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ICRF-187 rescue in etoposide treatment in vivo. A model targeting high-dose topoisomerase II poisons to CNS tumors

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Abstract The catalytic cycle of topoisomerase II is the target of some of the most successful antitumor agents used today, e.g., etoposide (VP-16), in the treatment of testicular cancer and small-cell lung cancer. The cell kill mediated by topoisomerase II poisons can be antagonized by distinct drug types. Thus, we have demonstrated etoposide antagonism with the type-II anthracycline aclarubicin, the antimalarial drug chloroquine, and the cardioprotective agent ICRF-187. In other setups, combinations of agonist and antagonists have led to high-dose regimens for counteracting drug resistance. Thus, the exploitation of folinic acid rescue for methotrexate toxicity and the use of mesna to protect against cyclophosphamide toxicity have enabled the use of high-dose methotrexate and cyclophosphamide protocols. Using a similar approach, we have studied possible ways to apply antagonists to topoisomerase II poisons. NDF1-hybrid female mice were treated with the various drugs and drug combinations. Lethality (LD_{10} and LD_{50} values) was computed by use of the maximum-likelihood method, and the antitumor effect of the drugs was compared in mice inoculated i.p. with either L1210 cells or Ehrlich ascites tumor cells. In addition, the compounds were tested on L1210 cells inoculated intracranially. The toxicity of the various drugs was evaluated by weight and leukocyte counts. ICRF-187 rescues healthy mice from lethal doses of topoisomerase II poisons. In mice the ICRF-187 LD_{10} was 500 mg/kg. Within a wide nontoxic dose range (50–250 mg/kg) of ICRF-187 we found protection against m-AMSA and etoposide lethality. Thus, the LD_{10} of etoposide increased from 34 mg/kg for the single agent to 122 mg/kg for its combination with ICRF-187, corresponding to a 3.6-fold etoposide dose escalation. In contrast, ICRF-187 did not protect against lethal doses of the non-topoisomerase II-directed drug paclitaxel. We further investigated the antitumor effect of equitoxic schedules in mice inoculated i.p. with L1210 or Ehrlich ascites tumor cells. The L1210-bearing mice appeared to obtain a larger increase in life span from the etoposide and ICRF-187 combination as compared with etoposide alone, whereas this was not the case in mice inoculated with Ehrlich ascites tumor cells. As the hydrophilic ICRF-187 is not expected to cross the blood-brain barrier, in contrast to the lipophilic etoposide, we investigated the effect of the drug combination in mice inoculated intracranially with L1210 cells. We obtained a significant increase in life span in mice treated with ICRF-187 + etoposide as compared with mice treated with an equitoxic dose of etoposide alone. Thus, there appear to be potential routes by which one can benefit from this antagonism. ICRF-187 is a powerful nontoxic protector against the lethality of the topoisomerase II-directed drugs etoposide and m-AMSA in vivo. A brain tumor model demonstrates the superiority of high-dose etoposide treatment with ICRF-187 protection as compared with etoposide treatment alone. This implies that tumors in the brain can be reached by cytotoxic drug doses and that normal tissues can be protected due to differences in drug transport across the blood-brain barrier. ICRF-187 is therefore a promising lead compound for the development of schedules using high-dose topoisomerase II poisons in the treatment of brain tumors and metastases.

Key words Topoisomerase II poisons · High-dose-chemotherapy · Topoisomerase II rescue · Etoposide effect regulation in vivo · ICRF-187, ADR-529 · Brain tumor model

Abbreviations *m-AMSA* 4′-(9-acridinylamino) methanesulfon-*m*-anisidide, amsacrine) · *ICRF*-187 ADR-529,

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dexrazoxane, [(+)-1,2-bis(3,5-dioxopiperazinyl-1-yl) propane] · *mesna* Sodium 2-mercaptoethane sulfonate

Introduction

The essential nuclear enzyme topoisomerase II allows the separation of intertwined DNA strands by creating a transient double-strand break in the DNA backbone. This catalytic cycle of topoisomerase II is the target of some of the most successful antitumor agents used today, e.g., etoposide (VP-16), in the treatment of testicular cancer and small-cell lung cancer [2]. There is solid evidence that etoposide as well as a number of other clinically successful antitumor agents, such as daunorubicin and doxorubicin (Adriamycin) [28], exert their activity by inhibiting the resealing of the DNA breaks created by topoisomerase II [19, 20]. Although the precise cell-killing mechanism is unknown, an obligatory step for the cytotoxicity of the topoisomerase II-targeting agents is an increase in cleavable complexes between DNA and topoisomerase II [19]. This complex mechanism of cell kill is susceptible to drug modulation.

Our interest in this type of regulation of drug effect was raised by the finding that the clinically active DNA-intercalating drug aclarubicin completely antagonized the cytotoxicity of topoisomerase II-targeting agents such as etoposide, teniposide, m-AMSA, daunorubicin, and oxaunomycin [15–17]. Not only aclarubicin but also several other DNA-binding agents such as ethidium bromide [24], 9-aminoacridines [7, 21], and chloroquine [18] can antagonize the cytotoxicity of topoisomerase II-targeting agents. It is believed that these DNA-binding drugs inhibit the initial DNA-binding step of the enzyme and thereby suppress the interaction between the enzyme, the topoisomerase II-targeting drug, and the DNA. Recently, more specific interactions with topoisomerase II have been described. Thus, it appears that cation-chelating bisdioxopiperazines may lock topoisomerase II at its magnesium adenosine triphosphate (ATP)-binding site at the stage of the catalytic cycle where the homodimeric enzyme is thought to exist in the form of a closed bracelet surrounding the DNA [22, 23]. By locking the enzyme, the bisdioxopiperazine hinders topoisomerase II poisons from exerting their cytotoxicity. Thus, the bisdioxopiperazine derivative ICRF-187 abolishes both the DNA breaks and the cytotoxicity caused by the topoisomerase II poisons etoposide and daunorubicin [25].

We have studied possible ways of utilizing these various antagonists as a means of differentially protecting normal tissue. Drugs such as etoposide are usually given at maximally tolerated doses in the clinic, wherefor dose increments that otherwise might have overcome drug resistance are not feasible. However, use of antagonists together with agonist may give new prospects. Thus, folinic acid rescue and mesna are in clinical use for protection against methotrexate and cyclophosphamide toxicity, respectively, enabling the use of high-dose methotrexate and cyclophosphamide protocols [1, 3]. If such models of manipulation of etoposide effect are to be useful, they should enable significant dose escalations in vivo. We have therefore screened in vitro antagonists for in vivo protection against etoposide lethality [13]. Herein we demonstrate that ICRF-187 markedly antagonizes the toxicity of etoposide in vivo and, accordingly, carries the prospect of powerful effect regulation.

Materials and methods

Drugs

ICRF-187 (Cardioxane, purchased from EuroCetus B.V., Amsterdam, The Netherlands) was dissolved in saline to a concentration of 25 mg/ml. Etoposide (20 mg/ml) and paclitaxel (6 mg/ml) were bought from Bristol-Myers Squibb, Copenhagen, in solution for clinical use. m-AMSA (purchased from Parke-Davis, Pontypool, Gwent, United Kingdom) was obtained in an *N*, *N*-dimetylacetamide solution and was further diluted in acid lactose to a concentration of 5 mg/ml.

In vivo experiments

First-generation hybrids of female randomly bred Swiss mice and male inbred DBA (NDF1-hybrid) mice were used as previously described [5]. The mice weighed between 19 and 21 g at the start of the experiments. Doses of etoposide, m-AMSA, and paclitaxel were adjusted according to weight, and ICRF-187 was given in fixed doses either i.p. or i.v. in a tail vein 20 min before administration of the investigated drug. Lethality was recorded and surviving mice were killed after 60 days. Toxicity was evaluated by weight and leukocyte counts. For weight evaluations, mice were treated with drugs, marked, and weighed for 11 consecutive days. Blood for leukocyte counts was obtained from a tail vein and counted in a hemocytometer on days 3, 5, and 7 after treatment.

In therapy studies, mice were inoculated i.p. with either 10^5 L1210 leukemia cells or 15×10^6 Ehrlich ascites tumor cells on day 0 and treated with drugs i.p. on day 4 after inoculation. The brain tumor model consisted of 10^4 L1210 cells in a volume of 30 µl isotonic sodium chloride, which was inoculated on day 0 into the temporal region of mice, which were then treated i.p. on day 2, 3, or 4 after inoculation.

Results

Using the log-probit method [4, 5, 14], we estimated the LD_{90} of ICRF-187 in mice treated once i.p. to be 1500 mg/kg and the LD_{10} to be 500 mg/kg. First we investigated the range of ICRF-187 doses capable of protecting against etoposide-induced lethality. In drug-combination studies we used concentrations in the nontoxic 50- to 250-mg/kg range except in one experiment, where we used 500 mg/kg. These varying

Table 1 Lethality of etoposide given alone and in combination with ICRF-187. The etoposide dose is fixed and the doses of ICRF-187 vary[a]

Experiment number	Number of mice	VP-16 (mg/kg)	Survivors/ treated	ICRF-187 + VP-16 (mg/kg)	Survivors/treated
1	11	90	1/11 (9%)	50 + 90	11/11 (100%)
				125 + 90	11/11 (100%)
				250 + 90	11/11 (100%)
2	11	90	3/11 (27%)	50 + 90	9/11 (82%)
				125 + 90	11/11 (100%)
				250 + 90	11/11 (100%)
3	11	90	5/11 (45%)	250 + 90	11/11 (100%)
				500 + 90	11/11 (100%)
4	11	90	2/11 (18%)	50 + 90	11/11 (100%)
				125 + 90	11/11 (100%)
				250 + 90	11/11 (100%)

[a]The lethality of etoposide is decreased by pretreatment with ICRF-187 in low, nontoxic doses. Drugs were given once i.p. ICRF-187 was given immediately before etoposide

Table 2 Lethality of etoposide given alone and in combination with ICRF-187. The ICRF-187 dose is fixed and the doses of etoposide vary[a]

Experiment number	Number of mice	VP-16 (mg/kg)	Survivors/ treated	ICRF-187 + VP-16 (mg/kg)	Survivors/ treated
1	11	90	8/11 (73%)	125 + 90	11/11 (100%)
		100	2/11 (18%)	125 + 100	11/11 (100%)
		120	1/11 (9%)	125 + 120	11/11 (100%)
		140	0/11 (0%)	125 + 140	11/11 (100%)
2	11	90	3/11 (27%)	125 + 90	11/11 (100%)
		100	2/11 (18%)	125 + 100	10/11 (91%)
		120	0/11 (0%)	125 + 120	8/11 (73%)
		140	1/11 (9%)	125 + 140	6/11 (55%)
3	11	90	8/11 (73%)	125 + 90	11/11 (100%)
		100	3/11 (27%)	125 + 100	11/11 (100%)
		120	1/11 (9%)	125 + 120	11/11 (100%)
		140	2/11 (18%)	125 + 140	9/11 (82%)
4	11	90	3/11 (27%)	125 + 90	9/11 (82%)
		140	1/11 (9%)	125 + 140	9/11 (82%)
		180	0/11 (0%)	125 + 180	1/11 (9%)
		200	0/11 0%	125 + 200	0/11 (0)
5	11	90	3/11 (27%)	125 + 90	11/11 (100%)
		140	4/11 (36%)	125 + 140	11/11 (100%)
		180	0/11 (0%)	125 + 180	5/11 (45%)
		200	2/11 (18%)	125 + 200	2/11 (18%)
6	11	90	1/11 (9%)	125 + 90	11/11 (100%)
		140	0/11 (0%)	125 + 140	8/11 (73%)
		180	2/11 (18%)	125 + 180	5/11 (45%)
		200	1/11 (9%)	125 + 200	2/11 (18%)

[a]In etoposide dose-escalation experiments ICRF-187 provides significant protection, even at an etoposide dose of 140 mg/kg

doses were combined with a fixed etoposide dose of 90 mg/kg. The results, shown in Table 1, demonstrate that doses of ICRF-187 as low as 50 mg/kg provide nearly full protection.

Next we escalated the dose of etoposide to 200 mg/kg and used a fixed dose of ICRF-187 as a protector against etoposide-induced lethality. The results are shown in Table 2. ICRF-187 provides significant protection, even at an etoposide dose of 140 mg/kg, whereafter the ICRF-187-mediated protection decreases and is negligible at an etoposide dose of 180 mg/kg. LD_{10} and LD_{50} values were computed using the maximum-likelihood method on the compiled data (Table 3), showing that whereas the LD_{10} of etoposide alone is 34 mg/kg, it is 122 mg/kg when the drug is combined with 125 mg/kg ICRF-187, corresponding to an etoposide dose increment of 360%. Similar results were obtained when ICRF-187 was given i.v. and etoposide was injected i.p. (data not shown). Thus, ICRF-187 is a powerful protector against etoposide-induced lethality in mice.

To test whether the ICRF-187-mediated antagonism translated to other topoisomerase II poisons in vivo, we investigated the toxicity of the combination of ICRF-187 and m-AMSA in healthy mice using the same schedule described above. As can be seen in Fig. 1, ICRF-187 protects not only against the non-intercalative etoposide but also against death induced

Table 3 Estimation of LD_{10} and LD_{50} values[a]

	log LD_{10}	SE	LD_{10} (mg/kg)	log LD_{50}	SE	LD_{50} (mg/kg)
VP-16	1.531	0.123	34.0	1.853	0.051	71.3
ICRF + VP-16	2.088	0.009	122.4	2.214	0.011	163.8

[a]Calculation of LD_{10} and LD_{50} values using the maximum-likelihood estimation. The 6 experiments listed in Table 2 are included in the computations

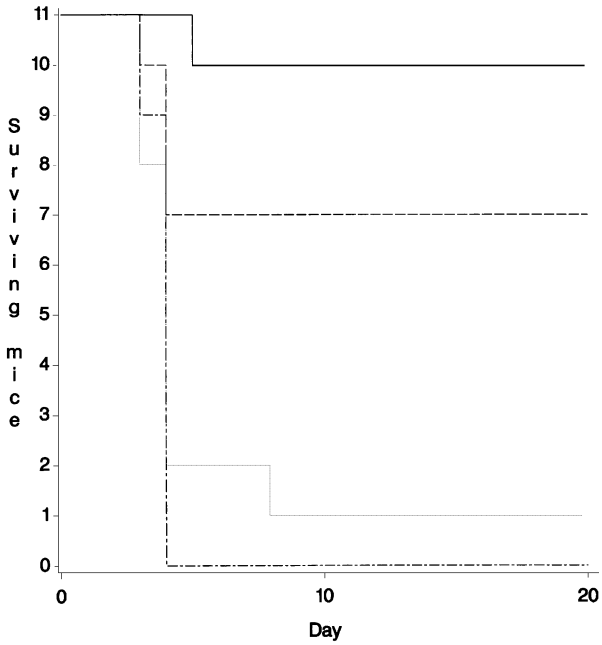

Fig. 1 The effect of ICRF-187 on the survival of mice treated with high-dose m-AMSA. Groups of 11 mice were treated as described in Materials and methods. Survival is increased in the two groups treated with the combination of drugs as compared with the groups treated with m-AMSA alone. No mouse died after day 20 (*Dotted line* 45 mg/kg m-AMSA, *uneven dashes* 55 mg/kg m-AMSA, *solid line* 125 mg/kg ICRF-187 + 45 mg/kg m-AMSA, *even dashes* 125 mg/kg ICRF-187 + 55 mg/kg m-AMSA)

by the DNA-intercalative topoisomerase II poison m-AMSA. As we consider the interaction between ICRF-187 and etoposide to involve the target enzyme topoisomerase II, we do not expect ICRF-187 to provide protection against a non-topoisomerase II-directed drug. Therefore, we investigated the tubulin-directed drug paclitaxel (Taxol) in combination with ICRF-187. As shown in Table 4, paclitaxel-induced lethality cannot be antagonized by ICRF-187.

We then studied the effect of combining etoposide and ICRF-187 in mice inoculated i.p. with either Ehrlich ascites tumor or L1210 tumor cells. ICRF-187 had no antitumor effect, whereas as expected, etoposide given at 33 mg/kg produced an increase in life span. In combination with ICRF-187 the dose of etoposide was escalated to 120 mg/kg, and we observed a nonsignificant increase in life span in three consecutive experiments using L1210 cells, whereas no synergy was found in Ehrlich ascites tumor cells (Table 5).

We then investigated the hypothesis that this difference in the increase in life span might be caused by the metastatic potential of the L1210 leukemia cells and a possible difference in transport of the two drugs across the blood-brain barrier. L1210 cells were therefore inoculated into the cerebrum and the animals were treated i.p. The survival curves generated in one such experiment are shown in Fig. 2. As demonstrated in Table 6, a significant increase in life span was obtained using the high-dose etoposide schedule combined with ICRF-187 as compared with etoposide alone.

The toxicity of drug combinations was evaluated in healthy mice by weight measurements and leukocyte counts. As shown in Table 7, the etoposide-induced weight loss is largely prevented by ICRF-187. However, as shown in Table 8, ICRF-187 does not prevent etoposide-induced leukopenia.

Discussion

The use of folinic acid for rescue from methotrexate toxicity and of mesna for protection against cyclophosphamide toxicity have enabled the use of high-dose methotrexate and cyclophosphamide protocols to counteract drug resistance. This concept of pharmacological rescue serves as a model for our interest in an effect regulation of topoisomerase II poisons.

The present study demonstrates that ICRF-187 antagonizes m-AMSA- and etoposide-mediated lethal toxicity. Thus, ICRF-187 is an antidote that is effective against both intercalating and nonintercalating types of topoisomerase II poisons. This antagonism is marked as ICRF-187 enables a 3.6-fold increase in the LD_{10} of etoposide. It is also remarkable that this protection was obtained within a large range of nontoxic ICRF-187 doses.

These results obtained with ICRF-187 are in line with our previous in vitro studies demonstrating an antagonistic effect of ICRF-187 on the single-strand breaks and cytotoxicity induced by the clinically important drugs etoposide and daunorubicin [25]. All in vitro evidence suggests that this protection is related to an effect on topoisomerase II [23, 25, 27] and not to an inhibition of the formation of toxic free radicals by

Table 4 Lethality of paclitaxel given alone and in combination with ICRF-187[a]

Paclitaxel (mg/kg)	Survivors/ treated	%	ICRF-187 + Paclitaxel (mg/kg)	Survivors/ treated	%
30	22/22	100	125 + 30	22/22	100
40	12/22	55	125 + 40	11/22	50
50	0/22	0	125 + 50	2/22	9

[a]Compiled data from two experiments showing that paclitaxel-induced lethality cannot be prevented by pretreatment with ICRF-187. Groups of 11 mice were treated once i.p. with or without pretreatment with ICRF-187

Table 5 Treatment with etoposide and ICRF-187 in tumor-bearing mice[a] (*ILS%* Percentage of increase in life span, *NS* not significant)

Ehrlich tumor cells				L1210 tumor cells			
Etoposide		ICRF-187 + Etoposide		Etoposide		ICRF-187 + Etoposide	
Dose (mg/kg)		Dose (mg/kg)		Dose (mg/kg)		Dose (mg/kg)	
33		125 + 120		33		125 + 120	
n	ILS(%)	ILS(%)	*P*	*n*	ILS(%)	ILS(%)	*P*
11	53	64	NS	22	113	131	NS
11	40	43	NS	22	100	138	NS
11	35	36	NS	20	88	219	< 0.01

[a]Calculated LD_{10} values for etoposide given alone (33 mg/kg) and in combination with ICRF-187 (120 mg/kg) were used for treatment studies, on day 0, 1×10^5 L1210 tumor cells or 15×10^6 Ehrlich ascites tumor cells were inoculated i.p., and mice were treated i.p. on day 4. The Mann-Whitney test was used for statistical evaluation

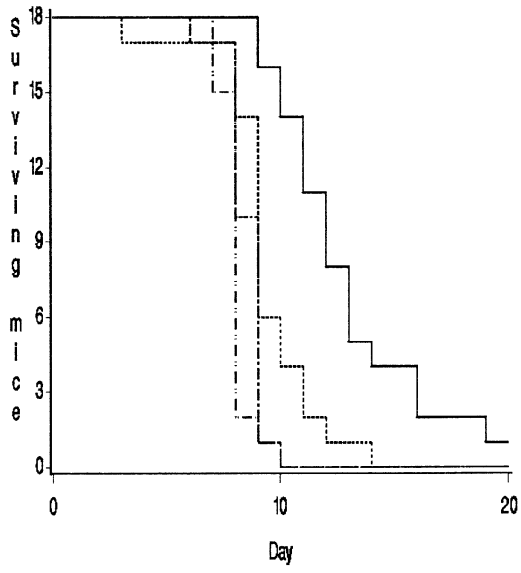

Fig. 2 Survival curves generated for groups of 18 mice inoculated intracerebrally with 1×10^4 L1210 tumor cells. The tumor-bearing mice were treated i.p. on day 2. The group treated with high-dose etoposide in combination with ICRF-187 shows a significant increase in survival as compared with that given etoposide alone at an equitoxic dose, with that receiving ICRF-187 alone, and with saline-treated controls (*Double dots alternating with dashes* NaCl + NaCl, *even dashes* 33 mg/kg etoposide, *uneven dashes* 125 mg/kg ICRF-187, *solid line* 125 mg/kg ICRF-187, + 120 mg/kg etoposide)

Table 6 Treatment of mice inoculated intracerebrally with 10^4 L1210 tumor cells[a]

L1210 tumor cells inoculated into the cerebrum			
Etoposide		ICRF-187 + Etoposide	
Dose (mg/kg)		Dose (mg/kg)	
33		125 + 120	
n	ILS(%)	ILS(%)	*P*
18	13	38	< 0.01
18	21	38	< 0.01
18	13	63	< 0.01

[a]Groups of 18 mice were inoculated on day 0 and treated on day 2. The Mann-Whitney test was used for statistical evaluation

Table 7 Median weight of mice at nadir[a]. Ranges are given in brackets

Control	21.4 [20.4–21.8] g
ICRF-187 (125 mg/kg)	21.2 [19.7–22.2] g
Etoposide (90 mg/kg)	15.4 [15.2–21.4] g
ICRF-187 + Etoposide (125 + 90 mg/kg)	19.9 [18.0–20.8] g

[a]Groups of 5 mice were treated with drugs as shown and weighed for 11 consecutive days. Etoposide alone caused a median 6-g decrease in body weight, whereas the combination of drugs resulted in a weight loss of only 1.5 g

chelation of free iron. As ICRF-187 is a divalent cation chelator, one hypothesis would be that ICRF-187 interacts at the late magnesium/ATP-binding stage of the

Table 8 Median leukocyte counts of mice[a]

	Day 3	Day 5	Day 7
Control	5.9	7.4	6.2
ICRF-187 125 mg/kg	5.3	7.7	7.6
Etoposide 90 mg/kg	1.3	5.7	8.8
ICRF-187 + Etoposide 125 mg/kg + 90 mg/kg	0.6	3.9	6.3

[a]Toxicity of etoposide alone and of the combination of ICRF-187 and etoposide as evaluated by leukocyte counts ($n \times 10^9$/l blood). There is no significant difference in the effect of etoposide and that of etoposide plus ICRF-187. Groups of 9 mice were treated with the various drugs and leukocytes were counted

enzyme's catalytic cycle, where the homodimeric topoisomerase II is thought to have the form of a closed bracelet surrounding the DNA. In accordance with this, Roca et al. [23] recently performed in vitro studies demonstrating a bisdioxopiperazine-induced trapping of the enzyme in the form of a closed protein clamp. By reversible blocking at this stage, ICRF-187 is capable of antagonizing the religation inhibition invoked by topoisomerase II poisons.

This effect on topoisomerase II clearly explains earlier puzzling data showing that ICRF-187 and its racemic form ICRF-159 protected against high-dose daunorubicin toxicity in vivo [8–10, 12, 30, 31]. Despite speculation as to the cause of this protection, its nature was unknown [11] until it became evident that bisdioxopiperazines act on topoisomerase II [22, 23, 27] and that the acute protection they provide against topoisomerase II poisons is unlikely to be due to inhibition of the formation of toxic free radicals by chelation of free iron.

The obvious question is whether this marked in vivo protection of topoisomerase II poisons by ICRF-187 can be put to clinical use. Earlier studies with daunorubicin have indicated that the combination may indeed be useful. Thus, a synergistic effect of ICRF-159 together with high-dose daunorubicin in both MLV-M leukemia and MS-2 sarcoma [8] as well as L1210 leukemia [30, 31] has been reported in mice. However, as the underlying mechanism was unknown at the time, these studies did not include the nonintercalating, clinically very important topoisomerase II-directed drugs etoposide (VP-16) and teniposide (VM-26).

Accordingly, we tested the antitumor effect of equitoxic doses of etoposide and etoposide plus ICRF-187 in mice bearing L1210 leukemia and found a trend toward a synergistic effect of the combination. From our knowledge of the antagonism of etoposide and daunorubicin cytotoxicity to tumor cells in clonogenic assay [25], we would not expect any advantage for the i.p./i.p. cotreatment of an ascites tumor with ICRF-187 and etoposide. In accordance with this, the antitumor effect of equitoxic doses of etoposide and etoposide plus ICRF-187 was identical in mice with Ehrlich ascites tumor cells, which are basically confined to the peritoneal cavity (Table 5). In contrast, however, when we used L1210 cells, which are known to metastasize readily [26], there was a trend toward a synergistic effect of the drug combination (Table 5). Finally, a significant difference between etoposide alone and etoposide and protector was obtained when L1210 cells were inoculated into the cerebrum.

Thus, there appear to be potential routes by which one can benefit from this antagonism, one of which is utilization of dissimilar barriers to the drugs. Such barriers could be due to variations in drug transport by virtue of different acid/base characteristics or lipophilicity. One pharmacological obstacle is the blood-brain barrier. At least to some extent, etoposide and its analog teniposide pass the blood-brain barrier (for review see [6]), and the concentration of these drugs is especially high in CNS metastases. In contrast, the concentration of the hydrophilic ICRF-187 is very low in the cerebrospinal fluid [29], wherefore the combination of ICRF-187 and etoposide could be of value in patients with etoposide-sensitive brain tumors or metastases, as the combination would allow significant etoposide dose escalation by way of protection of normal tissues outside the CNS. The results obtained in this study indicate that there is differential transport across the blood-brain barrier. In this context it is noteworthy that etoposide is the most important single agent in the treatment of small-cell lung cancer (SCLC), a disease that very often relapses in the CNS. This combination of drugs might be valuable in patients with SCLC and brain metastases.

In conclusion, the present study is a preclinical in vivo validation of in vitro data demonstrating the antagonistic effect of ICRF-187 on topoisomerase II-directed drugs. We demonstrated that ICRF-187 is a powerful nontoxic protector against m-AMSA and etoposide toxicity in vivo, allowing a 3.6-fold etoposide dose escalation. The etoposide dose increment made possible by treatment with ICRF-187 at nontoxic doses improved the effectiveness of treatment in mice inoculated intracranially with L1210 tumor cells. ICRF-187 is therefore a promising lead compound for the development of systems based on increased tumor versus host selectivity.

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