclusion criteria were histologically and/or cytologically/immunocytologically (in CSF) confirmed PCNSL without prior cytostatic treatment, written informed consent, age ≥18 years, an absolute neutrophil count (ANC) of >1500/μl, platelets ≥100 000/μl, normal total bilirubin, transaminases <3× the normal value and a creatinine clearance of ≥50 ml/min.

Exclusion criteria were a creatinine clearance of <50 ml/min, positive HIV serology, active infection, a Karnofsky performance status (KPS) <50% for reasons not related to PCNSL and <30% for PCNSL-related reasons, concomitant malignant disease, concomitant immunosuppression, pregnancy, no effective contraception, breast feeding in women with child-bearing potential, and treatment with salicylates, non-steroidal anti-inflammatory drugs, sulfonamides or penicillins within 1 week prior to HDMTX.

One hundred and fifty-four patients from 42 institutions were enrolled at the time of this analysis (Table 1). HDMTX toxicity was evaluated prospectively. KPS before treatment was available for 80 patients. The median KPS was 70% for all patients (range 30% to 100%), as well as for those >60 years (range 35% to 100%) and >70 years old (range 40% to 80%).

**Treatment**

HDMTX doses were adapted to the creatinine clearance determined prior to each HDMTX cycle. The glomerular filtration rate (GFR) was calculated as follows:

\[
GFR = \frac{Cr_U (mg/dl) / Cr_S (mg/dl)}{U_v (ml)} \times \frac{1}{1440 \text{ min}},
\]

where \(Cr_U\) is the urinary creatinine concentration in a 24-h urine sample, \(Cr_S\) is the serum creatinine concentration and \(U_v\) is the urine volume in 24 h.

The MTX dose was reduced according to the decrease of the GFR relative to 100 ml/min. For example, if the GFR was beyond 100 ml/min, the dose was not reduced; if the GFR was >80 ml/min, the MTX dose was reduced by 20%. Unless a dose reduction was required, all patients received a HDMTX dose of 4 g/m² intravenously (i.v.) over 4 h per cycle, repeated every 2 weeks up to a maximum of six cycles. The dose of 4 g/m² was chosen based on the promising results published by Guha-Thakurta et al. [8]. In addition, 8 mg of oral dexamethasone was administered thrice daily over 10 consecutive days during cycle 1. Serum MTX concentrations were measured 24, 42 and 68 h after the beginning of the infusion. All patients received i.v. hydration with 24 h of sodium bicarbonate beginning on day 1, as well as 25 mg of leucovorin i.v. every 6 h starting 24 h after the beginning of the MTX infusion. Leucovorin and i.v. hydration were continued until the serum MTX serum levels had dropped below 0.1 μM. Intensified leucovorin rescue was performed in patients with serum MTX levels >150, >0.1 μM at 24, 42, 68 h, respectively. Urine pH was evaluated after each micturition and kept above pH 7 with oral potassium sodium hydrogen citrate or additional sodium bicarbonate infusions until the serum MTX concentration had dropped below 0.1 μM. Toxicity was evaluated according to the WHO criteria [9].

Treatment termination was mandatory for the following reasons: patient’s desire, progressive leukencephalopathy, a serum creatinine >1.5× the normal value for 1 week, grade 4 toxicity (excluding alopecia and hematotoxicity) or repeated grade 3 toxicity, persisting myelosuppression (ANC <1500/μl or platelets <100 000/μl) or persistence of toxicity other than alopecia for ≥2 weeks after the next scheduled HDMTX cycle, severe protocol violation, and progressive disease under HDMTX.

**Figure 1.** Design of the German Primary CNS Lymphoma Study Group. 1. MTX, methotrexate; CR, complete remission; WBI, whole-brain irradiation; AraC, cytarabine.

**Table 1.** Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
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<tbody>
<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Male</td>
<td>89 (57.8)</td>
</tr>
<tr>
<td>Female</td>
<td>65 (42.2)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Median</td>
<td>61</td>
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<tr>
<td>Range</td>
<td>19–83</td>
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<tr>
<td>&gt;60</td>
<td>89</td>
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<tr>
<td>&gt;70</td>
<td>21</td>
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<tr>
<td>Comorbidities</td>
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<td>Cardiovascular disease</td>
<td>43 (29.5)</td>
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<td>Renal disease</td>
<td>9 (6.3)</td>
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<td>Hepatic disease</td>
<td>3 (2.1)</td>
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<td>Pulmonary disease</td>
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<td>Neurological symptoms at diagnosis</td>
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<tr>
<td>Psychosyndrome</td>
<td>61 (39.6)</td>
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<td>Hemiparesis</td>
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<tr>
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<tr>
<td>Cerebral nerve palsy</td>
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<td>Cerebellar syndrome</td>
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<tr>
<td>Epilepsy</td>
<td>19 (12.3)</td>
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<tr>
<td>Elevated intracranial pressure</td>
<td>6 (3.9)</td>
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<td>Diagnosis confirmed by</td>
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<td>Stereotactic biopsy</td>
<td>91 (59.1)</td>
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<td>Total resection</td>
<td>20 (13)</td>
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<td>Diffuse large B cell</td>
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<td>T cell</td>
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Statistics
Toxicity was analyzed separately in patients ≤60 years and in those >60 years and >70 years old with respect to the number of HDMTX cycles and patients. Differences in the incidence and severity of toxicity between patients ≤60 and those >60 years old were compared using the χ²-test for linear association. Moreover, the incidence of grade 3–4 toxicity, grade 4 toxicity, premature HDMTX termination and delayed serum MTX clearance rates were analyzed using Fisher’s exact test. With 154 patients and toxicity frequencies ranging from 25% to 75%, differences in toxicities of ~24% would have been detectable with a power of 80%.

Differences between patients ≤70 years and those >70 years old were only analyzed descriptively owing to the small number of patients >70 years old. The level of significance was 0.05 (two-sided) for all analyses. No adjustment was made for multiplicity. All analyses were performed using the software package SPSSWIN (release 11.5).

Late neurotoxicity was defined as a dementia syndrome in absence of cerebral lymphoma manifestations.

No interim efficacy analysis has been planned in this trial.

Results
Tables 2 and 3 show a summary of all toxicities.

Hematological toxicity and infections
Of 69 patients evaluable for toxicity before treatment, five patients (7%) had grade 1 anemia, one had grade 2 neutropenia and one had a grade 2 infection. When comparing the different grades of anemia, thrombopenia, leucopenia and infections, no significant differences in the severity and frequency were found in patients ≤60 and >60 years old, nor were they found for the comparison of all toxicity grades (grade 0–4, χ²-test for linear association) together or for the subgroup analysis of severe toxicity (grade 3–4 versus grade 0–2 and grade 4 versus grade 0–3, Fisher’s exact test). Elevation of transaminases (grade 1–3), creatinine elevation (grade 1–2), nausea (grade 1) and mucositis (grade 1–2) were most frequently seen. No acute HDMTX-related neurotoxicity was observed. On follow-up, 30 patients (19.5%) had evidence of leukencephalopathy on brain magnetic resonance imaging, and 11 patients (7.1%) demonstrated clinical evidence of late neurotoxicity.

Table 2. High-dose methotrexate (HDMTX)-associated hematological toxicity and infections in primary central nervous system lymphoma patients, analyzed separately for treated patients, applied HDMTX cycles, and patients ≤60/>60 and >70 years olda

<table>
<thead>
<tr>
<th>Toxicity WHO grade</th>
<th>≤60 years</th>
<th>&gt;60 years</th>
<th>&gt;70 years</th>
<th>≤60 years</th>
<th>&gt;60 years</th>
<th>&gt;70 years</th>
<th>≤60 years</th>
<th>&gt;60 years</th>
<th>&gt;70 years</th>
<th>≤60 years</th>
<th>&gt;60 years</th>
<th>&gt;70 years</th>
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<tr>
<td>Hemoglobin</td>
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<tr>
<td>Patients (%)</td>
<td>14 (22)</td>
<td>18 (20)</td>
<td>6 (29)</td>
<td>13 (20)</td>
<td>20 (23)</td>
<td>5 (24)</td>
<td>7 (11)</td>
<td>13 (15)</td>
<td>4 (19)</td>
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<td>0</td>
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<tr>
<td>Cycles (%)</td>
<td>55 (18)</td>
<td>59 (19)</td>
<td>18 (35)</td>
<td>25 (8)</td>
<td>35 (12)</td>
<td>8 (15)</td>
<td>8 (3)</td>
<td>14 (3)</td>
<td>4 (8)</td>
<td>0</td>
<td>0</td>
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<td>Leukocytes</td>
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<tr>
<td>Patients (%)</td>
<td>9 (14)</td>
<td>16 (18)</td>
<td>9 (43)</td>
<td>10 (15)</td>
<td>7 (8)</td>
<td>1 (5)</td>
<td>3 (5)</td>
<td>7 (8)</td>
<td>1 (5)</td>
<td>2 (3)</td>
<td>6 (7)</td>
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<tr>
<td>Cycles (%)</td>
<td>32 (10)</td>
<td>27 (9)</td>
<td>7 (14)</td>
<td>16 (5)</td>
<td>16 (5)</td>
<td>3 (6)</td>
<td>3 (1)</td>
<td>10 (3)</td>
<td>2 (4)</td>
<td>3 (1)</td>
<td>6 (2)</td>
<td>2 (4)</td>
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<tr>
<td>Granulocytes (neutrophils)</td>
<td>5 (8)</td>
<td>2 (3)</td>
<td>1 (5)</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>2 (3)</td>
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<td>2 (3)</td>
<td>1 (5)</td>
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<tr>
<td>Cycles (%)</td>
<td>10 (4)</td>
<td>2 (1)</td>
<td>1 (2)</td>
<td>5 (2)</td>
<td>0</td>
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<td>Patients (%)</td>
<td>9 (14)</td>
<td>11 (12)</td>
<td>3 (14)</td>
<td>3 (5)</td>
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<td>7 (8)</td>
<td>3 (14)</td>
<td>3 (5)</td>
<td>3 (3)</td>
<td>1 (5)</td>
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<tr>
<td>Cycles (%)</td>
<td>12 (4)</td>
<td>12 (4)</td>
<td>3 (6)</td>
<td>4 (1)</td>
<td>4 (1)</td>
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<td>9 (3)</td>
<td>3 (6)</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>1 (2)</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Patients (%)</td>
<td>1 (2)</td>
<td>5 (6)</td>
<td>3 (14)</td>
<td>9 (14)</td>
<td>11 (12)</td>
<td>4 (19)</td>
<td>8 (12)</td>
<td>9 (10)</td>
<td>3 (14)</td>
<td>1 (2)</td>
<td>3 (3)</td>
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</tr>
<tr>
<td>Cycles (%)</td>
<td>7 (2)</td>
<td>8 (3)</td>
<td>5 (10)</td>
<td>13 (4)</td>
<td>16 (5)</td>
<td>6 (11)</td>
<td>9 (3)</td>
<td>10 (3)</td>
<td>3 (6)</td>
<td>1 (0)</td>
<td>3 (1)</td>
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</tr>
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</table>

aNo statistically significant differences were observed between patients ≤60 and >60 years.

Non-hematological toxicity
Serum creatinine levels were elevated before treatment in six patients (9%). Prior to chemotherapy, grade 1 mucositis and pulmonary impairment were found in one patient each, while grade 2 pulmonary impairment was seen in two patients. Comparing the different grades of gastrointestinal toxicity, pulmonary toxicity and alopecia in patients ≤60 and >60 years old, no significant differences in the severity and frequency were found, nor were they found for the comparison of all toxicity grades (grade 0–4, χ²-test for linear association) together or for the subgroup analysis of severe toxicity (grade 3–4 versus grade 0–2 and grade 4 versus grade 0–3, Fisher’s exact test). Elevation of transaminases (grade 1–3), creatinine elevation (grade 1–2), nausea (grade 1) and mucositis (grade 1–2) were most frequently seen. No acute HDMTX-related neurotoxicity was observed. On follow-up, 30 patients (19.5%) had evidence of leukencephalopathy on brain magnetic resonance imaging, and 11 patients (7.1%) demonstrated clinical evidence of late neurotoxicity.

MTX dose reduction, treatment termination and delayed MTX clearance
Owing to a reduced GFR, the MTX dose was reduced in 11 (18%) patients ≤60 years, in 36 (44%) >60 years, and in 14
(70%) >70 years old. Patients ≤60 years old differed significantly from those >60 years (P=0.001). The mean amount of MTX dose reduction required in dose-reduced patients was 15.6% (range 1.3% to 80%).

HDMTX was stopped prematurely due to toxicity in three patients (5%) <60 years versus seven patients (8%) >60 years old (P=0.52). The main reason was nephrotoxicity in two patients (3%) ≤60 years old and in six patients (7%) >60 years old (P=0.469).

Delayed MTX clearance was observed in two patients (3%) ≤60 years old versus nine patients (11%) >60 years old (P=0.116).

**Discussion**

Provided that renal function is adequate, current evidence suggests that HDMTX can be tolerated without life-threatening toxicity as long as dose escalation is accompanied by hydration, urine alkalinization and adequate leucovorin rescue guided by monitoring of serum MTX concentrations [8, 10–13].

This is the first report on a prospective multicenter evaluation of age-dependent HDMTX toxicity in a uniformly treated representative patient population. The toxicity observed was transient and reversible in all patients and usually of minor clinical importance. Hematological toxicity (especially anemia) was most frequently seen. It was demonstrated for the first time that the incidence and severity of the toxicities do not significantly differ between older and younger patients; however, there was a tendency towards higher rates of anemia, infections, nephrotoxicity and total bilirubin elevation in older patients. The HDMTX dose was reduced much more frequently in the elderly, suggesting that HDMTX dose reduction according to the pretreatment GFR probably plays a critical role.
role for the prevention of toxicity in elderly patients, especially nephrotoxicity.

Five small studies with single-agent HDMTX at a dose of 3.5–8 g/m² are available for comparison with our study [8,10–13]. The reported overall acute and subacute toxicity was mild, which supports the data from our study. In a study with 25 patients (median age 61 years, 13 patients ≥60 years old, median KPS 60%), there were three occurrences of mucositis, one of chest and back pain associated with dyspnea, nausea and vomiting, two of deep venous thrombosis, and one each of pulmonary embolism, transient encephalopathy, isolated nausea, acute renal failure (rapidly reversed) and skin rash, out of a total of 79 HDMTX cycles. Agranulocytosis and thrombocytopenia were seen in one patient in the setting of an ileus and presumed malabsorption of oral leucovorin [10]. In a prospective multicenter phase II trial with 25 patients (mean age 60 years, median KPS 80%) and 287 treatment courses, 12 patients had 18 episodes (6%) of unspecified grade 3 or 4 toxicity [11]. In two prospective studies, primary dose reduction was performed based on the pretreatment creatinine clearance. In one of the prospective single-center studies, which included 31 patients (median age 63 years, median KPS 40%), the dose was reduced in 139 of 375 cycles (37%). Grade 3 mucositis was seen in six courses (2%) and transient renal failure in three courses (1%) [8]. In the other prospective study, with 37 patients (median age 60 years, median KPS 70%), WHO grade 3 and 4 toxicity was observed in 19 of 179 courses (11%). One patient with WHO grade 4 leukopenia died of septicemia, accounting for the toxic death rate of 2.7% [12].

Data concerning HDMTX toxicity in elderly patients are rare, and there are no studies comparing toxicity rates and grades with those in younger patients. In a retrospective study, grade 3 nausea was found in one, grade 2 mucositis in two, and grade 2 elevation of transaminases in two of 10 elderly patients (median age 72.5 years, eight patients >70 years, six patients with Eastern Cooperative Oncology Group performance score 2 or higher) [13].

In conclusion, single-agent HDMTX is a safe treatment regardless of age when dose reduction schedules based on the GFR calculated before each treatment cycle are implemented. Reducing the MTX dose simply according to the patient’s age is not justified, especially considering the poor prognosis of elderly patients with a malignant disease. Life expectancy for elderly tumor patients is usually determined by the malignant disease. Thus, careful monitoring and assessment of organ function prior to and during treatment should be the rule in these patients, rather than therapeutic nihilism.

Acknowledgements

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References

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