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Enhancement of irinotecan (CPT-11) activity against central nervous system tumor xenografts by alkylating agents

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Abstract Two major obstacles in the treatment of patients with central nervous system malignancies are drug resistance and host toxicity. The goal of combination chemotherapy is to achieve therapeutic effects that are more favorable than using a single drug alone, but without an increase in normal organ toxicity. The study reported here examined the combination of a topoisomerase I inhibitor, irinotecan (CPT-11), with three different alkylating agents: 1,3-bis(2-chloroethyl)-1-nitrosourea, busulfan, and cyclophosphamide. We evaluated the antitumor effects of these three combinations against a panel of human tumor xenografts derived from central nervous system malignancies, including adult high-grade gliomas (D-54 MG, D-245 MG) and a childhood ependymoma (D-612 EP). In replicate experiments, the alkylating agents were given on day 1 in doses varying from 10% to 75% of the dose lethal to 10% of the animals, and CPT-11 was given on days 1–5 and 8–12 in doses varying from 10% to 100% of the dose lethal to 10% of the animals. The antitumor effects of the various combinations ranged from less than additive (7.61 days below additive with 0.5 CPT-11 + 0.75 cyclophosphamide in D-54 MG) to statistically significant ($P < 0.001$) supraadditive effects (18.80 days above additive with 0.5 CPT-11 + 0.5 1,3-bis(2-chloroethyl)-1-nitrosourea in D-54 MG). These studies show that the combination of the topoisomerase inhibitor CPT-11 and alkylating agents may increase the antitumor effect in some cases well above additive with no increase in host toxicity (0/10 deaths in both experiments cited above) and should be considered for combination chemotherapy of central nervous system malignancies.

Key words Irinotecan (CPT-11) · Alkylators
Glioma · Medulloblastoma · Ependymoma

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Introduction

Malignant brain tumors are a major cause of death in both children and adults, with current therapy being of limited benefit. Although treatment options include surgery, radiotherapy, and chemotherapy [8], the recognition that these tumors have almost invariably disseminated beyond the original site of presentation has moved chemotherapy to the forefront of therapy. The challenges of chemotherapy include selective destruction of the rapidly dividing tumor cells while minimizing damage to the other rapidly proliferating cells in the body.

Combination chemotherapy is a treatment strategy designed to produce therapeutic effects that are more favorable than are those of a single drug, but minimizing normal organ toxicity and preventing emergence of drug-resistant tumor cells [7]. An optimal combination involves drugs that are less than additive in producing host organ toxicity, but more than additive in producing an antitumor effect.

Irinotecan (CPT-11) is a topoisomerase I inhibitor that stabilizes the covalent bond between topoisomerase I and DNA – a bond formed during synthesis of new DNA – thereby inhibiting the re-ligation of the DNA,

and ultimately leading to the death of the cell. The dose-limiting toxicity of CPT-11 is diarrhea [9]. Alkylating agents, such as 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), busulfan, and cyclophosphamide produce their antitumor effect by covalently binding an alkyl group to a cellular molecule to form an adduct and ultimately to crosslink. Although alkylating agents may react with many different classes of molecules in cells, the major target is DNA [5]. The dose-limiting toxicity of the alkylating agents is myelosuppression [2].

CPT-11 and alkylating agents are ideal candidates for combination chemotherapy because they exert their antitumor effects through interactions with different targets and have different organ toxicities. The study reported here examined the combination of CPT-11 with either cyclophosphamide, BCNU, or busulfan against a panel of human tumor xenografts derived from adult malignant glioma and childhood ependymoma and growing in athymic nude mice.

Materials and methods

Animals

Male and female athymic BALB/c mice (*nu*/*nu* genotype, 6 weeks of age or older) were used for all studies and were maintained as described previously [1].

Xenografts

A panel of three xenografts derived from human central nervous system (CNS) tumors, including adult high-grade gliomas (D-54 MG, D-245 MG) and a childhood ependymoma (D-612 EP), was used for all in vivo studies. The xenografts were maintained as previously described [4].

Drugs

CPT-11 was provided by Pharmacia & Upjohn (Global Distribution Center, Kalamazoo, Mich.). Busulfan, BCNU, and cyclophosphamide were provided by the Pharmaceutical Research Division of the National Cancer Institute.

Subcutaneous xenograft transplantation

Subcutaneous tumor transplantation into the right flank of the animals was performed as described previously, with inoculation volumes of 50 μl [3].

Tumor measurements

Tumors were measured twice weekly with hand-held vernier calipers (Scientific Products McGraw, Ill.). Tumor volume was calculated according to the following formula: $[(\text{width})^2 \times (\text{length})]/2$.

Xenograft therapy

In replicate experiments, CPT-11 was given to mice on days 1–5 and 8–12 via intraperitoneal (i.p.) injection at doses ranging from 4 to 40 mg/kg per dose in saline containing 10% dimethyl sulfoxide. The highest dose (40 mg/kg per dose) represents the dose lethal to 10% of treated animals (LD_{10}). Cyclophosphamide was given to mice on day 1 via i.p. injection at doses ranging from 348 to 1391 mg/m^2 in saline. The highest dose (1391 mg/m^2) represents the LD_{10} of cyclophosphamide. BCNU was given to mice on day 1 via i.p. injection at doses ranging from 25 to 75 mg/m^2 in saline containing 10% ethanol. The LD_{10} of BCNU is 100 mg/m^2. Busulfan was given to mice on day 1 via i.p. injection at doses ranging from 15 to 60.3 mg/m^2 in saline containing 10% dimethyl sulfoxide. The highest dose (60.3 mg/m^2) represents the LD_{10} of busulfan. Groups of nine or ten randomly selected mice began receiving treatment when the median tumor volume exceeded 200 mm^3 and were compared with control animals receiving drug vehicle. The volumes injected per mouse were approximately 0.4–0.8 ml. The day (after tumor implantation) that therapy started ranged between days 7 and 8 for D-54 MG, days 12 and 14 for D-245 MG, and days 24 and 35 for D-612 EP. The doubling times (days) for the three xenografts were 3.4 for D-54 MG, 2.5 for D-245 MG, and 4.6 for D-612 EP.

Assessment of response

The response of subcutaneous xenografts was assessed by delay in tumor growth and by tumor regressions. Growth delay, expressed as T−C, was defined as the difference in days between the median time required for tumors in treated (T) and control (C) animals to reach a volume five times greater than that measured at the start of treatment. Tumor regression was defined as a decrease in tumor volume over two successive measurements. Statistical analyses were performed using a personalized SAS statistical analysis program, the Wilcoxon rank order test for growth delay, and the Fisher's exact test for tumor regression as described previously [3].

Results

The antitumor effects of the various combinations ranged from substantially above additive to less than additive. The combination of CPT-11 and BCNU in D-54 MG produced growth delays substantially above those seen with the two agents alone (Table 1, Fig. 1). There was a slight increase in toxicity with this combination, but as the doses of either CPT-11 or BCNU were lowered, the potentiation was still evident without enhanced toxicity. The combination of 0.5 (fraction of LD_{20}) CPT-11 and 0.5 BCNU produced a growth delay that was 3.3 days less than additive in D-245 MG and 9.5 days less than additive in D-612 EP, indicating that the therapeutic benefit of combining these two agents was cell line-specific.

The combination of 0.5 CPT-11 and 0.75 busulfan produced a growth delay 6.7 days above additive in D-245 MG and 3.2 days above additive in D-54 MG without enhanced toxicity (Table 2). The combination of 0.5 CPT-11 and 0.75 busulfan produced variable results with the D-612 EP xenograft. In experiment 6, the effect of the combination was 10.7 days greater than additive, but in experiment 7, it was 4.7 days less than additive. When 0.5 busulfan was given with either 0.5 or 0.25 CPT-11, the results were additive (Table 3, Fig. 2). In all cases, there was minimal enhancement of toxicity.

The combination of CPT-11 and cyclophosphamide produced growth delays that were less than additive with increased toxicity in D-54 MG (Table 4).

Table 1 Effect of CPT-11 and BCNU, alone and in combination, on the growth of s.c. human CNS xenografts D-54 MG, D-245 MG, and D-612 EP in mice (nine or ten per treatment group). CPT-11-11 and BCNU were administered via i.p. injection. In the groups treated with a combination of the two drugs, BCNU was given on day 1; CPT-11 was given 5 h later on day 1 and on days 2–5 and 8–12 (*T–C* growth delay in days, is defined as the difference between the median time required for tumors in treated (T) and control (C) animals to reach five times the volume measured at the initiation of treatment; *Regression* is defined as a decrease in tumor volume over two successive measurements)

Cell lin	Treatment (fraction of LD_{10})	T–C (days)	Regressions	Deaths
Experiment 1				
D-54 MG	0.5 CPT-11	23.0*	10/10	0/10
D-54 MG	0.75 BCNU	4.1	0/10	0/10
D-54 MG	0.5 CPT-11 + 0.75 BCNU	49.0*	7/7	3/10
Experiment 2				
D-54 MG	0.5 CPT-11	19.0*	5/10	0/10
D-54 MG	0.75 BCNU	5.5	1/9	1/10
D-54 MG	0.5 CPT-11 + 0.75 BCNU	48.4*	7/7	3/10
Experiment 3				
D-54 MG	0.5 CPT-11	25.6*	7/8	2/10
D-54 MG	0.5 BCNU	1.2	0/10	0/10
D-54 MG	0.25 BCNU	0.5	0/10	0/10
D-54 MG	0.5 CPT-11 + 0.5 BCNU	45.6*	10/10	0/10
D-54 MG	0.5 CPT-11 + 0.25 BCNU	31.7*	9/10	0/10
Experiment 4				
D-54 MG	0.25 CPT-11	4.8	0/10	0/10
D-54 MG	0.75 BCNU	6.0*	2/10	0/10
D-54 MG	0.5 BCNU	1.9	0/10	0/10
D-54 MG	0.25 BCNU	0.6	0/9	1/10
D-54 MG	0.25 CPT-11 + 0.75 BCNU	24.5*	10/10	0/10
D-54 MG	0.25 CPT-11 + 0.5 BCNU	19.6*	10/10	0/10
D-54 MG	0.25 CPT-11 + 0.25 BCNU	15.6*	7/9	1/10
Experiment 5				
D-245 MG	1.0 CPT-11	29.5*	10/10	0/10
D-245 MG	0.5 CPT-11	27.1*	10/10	0/10
D-245 MG	0.5 BCNU	25.4*	10/10	0/10
D-245 MG	0.5 CPT-11 + 0.5 BCNU	49.2*	8/8	2/10
Experiment 6				
D-612 EP	0.5 CPT-11	45.2*	10/10	0/10
D-612 EP	0.5 BCNU	14.2*	10/10	0/10
D-612 EP	0.5 CPT-11 + 0.5 BCNU	49.9*	8/8	2/10

* $P \leq 0.001$

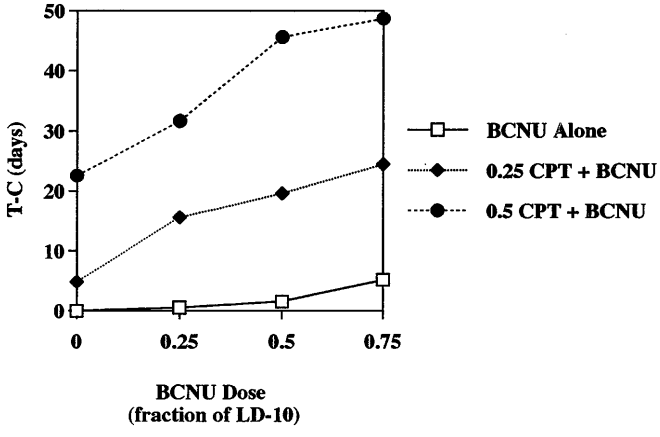

Fig. 1 Growth delay in D-54 MG produced by the combination of CPT-11 and BCNU. The values shown are the average from two experiments

Toxicity

Among 662 treated animals, 20 deaths were attributable to drug toxicity. The median weight loss was 4.5% among treated surviving animals, with no differences noted between any groups treated with single or combination therapy. No neurologic toxicity was noted.

Discussion

Successful treatment of human malignancies with chemotherapy has almost invariably required combination therapy with two or more agents. Combinations of agents that affect different tumor cell targets can theoretically preclude emergence of drug-resistant tumor cells, preventing tumor regrowth and patient death. Rational design of combination chemotherapy typically includes agents with nonoverlapping toxicity, which may enhance antineoplastic activity without enhancing normal organ toxicity.

CPT-11 and the alkylating agents are ideal candidates for a trial of combination chemotherapy because they have different targets and different dose-limiting toxicities. Each of the three classes of alkylating agents studied form unique DNA adducts. The nitrogen mustards, such as cyclophosphamide, alkylate the N-7 position of guanine, while the nitrosoureas, such as BCNU, alkylate the O-6 position of guanine as well as the N-3 position of cytidine [5]. After the agent forms a covalent link with a nucleotide, the free arm of the drug can react with a low-molecular-weight molecule, such as water or glutathione, or with a macromolecule, such as protein or DNA. When the free arm reacts with DNA, this leads to the

Table 2 Effect of CPT-11 and busulfan, alone and in combination, on the growth of s.c. human CNS xenograft D-245 MG in mice (nine or ten per treatment group). CPT-11 and busulfan were administered via i.p. injection. In groups treated with a combination of the two drugs, busulfan was given on day 1; CPT-11 was given 5 h later on day 1 and on days 2–5 and 8–12 (*T–C* growth delay in days, is defined as the difference between the median time required for tumors in treated (T) and control (C) animals to reach five times the volume measured at the initiation of treatment; *Regression* is defined as a decrease in tumor volume over two successive measurements)

Cell line	Treatment (fraction of LD_{10})	T–C (days)	Regressions	Deaths
Experiment 1				
D-245 MG	0.5 CPT-11	27.1*	10/10	0/10
D-245 MG	0.75 busulfan	4.3*	0/10	0/10
D-245 MG	0.5 CPT-11 + 0.75 busulfan	38.0*	10/10	0/10
Experiment 2				
D-245 MG	0.5 CPT-11	28.2*	10/10	0/10
D-245 MG	0.75 busulfan	10.1	3/9	0/9
D-245 MG	0.5 CPT-11 + 0.75 busulfan	45.1*	10/10	0/10
Experiment 3				
D-245 MG	0.5 CPT-11	28.0*	10/10	0/10
D-245 MG	0.5 busulfan	3.6	0/10	0/10
D-245 MG	0.25 busulfan	0.5	0/10	0/10
D-245 MG	0.5 CPT-11 + 0.5 busulfan	35.1*	10/10	0/10
D-245 MG	0.5 CPT-11 + 0.25 busulfan	30.9*	10/10	0/10
Experiment 4				
D-245 MG	0.25 CPT-11	21.8*	9/9	0/9
D-245 MG	0.75 busulfan	9.8*	0/9	0/9
D-245 MG	0.5 busulfan	1.6	0/10	0/10
D-245 MG	0.25 busulfan	−1.6	0/10	0/10
D-245 MG	0.25 CPT-11 + 0.75 busulfan	40.9*	10/10	0/10
D-245 MG	0.25 CPT-11 + 0.5 busulfan	30.9*	10/10	0/10
D-245 MG	0.25 CPT-11 + 0.25 busulfan	29.4*	10/10	0/10
Experiment 5				
D-245 MG	0.1 CPT-11	14.4*	4/10	0/10
D-245 MG	0.75 busulfan	9.0*	2/10	0/10
D-245 MG	0.5 busulfan	1.4	0/10	0/10
D-245 MG	0.25 busulfan	0.2	0/10	0/10
D-245 MG	0.1 CPT-11 + 0.75 busulfan	25.1*	5/10	0/10
D-245 MG	0.1 CPT-11 + 0.5 busulfan	11.3	4/10	0/10
D-245 MG	0.1 CPT-11 + 0.25 busulfan	12.4*	4/10	0/10

*$P \leq 0.001$

Table 3 Effect of CPT-11 and busulfan, alone and in combination, on the growth of s.c. human CNS xenografts D-54 MG and D-612 EP in mice (nine or ten per treatment group). CPT-11 and busulfan were administered via i.p. injection. In the groups treated with a combination of the two drugs, busulfan was given on day 1; CPT-11 was given 5 h later on day 1 and on days 2–5 and 8–12 (*T–C* growth delay in days, is defined as the difference between the median time required for tumors in treated (T) and control (C) animals to reach five times the volume measured at the initiation of treatment; *Regression* is defined as a decrease in tumor volume over two successive measurements)

Cell line	Treatment (fraction of LD_{10})	T–C (days)	Regressions	Deaths
Experiment 1				
D-612 EP	0.5 CPT-11	45.2*	10/10	0/10
D-612 EP	0.75 busulfan	17.6*	6/10	0/10
D-612 EP	0.5 CPT-11 + 0.75 busulfan	73.6*	9/9	1/10
Experiment 2				
D-612 EP	0.5 CPT-11	44.4*	8/8	1/9
D-612 EP	0.75 busulfan	27.3*	8/9	0/9
D-612 EP	0.5 busulfan	12.6*	5/9	0/9
D-612 EP	0.25 busulfan	3.5	0/9	0/9
D-612 EP	0.5 CPT-11 + 0.75 busulfan	67.0*	10/10	0/10
D-612 EP	0.5 CPT-11 + 0.5 busulfan	54.6*	10/10	0/10
D-612 EP	0.5 CPT-11 + 0.25 busulfan	48.0*	9/9	1/10
Experiment 3				
D-612 EP	0.25 CPT-11	41.0*	10/10	0/10
D-612 EP	0.75 busulfan	17.5*	4/10	0/10
D-612 EP	0.5 busulfan	9.6*	1/9	1/10
D-612 EP	0.25 busulfan	3.1	0/9	0/9
D-612 EP	0.25 CPT-11 + 0.75 busulfan	56.7*	10/10	0/10
D-612 EP	0.25 CPT-11 + 0.5 busulfan	54.5*	10/10	0/10
D-612 EP	0.25 CPT-11 + 0.25 busulfan	43.1*	9/9	1/10
Experiment 4				
D-54 MG	0.5 CPT-11	23.0*	10/10	0/10
D-54 MG	1.0 busulfan	0.3	0/10	0/10
D-54 MG	0.5 CPT-11 + 1.0 busulfan	26.5*	10/10	0/10

*$P \leq 0.001$

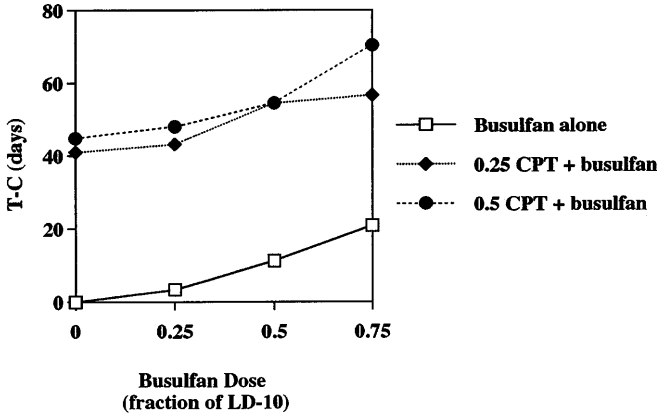

Fig. 2 Growth delay in D-612 EP produced by the combination of CPT-11 and busulfan. The values shown are the average from two experiments

formation of inter- or intrastrand crosslinks that inhibit cell replication. These agents are active against CNS tumors of glial and neuronal cell origin, and are the mainstay of current clinical trials for these malignancies. The dose-limiting toxicity of the alkylating agents is myelosuppression [5].

CPT-11, a topoisomerase I inhibitor, has a target different from that of the alkylators. Topoisomerase I is a nuclear enzyme that induces a single-strand break in the phosphodiester backbone of supercoiled DNA, allows the intact strand to pass through the nick, then re-anneals the broken strand. During this process, a covalent bond is formed between the tyrosine group at the active site of topoisomerase I and the 3' phosphate group of DNA [9]. CPT-11 stabilizes the intermediate that is formed by the covalent bond between topoisomerase I and DNA. CPT-11 allows the topoisomerase to cleave the DNA, but strongly inhibits re-ligation of the DNA. Single-strand breaks are irreversibly converted to double-strand breaks through interaction with the replication machinery, and the cell is killed [9]. CPT-11 toxicity includes both mild myelosuppression and potentially severe diarrhea [10]. Hare et al. tested CPT-11 against an extensive panel of human CNS xenografts, including D-54 MG, D-245 MG, and D-612 EP, and demonstrated substantial activity of CPT-11 against both subcutaneous and intracranial tumors [6].

Preliminary results of our phase II trial for patients with newly diagnosed or recurrent high-grade glioma have confirmed the activity of CPT-11. The results for this agent in the current experiments demonstrate that the interaction of CPT-11 with two of the alkylating agents can produce enhanced antineoplastic activity but that this is dependent on both the alkylating agent and the tumor line. For D-54 MG, which was the cell line least sensitive to 0.5 CPT-11 alone, and was insensitive to both BCNU and busulfan alone, the combination of CPT-11 and BCNU showed strong potentiation of antitumor activity. The combination of CPT-11 and busulfan was slightly better than additive, while cyclophosphamide had a less than additive effect when combined with CPT-11, even though D-54 MG was relatively sensitive to cyclophosphamide alone.

The sensitivity of D-245 MG to CPT-11 alone was somewhat greater that that of D-54 MG; it was also sensitive to BCNU, but not to busulfan. The combination of CPT-11 and BCNU produced better than additive activity against D-245 MG. Moreover, 0.5 CPT-11 plus BCNU produced a T−C of 49.2 days, much higher than was achieved with 1.0 CPT-11 alone (T−C of 29.5 days). The combination of CPT-11 and busulfan also showed potentiation, even though busulfan alone is

Table 4 Effect of CPT-11 and cyclophosphamide, alone and in combination, on the growth of s.c. human CNS xenograft D-54 MG in mice (nine or ten treatment group). Both CPT-11-11 and cyclophosphamide were administered via i.p. injection. In the groups treated with a combination of the two drugs, cyclophosphamide was given on day 1; CPT-11 was given 5 h later on day 1 and on days 2–5 and 8–12 (T − C growth delay in days, is defined as the difference between the median time required for tumors in treated (T) and control (C) animals to reach five times the volume measured at the initiation of treatment; *Regression* is defined as a decrease in tumor volume over two successive measurements)

Cell line	Treatment (fraction of LD_{10})	T − C (days)*	Regressions	Deaths
Experiment 1				
D-54 MG	0.5 CPT-11	24.3	9/10	0/10
D-54 MG	1.0 cyclophosphamide	17.3	10/10	0/10
D-54 MG	0.75 cyclophosphamide	15.4	8/10	0/10
D-54 MG	0.5 cyclophosphamide	9.7	4/10	0/10
D-54 MG	0.25 cyclophosphamide	4.5	0/10	0/10
D-54 MG	0.5 CPT-11 + 1.0 cyclophosphamide	38.8	9/9	1/10
D-54 MG	0.5 CPT-11 + 0.75 cyclophosphamide	32.2	10/10	0/10
D-54 MG	0.5 CPT-11 + 0.5 cyclophosphamide	23.8	9/9	1/10
D-54 MG	0.5 CPT-11 + 0.25 cyclophosphamide	21.6	9/9	1/10
Experiment 2				
D-54 MG	0.25 CPT-11	16.8	8/10	0/10
D-54 MG	0.25 CPT-11 + 1.0 cyclophosphamide	25.8	7/10	0/10
D-54 MG	0.25 CPT-11 + 0.75 cyclophosphamide	20.7	7/10	0/10
D-54 MG	0.25 CPT-11 + 0.5 cyclophosphamide	14.5	4/10	0/10
D-54 MG	0.25 CPT-11 + 0.25 cyclophosphamide	15.8	5/10	0/10

* $P \leq 0.001$, all values

inactive on this tumor. Neither BCNU nor busulfan enhanced the activity of CPT-11 against D-612 EP.

The very high activity of CPT-11 alone on D-612 EP made isobologram analysis inapplicable. However, it is clear from the graphic representation of the data that there was marked potentiation of CPT-11 combined with BCNU for effectiveness against D-54 MG. The precise mechanism of this interaction is unclear, although the potential role of topoisomerase I in mediating alkylator-induced crosslink repair is a likely possibility. Future studies will examine schedule dependency of CPT-11 and alkylator combinations to evaluate this further. In addition, a phase I trial of CPT-11 plus BCNU in the treatment of adults with recurrent high-grade glioma has been opened to evaluate this interaction clinically.

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