Pharmacokinetics and efficacy of ifosfamide or trofosfamide in patients with intraocular lymphoma

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Received 6 June 2005; revised 2 August 2005; accepted 4 August 2005

Background: The prognosis of intraocular lymphoma (IOL) is poor, and the optimal treatment has not yet been defined. The study assesses ifosfamide (IFO) and trofosfamide (TRO) for treating IOL.

Patients and methods: We prospectively evaluated the efficacy and aqueous penetration of intravenous IFO, oral TRO and their active 4-hydroxy (4-OH) metabolites in 10 patients with IOL. Doses varied from 1500 to 2000 mg/m²/day on days 1–3 for IFO and from 150 to 400 mg/day (continuous or intermittent administration) for TRO. Four patients had newly diagnosed disease, and six had relapsed after pretreatment.

Results: All patients responded to first treatment with IFO or TRO, and both of two patients responded to re-treatment with IFO on ocular relapse. Progression-free survival from the first treatment with IFO or TRO was ≥6–18 months. In six of six patients, 4-OH metabolites were detected in the aqueous humor at a concentration of 0.32–1.56 μM immediately after IFO infusion with an aqueous/serum ratio of 0.19–0.54. 4-OH metabolites could be detected in one of three patients at a concentration of 7.2 μM 3–16 h after ingestion of TRO.

Conclusions: IFO and TRO are active in IOL. IOL patients evidence aqueous penetration of 4-OH metabolites after intravenous administration of IFO.

Key words: aqueous, ifosfamide, intraocular lymphoma, trofosfamide

Introduction

Intraocular lymphoma (IOL) can occur as either primary IOL (PIOL) or secondary IOL. The former can arise either independently or in association with primary central nervous system lymphoma (PCNSL; ‘oculocerebral’ lymphoma). Secondary IOL is defined as an ocular manifestation of an extracerebral systemic lymphoma. PIOL involves the retina, the vitreous chamber and/or the optic nerve, whereas secondary IOL usually manifests itself in the choroid [1, 2]. Most PIOLs can be classified as diffuse large B-cell lymphomas, according to the World Health Organization (WHO) classification [3]; secondary IOL usually corresponds to the subtype of systemic lymphoma [2]. PIOL, a previously rare disease, has become more frequent because of a 3-fold increase in the incidence of PCNSL since 1970 [4]. PIOL usually presents in the fifth or sixth decade as a non-specific uveitis initially responsive to corticosteroids. The prognosis is poor, with a 2 year overall survival (OAS) of 39%, and the optimal treatment for IOL has not yet been defined [5].

This is because data on this subject are limited to small and usually retrospective treatment series or single-case reports. Compared with local treatment, systemic chemotherapy enables simultaneous treatment of the prognosis-determining intracranial disease with a relatively low risk of ocular toxicity. Ifosfamide (IFO) and trofosfamide (TRO), which are alkylating oxazaphosphorine derivatives, have been successfully used to treat non-Hodgkin lymphomas [6–8]. They are prodrugs which require hydroxylation at the cyclic carbon-4 position by hepatic cytochrome P-450 isoenzymes [8]. A penetration of IFO and TRO through the blood–brain barrier (BBB) can be assumed based on the lipid solubility, small molecular size, and minimal binding to plasma and tissue proteins. Active metabolites of IFO were detected in 89% of cerebrospinal fluid (CSF) samples in a study of children with acute lymphoblastic leukaemia, non-Hodgkin lymphoma, medulloblastoma and rhabdomyosarcoma; however, a high degree of interpatient variation was observed [9]. Since there is a free exchange between intercellular brain fluid and CSF, drug concentration in the CSF is generally regarded as a useful estimation of intracerebral tumour exposure to systematically administered cytostatics [9]. Based on this fact, IFO was included in a chemotherapy protocol for PCNSL and proved to be active against this lymphoma entity [10]. The ocular penetration of IFO and its metabolites has never been evaluated,
but appears probable when the similarities of the blood–retinal barrier (BRB) and the BBB are taken into consideration [11].

After oral administration, TRO is mainly metabolized to its active 4-hydroxy derivative IFO and, in smaller amounts, to another active metabolite 4-hydroxy (4-OH)-IFO. Compared with IFO, TRO seems to be much more strongly hydroxylated to the tumorstatically active 4-OH derivatives with a 20–30 times higher mean area under the curve and maximum concentration after TRO administration [12, 13]. Thus a better ocular penetration of TRO may be assumed. Both drugs are usually well tolerated, with side-effects being restricted to dose-dependent haematotoxicity and, rarely, haemorrhagic cystitis, nausea and vomiting [6, 7]. Activity of TRO against PIOL has already been demonstrated in two patients [14]. The present study was performed to evaluate the efficacy of IFO and TRO in IOL patients and the aqueous penetration of the 4-OH metabolites.

### Patients and methods

Informed consent was obtained from all patients before study entry, and the study was approved by the institutional ethics committee. Patients with newly diagnosed, relapsed or refractory primary or secondary IOL were included. In patients with isolated IOL, the diagnosis had to be confirmed by vitrectomy and/or chorioretinal biopsy. In those patients with a histologically proven cerebral or systemic lymphoma with high clinical suspicion of ocular involvement on fundoscopy, an additional pathological evaluation was not mandatory. Other inclusion criteria were age ≥18 years, an absolute neutrophil count ≥1500/μl, platelets ≥100 000/μl, normal total bilirubin, transaminases ≤3-fold of normal value and a creatinine clearance ≥50 ml/min. Patients were excluded from the study for the following reasons: positive HIV serology, active infection, Karnofsky performance status <40 for reasons not related to IOL/PCNSL and <20% for IOL/PCNSL-related reasons, concomitant malignant disease, immunosuppression, pregnancy, no effective contraception and breast feeding in women with child-bearing potential.

IFO was given as a i.v. infusion for 1 h at a dose of 1500–2000 mg/m²/day on days 1–3 every 3 weeks. TRO was given orally to those requesting outpatient treatment as one of two schedules: 150 mg/day continuously or 400 mg/day on days 1−5 followed by a 5 day drug-free interval. Safety measures were as follows: complete blood count every 2 weeks and additional serum electrolytes, creatinine and liver transaminases before each course in patients treated with IFO, and complete blood count, serum creatinine, electrolytes and liver transaminases every 4 weeks in patients treated with TRO. Ophthalmological evaluation was performed after every second treatment course during IFO therapy, every 4 weeks in patients on TRO and every 3 months during follow-up. The primary endpoint was ocular response; secondary endpoints were response duration and survival. Complete remission (CR) was defined as complete resolution of intraocular lymphoma manifestations on ophthalmoscopy for a minimum of 4 weeks without prior or concomitant steroid medication. Partial remission (PR) required a decrease in vitreous cells or retinal infiltrates with persistent malignant or suspicious cells. Progressive disease was defined as an increase in size and/or number of lymphoma infiltrates. Stable disease included all other conditions [15]. Progression-free survival was measured from start of treatment to ocular disease progression or death as a result of lymphoma progression. Survival was measured from the first treatment with IFO/TRO to death or last follow-up.

In patients 1–6, after having obtained 5 ml of blood as negative control, blood samples (5 ml) and a sample of aqueous humour (100 μl) were drawn immediately after infusion of IFO for 1 h. Another blood sample was collected 2 h later. In patients 8–10, the aqueous humour sample was collected together with 5 ml of blood 4–16 h after TRO ingestion. Patient 7 refused the puncture. All samples were immediately (‘bedside’) spiked with trichloroacetic (10% dilution) to avoid rapid decay of the 4-OH metabolites. Blood samples were shaken vigorously and centrifuged at 4g for 5 min. All samples were immediately stored at −70°C until analysis. IFO concentrations were analysed by gas chromatography, and the 4-OH metabolites were assayed by high-performance liquid chromatography as previously described [16, 17].

### Results

Patient characteristics, treatment and outcome are summarized in Table 1. All patients had visual impairment up to complete blindness (patient 6). One patient suffered from severe pain requiring high-dose analgesic therapy with opiates (patient 7). Patients 1 and 5 had secondary IOL due to immunocytoma and diffuse large B-cell lymphoma, respectively. Patients 2, 3, 7 and 9 were diagnosed with an ocular relapse of PCNSL. PIOL was newly diagnosed in patients 4, 6 and 8. Patient 10 had an isolated ocular relapse of PIOL. Four patients with ocular relapse of PCNSL were pretreated for PCNSL with high-dose methotrexate (HDMTX) and whole-brain irradiation (WBI) (patient 2), HDMTX alone (patient 3), HDMTX, high-dose cytarabine (HDAra-C), topotecan and WBI (patient 7), and HDMTX and topotecan (patient 9). Two patients were pretreated for ocular lymphoma with ocular radiotherapy (patient 7) and with HDAra-C and ocular radiotherapy (patient 10). One patient (patient 5) was pretreated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy for systemic lymphoma. All but two patients (patients 5 and 7) underwent vitrectomy before study treatment.

Patients 1–6 were treated with IFO and patients 7–10 were treated with TRO: 150 mg/day continuously (patients 7 and 8) and 400 mg/day on days 1–5 followed by a 5 day drug-free interval (patients 9 and 10). Neither steroids nor other concomitant anti-lymphoma therapy was given to any of the study patients, i.e. IFO or TRO were the only lymphoma-active substances administered. On first treatment with IFO or TRO, all patients responded with a significant increase in visual acuity and patient 6 experienced significant pain relief. An ocular lymphoma relapse occurred in three patients: 12 and 7 months after IFO in two patients (patients 1 and 2), and 18 months after TRO treatment in one patient (patient 7). All patients responded completely to salvage therapy: two (patients 1 and 2) responded to retreatment with IFO with a second response lasting for ≥8 and 4 months, respectively, and one (patient 7) responded to intravitreal MTX with a second response lasting for ≥17 months. In patient 2, a second ocular relapse occurred 4 months later. High-dose chemotherapy with carmustine and thiopeta was given, followed by autologous stem cell transplantation, and CR was achieved. One patient (patient 8) died 7 months after starting TRO without evidence of ocular lymphoma. An intracerebral relapse was suspected, but no imaging was performed.

Toxicity was mainly haematological; however, grade 3 leucopenia occurred in only one patient. Other toxicities were nausea up to grade 2 in two patients and grade 2 haemorrhagic cystitis in one patient.

4-OH metabolites were detected in the aqueous humour samples at a concentration of 0.32–1.56 μM immediately after IFO.
infusion with an aqueous/serum ratio of 0.19–0.54 in six of six patients (Table 2). 4-OH metabolites at a concentration of 7.2 μM could be detected in one of three patients 4–16 h after ingestion of TRO.

Discussion

The efficacy of chemotherapy as an exclusive treatment for IOL depends on intraocular pharmacokinetics, and these processes are not yet fully understood. The BRB and the blood–aqueous barrier (BAB) are physical hindrances for diffusion of drugs from the blood into ocular tissues. The BRB, represented by the endothelium of the retinal vessels and the retinal pigmented epithelium, is the counterpart of the BBB in the eye. The BAB is located in the non-pigmented ciliary epithelium and the endothelium of the iridic blood vessels [11, 18]. According to the most recent hypothesis, the BAB is a barrier between the blood and ocular tissues and fluids posterior to the iris plane [19]. Drug penetration through these barriers depends on several drug characteristics, with lipid solubility playing the major role. Intravitreal drug instillation bypasses the ocular barriers, which significantly improves the intraocular delivery of hydrophilic drugs like MTX. Intravitreal MTX is able to maintain therapeutic levels in the vitreous humour for 5 days [20]. After responses had been reported in several small studies [20–23], intravitreal MTX was considered as a kind of standard therapy in IOL. However, intravitreal chemotherapy can be painful, is associated with a high rate of local complications and frequently results in central nervous system relapses [2, 5].

Data on ocular penetration of cytostatics from the systemic circulation are limited to two reports. In the study by Batchelor et al. [24], micromolar MTX concentrations were reached in both ocular chambers with four remissions persisting after ≥8 to ≥36 months in eight of eight patients with PIOL treated with HDMTX [24]. In the case report by Bauman et al. [25], therapeutic levels were documented in the aqueous from the anterior chamber and the vitreous, and a response for ≥15 months was achieved following systemic application of HD Ara-C in one patient [25]. Applying very high doses of cytostatics with hematopoietic stem cell support may result in better intraocular penetration and longer disease control. Nine of 12 patients treated with high-dose thiopeta, busulfan and cyclophosphamide for refractory or relapsed PIOL achieved CR with a median survival of ≥53 months [26]. However, systemic toxicity was considerable; five of seven patients aged ≥60 years died during therapy. A pharmacokinetic analysis was not performed in this study.

Here, we demonstrate an aqueous penetration of active 4-OH metabolites after intravenous administration of IFO. Measuring vitreous drug levels would have been the most appropriate proof of drug penetration into the lymphoma sites. We have chosen the drug-level measurement in the anterior chamber since it is significantly less invasive and troublesome than vitreous aspirates. According to the most recent concept of the BAB [19], aqueous drug concentration in the anterior chamber possibly only provides an indirect estimation of penetration into the ocular lymphoma sites, which are the retina and the vitreous. For lipophilic drugs such as IFO and TRO, whose penetration from blood into ocular tissues is much less restricted compared with hydrophilic drugs, the concentration in the posterior eye segment presumably
approaches that in the anterior chamber. This has been confirmed by Mian et al. [27] who measured similar concentrations of fluconazole, another lipophilic small-molecule drug, in the vitreous and aqueous of the anterior chamber after systemic application. In contrast, levels of hydrophilic MTX in the vitreous were 13–51% of the concentration in the aqueous in four of six evaluable patients, and higher or similar concentrations in the vitreous compared with the aqueous were measured in one patient each in the study by Batchelor et al. [24].

There have not yet been any data on the ocular penetration of IFO and TRO or its metabolites. After a single short i.v. infusion, the terminal half-life of IFO in the serum ranged from 4 to 8 h with a peak plasma concentration of 1–5 μM and a wide interindividual variation [28]. Our data certainly support the wide variation of concentrations found, but serum IFO concentrations after i.v. administration were higher than expected. In contrast with IFO, 4-OH-IFO is extremely unstable in blood. Thus relatively low peak plasma concentrations with wide interindividual variations (1.5–2.7 μM) were found after applying therapeutic IFO doses [28], which is in agreement with our data. In the present study, IFO infusion led to aqueous 4-OH-IFO concentrations ranging from 19% to 54% of the corresponding serum concentrations. It is unclear to what extent the ocular penetration of IFO and its 4-OH metabolites measured in this study was influenced by the breakdown of the BRB by lymphoma infiltration or previous diagnostic surgery. Better penetration of several drugs into eyes affected by a malignant or inflammatory disease has been reported [11].

Neither TRO nor its metabolites could be detected in either serum or aqueous humour in two of three patients. This is most probably due to an inadequate interval between TRO ingestion and sampling. In our patients, this interval ranged from 4 to 16 h for logistic reasons (long distance between the patients’ homes and our institution, inadequate adherence to physician’s instructions). This must be considered an important bias, since TRO has a fast metabolism with a terminal half-life of only 1 h [16]. However, the only patient (patient 8) in whom aqueous 4-OH-IFO levels were detectable after TRO had the longest interval between ingestion and sampling. This patient was an 83-year-old obese female. The elimination half-life of IFO has been reported to be prolonged in adipose women (body weight >25% of the ideal value) [29]. Furthermore, slowed IFO metabolism in elderly patients may play a role in this case, even though no correlation was found between age and systemic IFO clearance in patients aged 40–71 years [30]. Interactions with other drugs may provide another possible explanation, but reports on drug interactions with IFO and TRO in humans are rare [31]. Only one of our patients treated with TRO (patient 8) was regularly taking other drugs (nifedipine and spironolactone). However, interactions with IFO or TRO have not yet been reported for either drug.

Our study demonstrates activity of IFO and TRO against IOL, even if long-term control of this highly aggressive tumour can probably not be achieved by monotherapy. Because of their low toxicity, both drugs may represent suitable combination partners for other cytostatics used for PCNSL and IOL treatment (e.g. HDMTX). As for TRO, prolonged exposure to the drug by continuous administration may be important for tumour regression, as postulated by others [23]. Furthermore, the fact that TRO can be administered on an outpatient basis renders it a candidate for maintenance treatment in PCNSL and IOL. However, a general treatment recommendation for IFO and TRO cannot be given based on only 10 treated patients. The standard treatment for IOL still remains to be defined. Further studies should be performed to assess the effectiveness of IFO and TRO in IOL patients.

References


