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Short communication

Ifosfamide cardiotoxicity in humans

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Summary. Ifosfamide (IFS) is a new alkylating oxazaphosphorine related to cyclophosphamide. Various side effects have been reported; however, cardiotoxicity is not known to occur in humans. We report for first time acute cardiac side effects upon IFS treatment in the form of supraventricular arrhythmias and ST-T wave changes. IFS dose ranged from 6.5 g/m^2 to 10 g/m^2 fractionated in 3 or 5 days and infused i.v. over 4 h daily together with 2-mercaptoethane sulphonate sodium (Mesna). Arrhythmias appeared to be reversible upon discontinuation of the drug. In one patient, readministration of IFS led to arrhythmia that was refractory to treatment. Factors predisposing to the development of cardiac side effects could not be determined in this study. We suggest that patients who receive IFS treatment should be monitored for the occurrence of cardiac abnormalities. Readministration of the drug may be contraindicated in such patients.

Introduction

Ifosfamide (IFS), like cyclophosphamide, is an alkylating oxazaphosphorine that needs to be activated in vivo. It has been effective in various malignancies in humans, alone or in combination chemotherapy at doses of up to 6 g/m^2 [1, 4, 4a]. IFS toxicity include urotoxicity, leukopenia, thrombocytopenia, nausea and vomiting, alopecia, and CNS toxicity [2, 3]. Thus far, no direct IFS-related cardiotoxicity in humans has been reported. In dogs and rhesus monkeys, very high IFS as well as cyclophosphamide doses have caused changes in ECG, cardiac histology, and heart function, with negatively inotropic and chronotropic effects being more severe after IFS [5] or cyclophosphamide [7]. This report indicates that cardiotoxicity in the form of cardiac arrhythmias may occur with IFS monotherapy at higher doses of 6.25–10 g/m^2 fractionated over 3–5 days together with mesna in humans.

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Patients and treatments

Of the 33 patients who entered the IFS studies, 5 (15.2%) developed cardiac side effects that appeared to be related to the treatment (Table 1). ECGs were normal in all patients prior to treatment. In patient 1, atrial premature contractions (APCs) developed on the 3rd treatment day of the first IFS course and subsided within 3 days after discontinuation of the drug. The same ECG changes recurred on the 1st day of the second course and persisted after the discontinuation of the drug, in spite of antiarrhythmic treatment with propranolol.

In patient 2, APCs developed on the 1st day of the first course and led to atrial tachycardia (AT) and atrial fibrillation (AF), which resolved within 2 days after discontinuation of IFS. In patient 3, AF was observed during the first course on the 4 day of treatment. With disopyramide phosphate the arrhythmia reversed within 1 day after the discontinuation of the drug. In patient 4, APCs were observed on the 1st day of the first course; with disopyramide phosphate, the arrhythmia reversed within 1 day after the discontinuation of IFS and did not recur while the patient was off treatment.

In patient 5, IFS (1.25 g/m^2 × 5 days) was given together with doxorubicin (50 mg/m^2) for two cycles. The ECG was normal. Prior to the third cycle, the ECG showed bradycardia (56 beats/min) and ST-T wave changes. Chemotherapy was not given, and the ECG returned to normal within 14 days. The ECG changes did not recur while the patient was off IFS. Treatment was continued with doxorubicin (50 mg/m^2), cyclophosphamide (500 mg/m^2), vincristine (1.5 mg/m^2), and dacarbazine (250 mg/m^2) without untoward cardiac effects.

Discussion

Thus far, IFS-related cardiotoxicity in humans has not been reported. The present report suggests that about 15% of patients may experience adverse cardiac effects at a relatively high dose. APCs and AF were the most common arrhythmias observed; ST-T wave changes occurred in one patient with no clinical symptoms of ischemia. After the discontinuation of the drug, all cardiac abnormalities reversed and did not recur; in some patients with AF, antiarrhythmic drugs were also given to facilitate conversion to normal rhythm. One patient was rechallenged with IFS and developed AT refractory to antiarrhythmic medication. None of the others was given IFS in further treat-

Table 1. Characteristics of patients treated with IFS

Patient	Age sex	Diagnosis	IFS regimen	Cardiac side effects	Time observed	Prior therapy	Previous cardiotoxic drug, TD	Evolution of the arrhythmia
1	43 F	Breast cancer	IFS, 1.25 g/m^2 X 5 days	APCs	First course 3rd day Second course 1st day	CYCL, MTX 5FU, DOX VCR, TMX	DOX, 135 mg/m^2	Reversible after the first course Irreversible after the second course
2	60 F	Breast cancer	IFS, 2 g/m^2 X 3 days	APCs AT AF	First course 1st day	TMX, CYCL MTX, 5FU	–	Reversible with dixogin and disopyramide phosphate
3	70 F	Ovarian cancer	IFS, 2 g/m^2 X 5 days	AF	First course 4th day	CDDP, CYCL EPIDX	EPIDX 300 mg/m^2	Reversible with disopyramide phosphate
4	51 M	SCLC	IFS, 1.25 g/m^2 X 5 days	APCs	First course 1st day	VP-16, CCNU VCR, CDDP MTX, DOX CYCL	DOX 120 mg/m^2	Reversible with disopyramide phosphate
5	20 M	Sarcoma	IFS, 1.25 g/m^2 X 5 days + DOX, 50 mg/m^2 X 1 day	ABC ST-T wave changes	Second course 20th day	DAC, DOX RT chest	DOX, 150 mg/m^2	Reversible

SCLC, small-cell lung carcinoma; APC, atrial premature contractions; AT, atrial tachycardia; AF, atrial fibrillation; ABC, atrial bradycardia; CYCL, cyclophosphamide; MTX, methotrexate; 5FU, 5-fluorouracil; DOX, doxorubicin; VCR, vincristine; TMX, tamoxifen; CDDP, *cis*-diammine-dichloroplatinum; EPIDX, epidoxorubicin; VP-16, etoposide; CCNU, lomustine; DAC, dacarbazine; RT, radiotherapy; TD, total dose

ment. We could not find predisposing factors for the development of the observed cardiac effects in any patient.

In animals, very high doses of IFS have caused changes in ECG, cardiac histology, and heart function, with negatively inotropic and chronotropic effects [5, 7]. Kehl et al. [6] have described a toxic allergic reaction with respiratory failure 10 days after IFS was given in combination with cyclophosphamide, doxorubicin, and vincristine; the authors postulated cross-sensitivity between cyclophosphamide and IFS.

In conclusion, acute cardiac arrhythmias may occur during IFS treatment, with occasional ST-T wave changes. They are reversible after discontinuation of the drug. Antiarrhythmic treatment may be necessary for the conversion of the arrhythmia. Reexposure to IFS may lead to irreversible and refractory arrhythmia. These side effects appear to occur without any predisposing factor.

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