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Comparative activity of ifosfamide and cyclophosphamide

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Summary. Antitumor activity (increase in lifespan and cure) was greater for ifosfamide (IFO) in several experimental tumors, some of which were primarily resistant to cyclophosphamide (CYC).

IFO has been shown to be active in anthracycline-resistant and in adriamycin/cisplatin-resistant sublines of an Ehrlich ascites tumor, as well as in tumor cells primarily resistant to CYC. The few comparative controlled clinical trials available suggest superior single-agent activity of IFO compared with CYC in soft tissue sarcoma and ovarian cancer. Combination chemotherapy with IFO has been effective in second-line treatment of sarcomas, malignant lymphomas, lung cancer, and testicular cancer, most of them pretreated with or refractory to CYC.

Although it is difficult to obtain clinical proof that there is no cross-resistance between IFO and CYC, IFO has been shown to be active in multirefractory malignant lymphomas, in small cell lung cancer not responding to adriamycin, vincristine, and etoposide, and in soft tissue and bone sarcomas. Testicular cancer and pancreatic cancer are some of the tumors in which IFO activity is currently being evaluated and in which CYC has so far failed to show sufficient clinical activity.

More comparative controlled clinical trials are needed in ovarian cancer, breast cancer, malignant lymphomas, sarcomas and cervical cancer, in which IFO has already shown sufficient single-agent activity.

Due to its lower level of cross-resistance with a variety of heterocyclic products, but also with other alkylating agents, in addition to its use in induction chemotherapy, IFO is an important second-line agent in many clinical situations.

Introduction

The oxazaphosphorines cyclophosphamide (CYC) and ifosfamide (IFO) were developed in the laboratories of Asta Werke, Bielefeld, Federal Republic of Germany [20a]. They differ in their physicochemical, pharmacological and toxicological properties. The dose-limiting toxicities are urotoxicity for IFO and bone marrow toxicity for CYC. Due to the development of the uroprotector mesna acute urotoxicity (hemorrhagic cystitis) after IFO and high doses of CYC and bladder cancer after long-term administration of CYC can be prevented. The prevention of urotoxicity by mesna allows the administration of higher doses and increases the therapeutic potential of IFO in sensitive tumors. This, as well as the increasing therapeutic use of IFO + mesna in former target tumors for CYC, requires a comparative evaluation of the two oxazaphosphorines.

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Chemistry, metabolism

The oxazaphosphorines IFO and CYC are latent drugs and need to be activated in vivo [20] (Table 1).

While CYC is a mustard derivative with two chloroethyl groups at the mustard nitrogen, in IFO one chloroethyl group is attached to the exocyclic nitrogen and the second one to the ring nitrogen so that the linear distance of the two functional groups is different in IFO and CYC. According to Druckrey [44b], the optimization of the distance for cross-linkage of nucleic acids may be an important cause of the specific chemotherapeutic efficacy of IFO. The differential chemical structure is connected with physiochemical differences such as a higher water solubility of IFO and with differential pharmacological and toxicological properties [18a, 19, 19a, 38, 149]. The bulky chloroethyl group at the ring nitrogen of IFO might also be responsible for quantitative differences in metabolism [4, 149].

During metabolism both IFO and CYC are hydroxylated at the carbon 4 position, leading to 4-hydroxy compounds which are in equilibrium with aldo-IFO or aldo-CYC, which themselves split spontaneously into the directly alkylating IFO 'mustard' phosphoramide mustard, and acrolein [33, 54, 76, 78a, 139] (Table 1). 4-OH-IFO has a higher cytotoxic specificity than 4-OH-CYC and several other oxazaphosphorine metabolites and alkylating agents [20a].

Since overall metabolism of CYC and IFO is the same [104, 105, 149] the β-phase serum half-lives of IFO and CYC and of their 4-hydroxy metabolites are similar and in the range of 4–6 h.

Therapeutic range

Animal acute, subacute, and chronic toxicity studies and studies concerned with teratology and leukotoxicity have revealed a lower toxicity of IFO than of CYC [1, 19, 26, 91, 92, 102, 115].

Cumulation of curative activity and toxicity has been determined with methods developed by Druckrey [44a]

Table 1. Characteristics of cyclophosphamide and ifosfamide

	Cyclophosphamide	Ifosfamide
	2-(bis-[2-chloroethyl]-amino)-tetrahydro-2*H*-1,3,2-oxazaphosphorine-2-oxide (mol wt. 261.08)	(3-[2-chloroethyl]-2-C[2-chloroethyl]-amino)-tetra-hydro-2*H*-1,3,2-oxazaphosphorine-2-oxide (mol wt. 261.08)
Solubility	In water up to 4%; well soluble in alcohol, benzene, chloroform, dioxan and glycol	In water up to 10%; well soluble in alcohol and ether
Melting point	41–45°C	48–51°C
Alkylating Metabolite	Phosphoramide mustard	Ifosfamide "mustard"
Doses with equivalent alkylating activity in human plasma [38]	1.1 g/m²	3.8 g/m²
Proportion of concentration of 4-hydroxy metabolites in human plasma [149]	3	1

Table 2. Relationship between curative dose 50% (CD_{50}), leukotoxic dose 50% (GD_{50}), and lethal dose 50% (LD_{50}) after a single (D_1) and a dose fractionated over 4 days (D_{1-4}) of IFO or CYC in rats with Yoshida ascites sarcoma

	$\frac{LD_{50}}{CD_{50\,i.v.}} / D_1$	$\frac{LD_{50}}{CD_{50\,i.v.}} / D_{1-4}$	$\frac{GD_{50}}{CD_{50\,i.v.}} / D_1$	References
Ifosfamide, rat	56	82	6.8	[1, 19]
Cyclophosphamide, rat	65	27	4.8	[1, 19]

CD_{50}, curative dose 50%; LD_{50}, lethal dose 50%, GD_{50}, leukotoxic dose 50% (G = danger coefficient [19]

and Brock [20c] and revealed [128] that dose fractionation decreased the toxicity and increased curative activity of IFO as compared to CYC.

The therapeutic advantage with regard to LD_{50}/CD_{50} was also greater with IFO than with CYC in DS-carcinosarcoma and TA nephroblastoma [45, 135], as it was in terms of increase in life-span in L1210 leukemia [65, 66, 108]. Lewis lung carcinoma, the C3H mammary tumor and Ridgway osteogenic sarcoma [65, 66, 108]. In Lewis lung cancer the higher increase in life-span after IFO (65, 66] has not been paralleled in another study with reduction of tumor weight [67].

The antitumor activity of IFO was inferior to that of CYC in CD8F1 mammary cancer when given s.c. and in B16 melanoma when given i.p. [65]. The degree of attenuation of graft-versus-host activity of transplanted T-lymphocytes by pretreatment of donor mice [63] and the inhibition of plaqueformation of spleen cells in mice that had received sheep red blood cells [85] were similar after either of the oxazaphophorines. The T effector cell reactivity of spleen lymphocytes in sensitized Balb/c mice after a single injection of 60% of the LD_{50} of IFO showed a permanent suppression, in contrast to stimulation before and a suppression after the antigen by CYC [145].

Clinical toxicity

There are only two clinical studies which directly compare the side effects of the single agents IFO and CYC. One of them is a randomized phase II EORTC study in soft tissue sarcomas and is published in the same issue by Dr. Bramwell. In the first comparative study in ovarian cancer, published by Teufel and Pfleiderer in 1976 [141], a dose ratio of IFO 2.5 g/m²/day, 1,2(3) and CYC 1.2 g/m²/day, both without mesna, of 6:1 was used.

Despite the 5 times higher IFO dose, a similar incidence of leukopenia and anemia was observed for both the drugs, indicating the lower bone marrow toxicity of IFO. Micro- and macrohematuria was seen in 18% and 9% after IFO, as against 6% after CYC. Renal dysfunction occurred in 13% of the patients treated with IFO but without mesna including three with lethal renal failure, as against 5% of the CYC-treated patients. CNS symptoms were not seen

Table 3. Urotoxicity of long-term cyclophosphamide

Av. single dose (mg/d)	Av. total dose (g)	Av. duration of treatment (months)	Incidence of hematuria/patient treated	References
147	49.9	20.1	($N = 10$) single case reports	[13, 134] [74, 152]
100			2/16 (13%)	[97]
163	55.6	26.6	2/11 (18%)	[110]
163	46.0	28.9	5/43 (12%)	
117	34.0[c]	9.0	6/13 (46%)	[143]
175[a]	NR	NR	4/146 (3%)	[113]
175[b]	NR	NR	2/99 (2%)	
175[a]	2.5 × 24	NR	10/44 (23%)	[34]
NR	30.0	NR	21/159 (13%)	[62]
3500	14.0	4.0	37/110 (34%)[d]	[101]

[a] + MTX + 5-FU
[b] + VCR + 5-FU
[c] Estimated from single dose
[d] 2 virus-induced

NR = Not reported

Table 4. Bladder cancer after long-term treatment with cyclophosphamide

Av. single dose (mg/d)	Av. total dose (g)	Av. duration of treatment (months)	Tumor or disease treated (no. with bladder ca reported)	References
106	164	62	Myeloma (8)	[12, 41, 47, 56, 150]
102	109	65	Malignant lymphoma (18)	[2, 7, 28, 47, 49, 56, 64, 83, 90, 112, 117, 119, 127, 132, 150]
200	179	66	Granulocytic leukemia (1), Lymphocytic leukemia (1), Waldenström disease (1), ovarian ca (1), lung cancer (2), sarcoma (1), breast cancer (1)	[14, 46, 47, 49, 56, 98, 119]
72	169	89	Lupus erythematosus (2), Wegener's granulomatosis (1), rheumatoid arthritis (3), cerebral vasculitis (1)[a], pulmonary fibrosis (1)[b]	[8, 31, 32, 48, 60, 72, 124]

[a] Renal pelvic ca
[b] Ca of ureter

after CYC but occurred in 12% of the patients treated with IFO. Nausea and vomiting were observed in 59% after IFO, as against 41% after CYC.

This range of side effects has since been confirmed, except for urotoxicity, which can now be controlled by mesna [21a]. By giving mesna the incidence of micro- and macrohematuria after IFO can be reduced to about 5% [25, 149, 123] in most cases, whereas without mesna but with standard prophylaxis (i.e., high fluid intake, diuretics, forced diuresis, alkalinization of urin) it ranges from 20% to 40% [23, 123, 149].

With CYC the incidence of cystitis – although generally less common with acute dosing – varies from 0.5% to 50% [11, 43, 71, 86, 88, 137], and its severity varies from microhematuria to severe hemorrhagic cystitis, depending on the cumulative CYC dose and duration of treatment [Table 3].

Hemorrhagic cystitis generally occurred after treatment over 20–30 months with daily doses of CYC between 100 and 175 mg/day and average total doses between 30 and 50 g [Table 3].

Cystitis after long-term treatment was considered to be the bridge symptom to CYC-induced bladder cancer, which has been reported in the world literature in about 35 patients treated for malignant lymphomas and multiple myelomas, and also in some noncancer patients [Table 4]. Interestingly, the patients who developed bladder cancer received similar daily doses of CYC to those who developed cystitis but had been treated with three times higher total doses of CYC for three times longer periods of time [Table 4].

If oxazaphosphorine-induced cystitis can be prevented by mesna, it should also be possible to prevent CYC-induced bladder cancer with mesna. This has been clearly shown by Brock and Schmähl [20b, 68], in rats subjected to long-term treatment with CYC or CYC + mesna. The incidence of papillomas and carcinomas is reduced from 32% to 2% by the addition of the higher mesna dose to CYC [Table 5].

Comparative clinical activity

Four clinical trials compare the single agent activites of IFO and CYC. The superiority of IFO over CYC with regard to response rate in a prospective randomized EORTC

Table 5. Tumors of the urinary bladder observed in male Sprague-Dawley rats after repeated oral administration of cyclophosphamide alone or in combination with mesna or dimesna (from [20 b, 68])

Group	Treatment[a]	Animals with tumors of the urinary bladder					
		Total		Papillomas[b]		Carcinoma[b]	
		No.	%	No.	%	No.	%
1	Control	0	0	0	0	0	0
2	Mesna	0	0	0	0	0	0
3	Dimesna	0	0	0	0	0	0
4	Cyclophosphamide CP	32	32	15	15	17	17
5	CP + mesna l	12	24	6	12	6	12
6	CP + mesna h	1	2	0	0	1	2
7	CP + dimesna l	7	14	2	4	5	10
8	CP + dimesna h	3	6	2	4	1	2

[a] l, low dose; h, high dose
[b] The most advanced type of tumor is given i.e. if an animal had a papilloma and a carcinoma it is counted as carcinoma-bearing only

Table 6. Antitumor spectrum for ifosfamide and cyclophosphamide

Tumor	Ifosfamide			Cyclophosphamide		
	CR + PR/ no. of patients	%	References	CR + PR/ no. of patients	%	References
Small cell lung	77/125	62	[23, 73, 78, 82, 99, 100, 128, 142]	138/363	38	[29]
Non-small cell lung	78/250	31	[35, 36, 59, 99, 100, 116]	20/92	22	[29]
Ovarian cancer	84/129	65	[50, 61, 128, 155]	102/233	44	[5, 10, 42, 87]
Testicular cancer	147/230	64	[15, 107, 120, 121, 126, 128, 152]	9/10		[24]
Breast cancer	132/268	49	[3, 18, 40, 50, 58, 78, 106, 128, 147, 152]	113/282	40	[29, 52, 140]
Soft tissue sarcoma	40/72	56	[23, 39, 78, 122, 128, 136, 154]	12/34	35	[51, 69, 138]
Osteosarcoma	17/26	65	[23, 78, 93]		15	[53]
Ewing's sarcoma	7/13		[120, 146]	12/24	50	[70]
Melanoma	8/57	14	[23, 36, 44, 78]	9/55	16	[80]
Pancreatic cancer	10/14		[23, 58, 78]	4/20		[84]
	16/22					
Prostatic cancer	5/19		[6, 107]	14/186	8	[30, 81, 129]
Hodgkin's lymphoma	3/9		[39, 40, 128]		57	[27, 51, 95, 118]
	16/28	57			54	
Non-Hodgkin's lymphoma	11/24	40	[50, 114, 128]	89/127	70	[27]
	11/37	30				
	18/42	43	[114]			
Leukemias (ALL/AML)	6/27	22		86/237	36	[79, 109]

study in soft tissue sarcoma is reported in this issue by Dr. Bramwell. In ovarian cancer a higher objective reponse rate and a higher 2-year survival rate (5/19 for IFO vs 1/20 for CYC) was reported for IFO by Teufel and Pfleiderer in 1976 [141]. Two lung cancer studies showed superior response rates to IFO, i.e. 29% CR + PR after IFO vs 5% after CYC in non-small cell lung cancer [111] and superior survival after IFO, i.e., MDS of 7–9 months after IFO compared with 3–4.8 months after CYC in small cell and non-small cell lung cancer [144]. In all three studies, the dose ratios of IFO to CYC were about 4 or 5:1, without mesna.

Even without sufficient comparative data an assessment of clinical activity might also be possible from pooled single-agent data indicating similar or superior response rates for IFO in lung cancer, testicular cancer, and sarcomas [75, 16] (Table 6). The response parameters, patient selection criteria, drug dosages, and pretreatment status are often not comparable, so that conclusions drawn from such pooled single-agent data are of limited value for purposes of comparison. They suggest, however, since the responses with IFO were obtained mostly in patients heavily pretreated with combination chemotherapy often including CYC, a good second-line activity of IFO.

This has been confirmed recently by reports from study groups from the NCI (National Cancer Institute, USA), the Royal Marsden Hospital (London), the SAKK (Swiss Group of Clinical Research) and the West German Tumor Center in Essen on responses to IFO in soft tissue sarcoma and osteosarcomas pretreated or practically resistant to CYC or CYC-containing combinations (Table 7).

Similar response rates have been reported in leukemia, in lymphomas, in ovarian cancer, and in lung cancer treated with IFO after pretreatment with CYC-containing combinations ([100, 114, 141, 156, Thatcher this volume]; see Table 8). The discussion on clinical cross-resistance between CYC and IFO has to consider the problem of equitoxic dosage – since drugs used in combinations are often

Table 7. Single-agent activity of ifosfamide in sarcomas pretreated with cyclophosphamide alone or in combination

Sarcomas	Pretreatment with cyclophosphamide	IFO dose (g/m^2 per day)	Response to IFO (CR + PR/treated)	References
Soft tissue	Alone	5.0, day 1	3/15	[17]
Soft tissue	In combination	1.8, days 1–5	3/14	[89]
Soft tissue	In combination	2.0–2.5, days 1–4	3/15	[9]
Soft tissue	In combination	5–8, day 1	3/8	[136]
Soft tissue	In combination	2.4, days 1–5	2+4/15	[131]
Soft tissue	In combination	2.4–3.2, days 1–5	3/8	[103]
Osteosarcoma + Ewing's	In combination	2.4–3.2, days 1–5	3/15	[103]
Osteosarcoma + Ewing's	In combination	1.8, days 1–5	9/32	[89]
Osteosarcoma + Ewing's	In combination	2.4, days 1–5	1+3/15	[131]
Osteosarcoma	In combination	1.2–2.4, days 1–5	2/6	[94]

Table 8. Single-agent activity of ifosfamide in tumors pretreated with cyclophosphamide alone or in combination

Tumor	Pretreatment	IFO dose (g/m^2 per day)	Response to IFO (CR + PR/treated)	References
Leukemias Lymphomas	CYC, VCR, ADR, PRED	1.2, days 1–5	1/6 7/15	[114]
Ovarian ca	Cyclophosphamide combinations	2.5, days 1, 2, (3)	3/11	[141]
Ovarian ca	Cyclophosphamide combinations	2.0, days 1–5	0/4	[156]
Lung ca	Cyclophosphamide (2.5 g/m^2) combinations	5.0, day 1	2/5	(Thatcher et al., this volume)
Lung ca	Cyclophosphamide combinations	1.2, days 1–5, 12, 19, etc.	1/4	[100]

Table 9. In vivo efficacy of cyclophosphamide and ifosfamide in wild-type (ET_{WT}) and adriamycin/cisplatin-resistant $ET_{A/PT}$ sublines of an Ehrlich tumor [131]

	Optimal dose (mg/kg)	ET_{WT}		$ET_{A/PT}$	
		Cure rate	ILS (%)	Cure rate	ILS (%)
Cyclophosphamide	10–300 No effect	0/20	N.S.	0/20	N.S.
Ifosfamide	200–250	7/20	40	5/20	30
Adriamycin + cisplatinum	A: 3 DDP: 6	17/20	>500	0/20	N.S.

not used at their optimal dose levels – as well as the mandatory brief interval between the observation of resistance and the start of comparative treatment. In theory, if the mechanisms of resistance are the same for both the oxazaphosphorines cross-resistance is likely. This has been reported for an L 1210 leukemia line and a P 388 leukemia line, both resistant to CYC because of increased oxidation of the 4-aldophosphamide to the 4-carboxyphosphamide [133], which were also resistant to IFO [65, 66, 77].

Another premise that it is difficult to fulfill in animal model tumors for acquired cross resistance is equal sensitivity of the original tumor type to the drugs concerned. This applies to the LPC plasmocytoma in BALB/c mouse, which in terms of MDS was primarily less sensitive to IFO than to CYC and in the CYC-resistant form did not respond to IFO doses comparable to the curative CYC dose for CYC S line [55].

Human mammary cancer transplanted to nude mice was primarily less sensitive to IFO (20% of LD_{50}/day on days $1-5 \times 4$) and did not respond in the CYC R form to the same IFO dose and schedule [96]. In contrast, in an L 1210 subline resistant to L-PAM, IFO increased the life-span by 100% [65], and tumors primarily resistant to CYC, such as the Ridgway osteogenic sarcoma in mice [65, 66] and the DS carcinosarcoma and TA nephroblastoma in the rat [45, 135], respond to IFO.

In practice, primary and acquired resistance to chemotherapy strongly limits most therapeutic efforts in cytostatic cancer treatment. A number of laboratories and oncological clinics are involved in laboratory model studies and the development of non-cross resistant drug combinations for patients failing on induction therapy.

Seeber's group at the West German Tumor Center in Essen studied the resistance phenomena in vivo in a broad scale of resistant Ehrlich ascites tumors [130, 131]. In this model IFO gives cure rates of 7/20 and increases life-span to 40% in tumors resistant to CYC even at LD_{20} dose levels.

Special interest attaches to the findings on resistance to combination chemotherapy. Adriamycin plus cisplatin are curative in more than 80% of the animals carrying the wild-type tumor. After weekly treatment of this line with lower increasing doses of both drugs over more than 1 year the tumor became totally resistant to the combination of adriamycin and cisplatin. However, IFO again at its optimal dose cured 30%–40% of the animals carrying this mul-

tirefractory tumor with acquired resistance to the clinically important combination of ADR + cisplatin (Table 9).

The data from the Ehrlich ascites system and the clinical data seem to indicate that IFO possesses antitumor activity after pretreatment with various groups of antineoplastic drugs, such as anthracyclines, vinca alkaloids, podophyllotoxin, methotrexate, cisplatinum and sometimes even alkylating agents.

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