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EDITORIAL

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Introducing ifosfamide in innovative treatment modalities

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Despite the fact that ifosfamide, an isomeric analogue of cyclophosphamide, was introduced for use in the clinic in the early 1970s, continuing research, especially in the pharmacologic area, has been providing further new insights into this drug's mode of action [6]. During the last 2 years, several investigations on ifosfamide and its metabolites as well as their antitumoral and/or toxic effects have been published [10].

Cerny et al. [3] have described a saturable metabolism of continuous high-dose ifosfamide with mesna and GM-CSF. When the ifosfamide dose was stepwise increased from 12 g/m^2 to 18 g/m^2, the area under the curve (AUC) for the parent drug only increased linearly with dose.The AUCs of the metabolites did not increase, particularly not that of the final alkylating agent ifosforamide mustard yielding crosslinks resulting in cytotoxicity. Likewise, the AUC of the inactive metabolite carboxy-ifosfamide did not increase with dose. Therefore, the lack of increase in the AUC of isophosphoramide mustard cannot be attributed to an increase in inactivation by aldehyde dehydrogenase. The same behaviour was found for the inactive dechloroethylated metabolites. This clearly indicates a saturation of the metabolism of ifosfamide. Very recently, Dubourg et al. [7] have suggested that chloroacetaldehyde, a presumed nephrotoxic metabolite of ifosfamide, is detoxified by human kidney tubules. According to Börner et al. [2], this metabolite contributes to the antitumor activity of the drug in vivo. The administration of the isolated chloroacetaldehyde at a dosage of 75 mg/kg delayed significantly the tumor growth in mice. This dose was equitoxic to 40 mg/kg 4-hydroxy-ifosfamide. On a molar base, chloroacetaldehyde was 7-times less potent than 4-hydroxy-ifosfamide. Nevertheless, the authors concluded that, on the base of the AUC values achieved, chloroacetaldehyde seems to exhibit a similar antitumoral activitiy to 4-hydroxy-ifosfamide. With regard to toxicity, Pelgrims et al. [12] have reported ambiguous results on the use of methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy. General recommendation is a dosage of 50 mg methylene blue, applied orally every 4 hours in a 5% glucose solution. Glucose solution compensates for the disturbed fatty acid oxidation and decreases gluconeogenesis. Methylene blue was shown not to alter the pharmacokinetics and metabolism of ifosfamide. de Kraker et al. [5] did not succeed in detecting any protection of proximal tubular cells by amifostine in ifosfamide-containing regimens in children.

The continuing process of introducing new molecules which may be suitable new partners to be combined with well-established ones such as ifosfamide necessitates the systematic investigation of all combinations with regard to putative drug interactions. Ando [1] has reported such a possible metabolic interaction between the new taxane docetaxel and ifosfamide. In vitro studies using human liver microsomes showed cytochrome P450 3A4 to be involved in the metabolic pathways by detoxification of docetaxel and activation of ifosfamide. Thus, the metabolic activation of ifosfamide might be competitively inhibited by preceded docetaxel. This re-enforces the need for distinct phase I-studies before introducing new drug combinations into the clinic.

High clinical activity of ifosfamide has been established for conventional and high-dose single-agent therapy, especially of sarcomas, lymphomas, various

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pediatric malignancies, as well as germ cell, lung, breast, and ovarian cancers [8, 17]. Furthermore, ifosfamide has shown substantial clinical activity as a component of a high-dose regimen because of its known steep linear dose-response curve in cell culture experiments. Ifosfamide has also been tested clinically in combination chemotherapy regimens over recent years in urothelial cancer [9], thymic cancer [11], carcinosarcoma of the uterus [14], mixed Müllerian tumor of the ovary [13], Merkel cell carcinoma [16], nasopharyngeal cancer [4] and cervical cancer [15].

This supplement presents experiences with the use of ifosfamide in high-risk soft tissue sarcomas of adults, in inoperable pancreatic carcinoma, in non-small-cell lung cancer, in cervical cancer, in lymphomas.

Issels updates work in progress conducted either within the framework of the Soft Tissue and Bone Sarcoma Groups (STBSG) of the European Organization for Research and Treatment of Cancer (EORTC) or performed as an intergroup activity of the European Society of Hyperthermic Oncology (ESOH) and the STBSG. The ongoing EORTC activity is an open randomized trial of adjuvant chemotherapy in high-grade primary or recurrent soft tissue sarcoma of adults. After definitive surgery, patients receive either radiotherapy only (standard arm) or doxorubicin plus ifosfamide-containing chemotherapy followed by irradiation (experimental arm). In a less-favorable group of patients (large tumors + low differentiation + unfavorable site), a more aggressive chemotherapy (standard arm) and the same chemotherapy combined with regional hyperthermia (experimental arm) are compared. Thereafter, patients receive further local treatment in the form of surgery with subsequent irradiation followed by the same therapy as given prior surgery.

For patients with inoperable pancreatic cancer, a new drug delivery system has been established by Löhr et al. using microencapsulated cells transfected with the cytochrome P450-producing CYP2B1 gene. This system allows activation of ifosfamide locally after intraarterial positioning in the tumor. This system has completed phase II evaluation.

The Italian Lung Cancer Task Force (F.O.N.I.-C.A.P.) has performed a phase II study aimed at evaluating the activity and safety of a non-platinum-based three-drug combination therapy, consisting of gemcitabine, ifosfamide and vinorelbine, in non-pretreated non-small-cell lung cancer patients. High antitumoral activity with low toxicity has been observed.

Last but not least, data on various ifosfamide-containing regimens in relapsed patients with aggressive non-Hodgkin lymphomas and Hodgkin's disease are presented by Hagemeister. High response rates for all prognostically different subgroups have been achieved.

Ifosfamide is an excellent example of drug which, although having already been used successfully against various tumor entities for many years, still keeps on to be a substance of interest in the treatment of cancer. Specifically, the elucidation of the pharmacokinetic-pharmacodynamic interaction is an area of better insights gained very recently. In addition, the integration of the drug in new drug combinations represents a field of continuous work for the future. Additional insight in the mechanism of Ifosfamide-dependent toxicities and the integration of newer detoxifying agents may allow an even increased exploitation of the antitumoral activity of the substance.

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