Ifosfamide: pharmacokinetic properties for central nervous system metastasis prevention

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The incidence of central nervous system (CNS) recurrence in patients with lymphoma is about 5%. Nevertheless, this complication is very serious because it is almost always fatal. Its incidence is not sufficiently high to warrant the use of CNS prophylaxis in all patients. The identification of subgroups for whom CNS prophylaxis may be of benefit is therefore important and the age-adjusted international prognostic index (aa-IPI) may be useful in this respect. Ifosfamide (IFO) is a widely used antitumor agent, requiring activation to isophosphoramide mustard (IPM) for DNA alkylation. IFO anabolism occurs through the hepatic microsomal cytochrome P450 system. As with the majority of antineoplastic agents, IFO has toxic side-effects. These include neurotoxicity due to the chloroacetaldehyde (CAA) catabolite. However, the incidence of neurotoxicity is low when IFO is administered as a continuous intravenous infusion. Both inactive IFO and active IPM cross the blood–brain barrier, making IFO treatment effective in the prevention of CNS metastasis in lymphoma patients at high risk of recurrence. The benefit/risk ratio for such patients should evaluated.

Key words: central nervous system, ifosfamide, lymphoma, neurotoxicity, prevention of cerebral metastasis

introduction
Ifosfamide (IFO) is a widely used antitumor compound effective against solid tumours such as sarcomas and hematologic malignancies (Figure 1). The major clinical toxicities encountered are urotoxicity, nephrotoxicity and neurotoxicity. Ifosfamide is a prodrug that needs to be converted into active metabolites through the oxidative chain of the cytochromes P450 (CYP 450) system. Conversion of IFO to active 4-hydroxy-ifosfamide (4-OH IFO) is mainly catalyzed by the isoform CYP3A4. Isoforms 2A6, 2B6, 2C8, 2C9 and 2C19 make a minor contribution [1] (Figure 2). Competing with 4-OH IFO formation is the catabolic IFO dechloroethylation pathway, which leads to generation of the neurotoxic metabolite chloroacetaldehyde (CAA). The neurotoxicity induced by IFO is generally linked to development of an encephalopathy, with symptoms ranging from periods of minor depression and dizziness to stupor and, rarely, coma. The onset of symptoms is variable and may occur within hours to days of a dose. No risk factors for the development of neurotoxicity have been identified, but it has been suggested that pre-existing renal or hepatic failure, low serum albumin and poor performance status could contribute to its development [2].

Central nervous system (CNS) recurrence is an almost invariably fatal complication of aggressive lymphomas [3]. However, the overall incidence of CNS relapse is only around 5%, posing a question about the general use of CNS prophylaxis in such patients [4].

ifosfamide mechanisms of action
The efficacy of IFO depends on its ability, after extracellular activation, to alkylate DNA by attaching the N-7 position of guanine to its reactive electrophilic groups (Figure 3). The formation of intra and interstrand cross-links may result in cytotoxicity and cell death. Isophosphoramide mustard (IPM), the active form of IFO, is a bifunctional alkylator with one chloroethyl group on the exocyclic and the other on the endocyclic oxazaphosphorine nitrogen atom. This mechanism of alkylation facilitates interstrand DNA cross-linking that is more difficult to repair and hence promotes a greater cytotoxic effect [5]. Two other IFO metabolites, acrolein and aziridine, are involved in the formation of DNA adducts.

ifosfamide side-effects
IFO administration has been associated with a number of acute side-effects often seen with antineoplastic agents. These include neutropenia, thrombocytopenia, nausea, vomiting, alopecia and hypersensitivity reactions. With conventional doses of ifosfamide, these side-effects are usually mild.

Ifosfamide is also responsible for more specific toxicities such as hemorrhagic cystitis, nephropathy, encephalopathy and cardiac toxicity. Bladder toxicity, due to the urotoxin acrolein, is easily prevented by the use of mesna, a thiol compound that binds to the toxin [6]. IFO-induced encephalopathy is
manifested by cerebellar ataxia, mental confusion, complex visual hallucinations, extrapyramidal signs, seizures and/or mutism. The mechanisms of IFO neurotoxicity remain largely unknown [7]. One possible explanation involves 2- and 3-dechloroethylation, with liberation of CAA (Figures 2 and 3). CAA is structurally related to acetaldehyde and trichloroacetaldehyde, the neurotoxic metabolites of ethanol and chloral hydrate (Figure 4). CAA seems to have several mechanisms of action: glutathione depletion [8], inhibition of long-chain fatty acid oxidation [9] and glutamic effects when CAA is oxidized to 2-chloroacetic acid. This is conjugated to cysteine to give S-carboxymethyl-cysteine, which is further degraded into thioglycolic acid, an inhibitor of carnitine-dependent fatty oxidation [10].

The incidence of IFO neurotoxicity varies, but appears related to the route of administration. Risk is greater following oral administration than after short intravenous infusion, and least following continuous intravenous infusion [11].

The main question in the prevention of CNS metastasis in aggressive lymphoma is whether IFO and its active metabolites such as IPM cross the blood–brain barrier. Opinions expressed on this question remain somewhat contradictory. While there is general agreement that IFO crosses the blood–brain barrier, certain sources assert that this is not true for the major active metabolite IPM (Figure 5) [6]. However, Yule et al. [12] have shown a high penetration of both IFO and IPM in the cerebrospinal fluid (CSF) of children after intravenous IFO administration. The children received IFO as a 72-h intravenous infusion. CSF samples were collected 36 h after the beginning of the infusion.

The mean CSF/plasma ratios for IFO and IPM were 1.1 ± 0.4 and 5.2 ± 4.5, respectively. IPM, the most polar of all IFO metabolites, would be expected to cross the blood–brain barrier to a limited extent, producing very low concentrations in the CSF. The metabolism of IFO to 4-OH IFO, followed by the spontaneous production of IPM in the CNS, may be the basis for prevention of CNS lymphoma metastasis by IFO treatment.

The incidence of CNS recurrence is relatively low, at around 5% [4, 13, 14]. Feugier et al. [14] have reported univariate analyses showing that risk of CNS involvement is associated with advanced disease stage \( P = 0.014 \), elevated lactate dehydrogenase level \( P = 0.005 \), poor performance status \( P = 0.018 \) and increased aa-IPI \( P < 0.001 \). After a logistic regression analysis, aa-IPI (0 and 1 versus 2 and 3) was identified
as the only independent factor associated with a higher risk of CNS recurrence.

**Discussion**

IFO itself is not an active antineoplastic agent. To alkylate DNA it requires conversion by cytochromes P450 into active catabolites such as IPM. IFO and IPM cross the blood–brain barrier and IPM concentrations in the CSF are even higher than in plasma. IFO neurotoxicity can occur following its metabolism to CAA, but the incidence is low, particularly when IFO is administered by continuous intravenous infusion.

The overall incidence of cerebral lymphoma metastasis is small, but it is a fatal complication and seems to be related to

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**Figure 3.** Ifosfamide mechanisms of action (Derived from PharmGBK).

**Figure 4.** Chloraacetdehyde and chloral hydrate structures.

**Figure 5.** Distribution of ifosfamide and its metabolites according to Cancer Care Ontario.
aa-IPI score. Despite its potential toxicity, prophylactic treatment with IFO could be given in patients with high potential for CNS recurrence. Continuous intravenous infusion is the safest means of administration. Evaluation of the benefit/risk ratio should be carefully undertaken for populations at risk.

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references