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Antitumor activity of FCE 26644 a new growth-factor complexing molecule

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Abstract FCE 26644, or 7,7′-(carbonyl-bis[imino-*N*-methyl-4, 2 pyrrole carbonyl-imino{*N*-methyl-4, 2-pyrrole}carbonylimino])-bis-(1, 3-naphthalene)disulfonic acid, belongs to the newly synthesized class of sulfonated derivatives of distamycin A. FCE 26644 is a noncytotoxic molecule capable of inhibiting the binding of basic fibreblast growth factor (bFGF), platelet-derived growth factor (PDGFβ) and interleukin 1 (IL-7) to their receptors and to block bFGF-induced vascularization in vivo as well as neovascularization in the chorioallantoic membrane. FCE 26644 and suramin, a compound possessing the same terminal half-life ($t_{1/2}$) in mice and, presumably, the same mode of action, inhibit the growth of solid murine tumors, M5076 reticulosarcoma, and MXT and S180 fibrosarcoma and are inactive against B16F10 melanoma. The activity of FCE 26644 was constantly observed at nontoxic doses, at variance with suramin. FCE 26644 was also found to maintain activity against M5076 resistant to cyclophosphamide and to be equally active against UV 2237 and UV 2237/ADR fibrosarcoma.

Key words Growth factors · Angiogenesis · Suramin

Introduction

A number of growth factors are recognized to play a role in tumor progression, either through a direct stimulus to cell division and/or through activation of neovascularization, an essential event in tumor progression and metastasis [10, 15, 19, 32]. The increased production of platelet-derived growth factor (PDGFβ), basic fibroblast growth factor (bFGF), interleukin 1 (IL-1), and insulin growth factor (IGF-1) as well as the overexpression of their receptors has been reported in a variety of human tumors [1, 4, 8, 20, 26]. It is also well known that bFGF as well as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) are capable of stimulating angiogenesis in vitro and in vivo [14, 25, 29]. FCE 26644 has been found to inhibit bFGF, PDGFβ, and IL-1 binding; to inhibit angiogenesis in the chorioallantoic membrane (CAM) assay and angiogenesis induced by bFGF [6]; and to inhibit scatter activity induced by HGF [7].

The approach of modulating tumor progression with drugs that inhibit growth/angiogenic factors is a fascinating one and may represent a new concept in adjuvant chemotherapy when used alone or in combination with classic antitumor drugs. This approach is being explored either with the use of monoclonal antibodies directed to the factors [16, 18, 30] or with growth factor-complexing molecules of different origin such as suramin [17, 27, 28], polysaccharides [23, 33], and anionic compounds [5].

Suramin has recently been reported to be active in inhibition of angiogenesis on the CAM [11] and to inhibit in vivo bFGF-induced angiogenesis [24] as well as possessing antitumor activity on a number of experimental tumor models [31]. The molecule has demonstrated definite antitumor activity in patients with advanced prostatic carcinoma [22, 27]. We have recently synthesized a series of sulfonated distamycin A derivatives presumably possessing the same mode of action as suramin [6]. Distamycin A is an antiviral drug [2] produced by Streptomyces distallicus that is devoid of any in vivo antitumor activity [3].

This paper presents the results obtained testing the antitumor activity of FCE 26644, a molecule selected for clinical development, on different solid murine tumor models in comparison with suramin.

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Materials and methods

Drugs

FCE 26644 was synthesized in the chemical laboratories of Pharmacia Farmitalia C. Erba (Milan, Italy). Suramin (Germanin) was obtained from Bayer (Leverkusen, Germany). FCE 26644 and suramin were weighed and dissolved in saline immediately prior to use.

Animals

Female C57Bl/6, BALB/c, C57Bl/6 × DBA/2 (B6D2F1), and C3H/HeN mice aged 6–8 weeks and male Swiss nu/nu mice, supplied by Charles River (Calco, Como, Italy), were used. Animal health was monitored every 4–6 weeks by serological testing. The animals were free of infectious pathogens, including mouse hepatitis virus, Sendai virus, and *Mycoplasma pulmonis*. Animals were housed in plastic cages under temperature- and humidity-controlled conditions. Food and water were available ad libitum and a 12-h/12-h light/dark schedule was maintained. The body weight at the start of the experiments ranged between 20 and 23 g.

Evaluation of drug levels in plasma

Suramin and FCE 26644 were extracted from plasma and tissues using a solution containing 0.1 *M* tetrabutylammonium phosphate (TBPA), 25% CH_3CN, 25% methanol, and 10% 2 *M* ammonium acetate, with 2-naphthol serving as the internal standard. Samples were analyzed using a high-performance liquid chromatography HPLC system with an SP8490 detector (Spectra Physics) set to 313 nm, a C_{18}NovaPak column (Waters), and a mobile phase of 42% phosphate buffer (pH 6.6), 43% methanol, 15% CH_3CN, and 0.005 *M* TBPA. The detection limit of the method, expressed as the concentration that gives a signal-to-noise ratio of about 3, was 125 ng/ml.

Pharmacokinetic analysis

At each time point postdosing, mean FCE 26644 and suramin plasma concentrations, expressed as micrograms of FCE 26644 and Suramin free acid per milliliter, were calculated and used for the evaluation of pharmacokinetic parameters by standard noncompartmental analysis. The parameters estimated included the volume of the terminal half-life ($t_{1/2}$), plasma clearance (CL), and the area under the curve (AUC).

Murine solid tumors

The effect of the test compounds on tumor growth was evaluated in the following models: M5076 reticulosarcoma and its cyclophosphamide-derived subline M5076/CTX [9] were transplanted i.m. into compatible C57Bl/6 mice and s.c into Swiss nu/nu mice (5×10^5cells/mouse); B16F10 melanoma was transplanted s.c. into compatible C57Bl/6 mice (5×10^5 cells/mouse); MXT fibrosarcoma (10^5 cells/mouse) was transplanted s.c. into compatible B6D2F1 mice; S180 fibrosarcoma (10^5 cells/mouse) was transplanted s.c. into compatible BALB/c mice; and UV2237 fibrosarcoma and its multidrug-resistant subline UV2237/ADM were transplanted i.m. at 5×10^5 and 1×10^6 cells/mouse, respectively, into compatible C3H mice [11].

Antitumor activity

Solid-tumor growth was assessed by caliper measurements, and the tumor weight was estimated [12]. The antitumor effect was determined by calculating the difference between the tumor weights in the treated group and those in the control group. The AUC of the tumor-growth curve was calculated.

The percentage of inhibition (%Inhib. AUC) was calculated using the following formula:

$$100 - \frac{\text{AUC tumor growth treated mice}}{\text{AUC tumor growth control mice}} \times 100.$$

The percentage of increase in survival (T/C%) was calculated using the following formula:

$$\text{T/C\%} = \frac{\text{median survival time treated mice}}{\text{median survival time control mice}} \times 100.$$

Groups of ten were used. The number of long-term survivors (LTS) refers to mice surviving for > 120 days after tumor implantation.

Toxicity

A toxicological evaluation was made on the basis of laboratory, gross pathology, and histology findings in mice.

Results

The chemical structure of FCE 26644 is presented in Fig. 1. The antitumor activity of FCE 26644 was compared with that of suramin in four murine solid-tumor models employing various treatment schedules.

Pharmacokinetics and biodistribution

Single i.v. injections of suramin and FCE 26644 at 200 mg/kg were given to C57Bl/6 mice; no significant

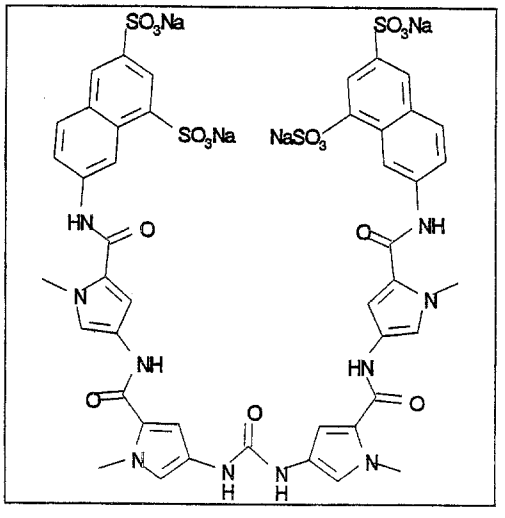

Fig. 1. Chemical structure 2,2′-(carbonyl-bis-[imino-*N*-methyl-4,2 pyrrolecarbonyl-imino-{*N*- methyl-4,2-pyrrole}-carbonylimino])-bis-(1,3- naphthalene)disulfonic acid (FCE 26644)

difference in plasma biodistribution was seen. The AUC values obtained for FCE 26644 and suramin, respectively, were 67.2 and 49.3 mg h ml^{-1}; the respective $t_{1/2}$ values were 165.11 and 174 h, and the CL values were 2.62 and 3.56 ml h kg^{-1}.

Efficacy against M5076 reticulosarcoma

Four i.v. injections of FCE 26644 given at 3-day intervals starting at 24 h after tumor cell implantation were associated with a significant percentage of AUC inhibition at total doses of 200, 400, 600, and 800 mg/kg, with 2/10 drug-related deaths being observed at the highest dose (Table 1). At equimolar doses of suramin, lower inhibition values were observed at the total dose of 220 mg/kg; higher doses resulted in drug-related deaths in all treated animals.

The effect of treatment at different stages of tumor growth was studied by starting treatment at days 1, 8, and 15 following tumor implantation. Compounds were injected i.p. at equimolar doses of 100 and 110 mg/kg for FCE 26644 and suramin, respectively. FCE 26644 was active and well tolerated at total doses of 1.2 and 1.1 g/kg when treatment was started at days 1 and 8. Activity was also observed when treatment was started at day 15, although the activity observed was marginal. Under the same experimental conditions, suramin proved to be less active than FCE 26644.

The antitumor activity of the two compounds was also assayed on M5076 murine reticulosarcoma implanted into athymic mice. From Table 2 it can be seen that FCE 26644 and suramin maintained their efficacy and that FCE 26644 was again the most active of the two. This result suggests that the observed antitumor activity is not mediated through T-cell-dependent mechanisms.

Efficacy against S180 fibrosarcoma

Comparable AUC inhibition values were obtained after treatment with FCE 26644 at total i.v. doses of 300 and 600 mg/kg (three weekly injections) or the i.p. dose of 600 mg/kg (six administrations given at 3-day intervals; Table 3). Comparable results in terms of

Table 1 Activity of FCE 26644 and suramin on M5076 reticulosarcoma[a]

Compound	Treatment		Route	AUC % inhib.[b]	T/C%[c]	Number of deaths/ total number of mice	LTS[d]
	Injection dose (mg/kg)	Schedule (day)					
FCE 26644	50	1, 4, 7, 10	i.v.	69	104	0/10	0/10
	100	"	i.v.	74	104	0/10	0/10
	150	"	i.v.	84	104	0/9	0/9
	200	"	i.v.	87	100	2/10	0/10
	100	d1, q4d × 12	i.p.	100	200	0/9	1/9
	100	d8, q4d × 11	i.p.	82	180	0/9	1/9
	100	d15, q4d × 5	i.p.	27	145	0/9	0/9
Suramin	55	1, 4, 7, 10	i.v.	42	125	0/10	0/10
	110	"	i.v.	Toxic	Toxic	10/10	0/10
	165	"	i.v.	Toxic	Toxic	10/10	0/10
	110	1, 5, 8, 12	i.p.	64	103	2/9	0/9
	110	8, 12, 15, 18	i.p.	43	118	1/9	0/9
	110	15, 18, 21	i.p.	15	113	0/9	0/9

[a] 5×10^5 cells/mouse were implanted i.m. into female C57B1/6 mice
[b] Inhibition of solid-tumor growth
[c] Median increase in survival time
[d] Number of mice surviving for more than 120 days fater tumor implantation

Table 2 Activity of FCE 26644 and suramin on M5076 reticulosarcoma implanted into athymic mice[a]

Compound	Treatment		Route	AUC % inhib[b]	Toxic deaths/ total number of mice
	Injection dose (mg/kg)	Schedule (day)			
FCE 26644	100	1, 5, 9, 13, 16	i.p.	95	0/8
	200	1	i.v.	91	0/7
Suramin	110	1, 5, 9, 13, 16	i.p.	63	0/8
	220	1	i.v.	47	0/8

[a] 5×10^5 cells/mouse were implanted i.m. into female Swiss nu/nu mice
[b] Inhibition of solid-tumor growth

Table 3 Activity of FCE 26644 and surmain on murine S180 fibrosarcoma[a]

Compound	Treatment		Route	AUC % inhib.[b]	T/C%[c]	Number of toxic deaths/ total number of mice
	Injection dose (mg/kg)	Schedule (day)				
FCE 26644	100	1, 8, 15	i.v.	56	132	0/10
	200	1, 8, 15	i.v.	55	138	0/10
	100	1, 4, 8, 11, 15, 18	i.p.	61	132	1/10
Suramin	100	1, 8, 15	i.v.	61	170	0/10
	100	1, 4, 8	i.p.	60	155	2/10

[a] 5×10^5 cells/mouse were implanted s.c. into female BALB/c mice
[b] Inhibition of solid-tumor growth
[c] Median increase in survival time

Table 4 Activity of FCE 26644 and suramin on MXT fibrosarcoma[a]

Compound	Treatment		Route	AUC % inhib.[b]	T/C%[c]	Number of toxic deaths/ total number of mice
	Injection dose (mg/kg)	Schedule (day)				
FCE 26644	100	1, 6, 9, 13, 15, 19, 22	i.p.	21	101	0/7
	150	1, 6, 9, 13, 15, 19, 22	i.v.	48	99	0/9
	200	1, 9, 15, 22	i.v.	32	111	0/9
Suramin	110	1, 6, 9	i.p.	59	141	2/10

[a] 5×10^5 cells/mouse were implanted s.c into female B6D2F1 mice
[b] Inhibition of solid-tumor growth
[c] Median increase in survival time

Table 5 Activity of FCE 26644 and suramin on murine B16F10 melanoma[a]

Compound	Treatment		Route	AUC % inhib.[b]	T/C%[c]	Number of toxic deaths/ total number of mice
	Injection dose (mg/kg)	Schedule (day)				
FCE 26644	100	1, 4, 7, 11	i.v.	25	120	0/9
	200	1, 4, 7, 11	i.v.	6	75	2/10
Suramin	110	1, 4, 7, 11	i.v.	18	83	2/9
	220	1, 4, 7, 11	i.v.	Toxic	67	4/9

[a] 1×10^5 cells/mouse were implanted s.c. into female C57B1/6 mice
[b] Inhibition of solid-tumor growth
[c] Median increase in survival time

tumor inhibition with a higher increase in survival time were observed with suramin at a total dose of 300 mg/kg i.v. The same dose given i.p. was equally active but was associated with 2/10 drug-related deaths.

Efficacy against MXT fibrosarcoma

In this tumor model, the best therapeutic result was obtained by giving FCE 26644 at 3-day intervals at a total i.v. dose of 1050 mg/kg, which was associated with 48% AUC inhibition and no drug-related death (Table 4). Suramin given at a total i.p. dose of 330 mg/kg was equally effective, producing 59% AUC inhibition and a 141% increase in survival time, but with 2/10 drug-related deaths.

Efficacy against B16F10 melanoma

No activity was observed against this tumor model, even at doses of both compounds that caused drug-related deaths (Table 5).

Table 6 Activity of FCE 26644 on M5076/CTX reticulosarcoma and UV2237 and UV2237/ADM fibrosarcoma

Tumor	Treatment		Route	AUC % inhib.[c]	T/C%[d]	Number of toxic deaths/ total number of mice
	Injection dose (mg/kg)	Schedule (day)				
M5076/ CTX[a]	100	d1;q4dx9	i.p.	96	200	0/10
	200	1	i.v.	46	131	0/10
UV2237[a]	150	1, 4, 7	i.v.	27		0/9
UV2237/ ADM[b]	150	"	i.v.	57		0/9

[a] 1×10^5 cells/mouse were implanted i.m. into female C57B1/6 mice (M5076) and female C3H mice (UV2237; body weight range, 20–22 g)
[b] 1×10^6 cells/mouse were implanted s.c. into female C3H mice (body weight range, 20–23 g)
[c] Inhibition of solid-tumor growth
[d] Median increase in survival time

Efficacy of FCE 26644 against M5076/CTX reticulosarcoma and UV2237 and UV2237/ADM fibrosarcoma

Against M5076/CTX reticulosarcoma, FCE 26644 was found to be active when injected i.p. at the cumulative dose of 900 mg/kg or i.v. at the single dose of 200 mg/kg, with AUC inhibition values being comparable with those observed in the sensitive model; against UV 2237 and UV 2237/ADM fibrosarcoma, the compound showed borderline efficacy and revealed no significant difference between the two models (Table 6).

Toxicity

At equimolar doses, suramin induced a higher incidence of mortality than did FCE 26644 as shown in Tables 1–6. Both compounds produced important decreases in platelets, but only with suramin was severe anemia also present. Enlargement of the spleen and liver (both compounds) and of the kidneys (suramin alone) was evident at necropsy. At the histopathology examination, the most prominent alteration was the presence of foamy macrophages in the lungs, spleen, and liver and was observed for both compounds. Animals treated with FCE 26644 at the highest doses showed liver necrosis, which was sometimes associated with changes in hepatic enzymes. Kidney lesions, namely, vacuolation, dilatation, and necrosis of cortical tubules, were seen only in animals treated with suramin.

Discussion

This paper reports data on the antitumor activity of a novel compound, FCE 26644, in parallel with suramin, a compound presumably possessing the same mode of action. Both molecules have the same pharmacokinetics, form complexes with several growth factors and cytokines, and inhibit both angiogenesis in the CAM assay and the neovascularization induced by bFGF-Gelfoam implanted s.c. into mice.

In the experimental tumor models evaluated, both molecules were effective in inhibiting tumor growth in the M5076 murine reticulosarcoma, MXT, and S180 murine fibrosarcoma models and were inactive against B16F10 melanoma. Moreover, FCE 26644 was found to be active against M5076/CTX and UV2237 fibrosarcoma, although with borderline values of activity, and to be equally effective on the subline made resistant to doxorubicin, UV2237/ADM.

Suramin appeared to be more toxic than FCE 26644, mainly due to the higher mortality observed on an equimolar basis. Morever, as regards hematology findings, FCE 26644 induced a transient decrease in platelets, whereas suramin had a long-lasting effect on thrombocytes, which was associated with severe anemia. The liver necrosis tended to regress after treatment and did not appear to threaten the life of affected animals. FCE 26644 did not induce any nephrotoxicity. The renal lesions observed with suramin persisted over a long observation period, showing a minimal trend toward recovery.

The mode of the antitumor activity of FCE 26644 is under investigation. The molecule exerts a cytostatic effect only at high in vitro concentrations ($> 100\ \mu M$) and the effect is promptly reverted by suspending the cells in drug-free medium (manuscript in preparation). The maintenance of antitumor activity on M5076 reticulosarcoma implanted into nude mice indicates that the observed effect is not mediated by T-cell activity. We can thus hypothesize that the ability of FCE 26644 to complex bFGF, PDGFβ, IL-1, and IGF-1 [6] may be the basis for its antitumor activity and that the compound acts by blocking the growth factors

produced by the tumor cells and inhibiting their growth and/or tumor vascularization. This hypothesis can, of course, be reinforced only when tumor cells from responsive and nonresponsive models have been characterized in terms both of their ability to produce growth factors and cytokines and of the presence of their respective receptors.

The concept of modulating tumor growth through inactivation of tumor-produced factors is a very interesting one in view of its possible use in combined therapy with cytotoxic drugs and, dealing with definite chemical entities, in modifying the structure and increasing the specific inhibition of target factors.

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