

Poly(ADP-ribose) polymerase-1 inhibition reverses temozolomide resistance in a DNA mismatch repair-deficient malignant glioma xenograft

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Abstract

Temozolomide is a DNA-methylating agent used in the treatment of malignant gliomas. In this study, we have examined if inhibition of poly(ADP-ribose) polymerase (PARP) could increase the cytotoxicity of temozolomide, particularly in cells deficient in DNA mismatch repair. Athymic mice, transplanted with mismatch repair-proficient [D-245 MG] or deficient [D-245 MG (PR)] xenografts, were treated with a combination of temozolomide and the PARP inhibitor, INO-1001. For the tumors deficient in mismatch repair, the most effective dose of INO-1001 was found to be 150 mg/kg, given i.p. thrice at 4-hour intervals with the first injection in combination with 262.5 mg/kg temozolomide (0.75 LD₁₀). This dose of temozolomide by itself induced no partial regressions and a 4-day growth delay. In two separate experiments, the combination therapy increased the growth delay by 21.6 and 9.7 days with partial regressions observed in four of eight and three of nine mice, respectively. The addition of INO-1001 had a more modest, yet statistically significant, increase in tumor growth delay in the mismatch repair-proficient xenografts. In these experiments, mice were treated with a lower amount of temozolomide (88 mg/kg), which resulted in growth delays of 43.1 and 39.2 days. When the temozolomide treatment was in combination with 200 mg/kg INO-1001, there was

an increase in growth delay to 48.9 and 45.7 days, respectively. These results suggest that inhibition of PARP may increase the efficacy of temozolomide in the treatment of malignant gliomas, particularly in tumors deficient in DNA mismatch repair. [Mol Cancer Ther 2005;4(9):1364–8]

Introduction

Each year, 17,400 new cases of primary intracranial tumors are diagnosed in the U.S. Sixty percent of these new cases are central nervous system gliomas, the most common being glioblastoma multiforme (1). Despite ongoing research, the prognosis of patients with primary malignant gliomas remains poor. For example, glioblastoma multiforme is rapidly progressive with a median survival of <1 year. Current treatment options include surgery, radiation, and chemotherapy with methylating agents and nitrosoureas (2). Unfortunately, the treatment options often fall short of a cure, leading to subsequent tumor progression and death of the patient. One of the reasons for failing treatment is due to *de novo* or acquired resistance to chemotherapeutic agents.

Temozolomide (Temodar) is a DNA-methylating agent that rapidly undergoes pH-dependent degradation to an active intermediate, 5-(3-methyltriazen-yl)imidazol-4-carboxamide (3). Temozolomide has been shown to be active in the treatment of malignant gliomas (4–6) with the ability to penetrate the blood-brain barrier with limited bone marrow toxicity. Its mechanism of action involves the addition of methyl adducts to three main locations: N⁷ guanine (70% of adducts), O⁶ guanine (5% of adducts), and N³ adenine (9% of adducts). The cytotoxicity of temozolomide has been attributed to the methylation of the O⁶ position of guanine. During replication, the O⁶ methylguanine incorrectly pairs with thymine, triggering the mismatch repair system. The repair of the mismatched bases leads to preferential reinsertion of thymine, which may result in repetitive and futile attempts at repair. This process leads to the generation of DNA strand breaks and eventually growth arrest and apoptosis (7, 8).

Two mechanisms of resistance to temozolomide have been elucidated. The first mechanism of resistance involves the DNA repair protein, O⁶-alkylguanine-DNA alkyltransferase (AGT; ref. 9). AGT acts by directly removing the methyl adduct on the O⁶ guanine position. High levels of this DNA repair protein have been shown in both cell culture and xenograft studies to produce resistance to temozolomide. AGT depletion by the substrate analogue O⁶-benzylguanine can resensitize tumor cells to temozolomide both *in vitro* (10, 11) and *in vivo* (12).

Independent of AGT levels, resistance to temozolomide has also been shown in tumor cells deficient in the DNA

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mismatch repair system (13, 14). This deficiency leads to tolerance of O⁶ methylguanine and the ability of the cell to survive despite the presence of persistent DNA damage. Recently, attempts to overcome resistance conferred by mismatch repair deficiency have focused on blocking base excision repair, which differentially repairs the methyl adducts at the N³ adenine and N⁷ guanine position rather than at the O⁶ guanine position. Studies have shown that temozolomide induced methyl adducts at the N³ adenine and N⁷ guanine position are not susceptible to AGT and produce cytotoxicity independent of the mismatch repair system (15–18). One of the strategies used to block base excision repair includes the inhibition of a key enzyme: poly(ADP-ribose) polymerase (PARP; refs. 16, 18, 19). PARP, which binds to and is activated by DNA strand breaks, is thought to be important in protecting and trimming the DNA ends for repair synthesis (20).

Here, we report the effects of PARP inhibition by INO-1001 on the sensitization of malignant glioma tumor xenografts, proficient as well as deficient in DNA mismatch repair, to temozolomide.

Materials and Methods

Animals

Athymic BALB/c (*nu/nu*) mice, 6 weeks of age and older, were used for all studies, and were maintained as previously described (21).

Cell Lines

D341 MED was grown in Improved MEM Zinc Option (Richter's modification; Invitrogen, Carlsbad, CA) supplemented with 10% fetal bovine serum.

Drugs

The following drugs were used: temozolomide from Schering-Plough (Kenilworth, NJ), and INO-1001, an isoindolinone-based PARP inhibitor (22–26), from Inotek Pharmaceuticals Corporation (Beverly, MA).

[³H]NAD Incorporation Assay

PARP activity was measured in cells as described previously (27).

Pharmacokinetics Studies

Non-tumor-bearing mice were used in the pharmacokinetic studies. The PARP inhibitor, INO-1001, dissolved in 5% dextrose, was given via i.p. injections at hours 0 and 4. Blood samples were obtained at hours 2 and 8. The resulting plasma fraction was analyzed by high-pressure liquid chromatography to determine INO-1001 concentrations as described (25).

Xenografts

The malignant glioma xenografts, D-245 MG and D-245 MG (PR), were maintained as previously described (28). The D-245 MG xenograft was derived from a human malignant glioma and is sensitive to methylating agents, including procarbazine and temozolomide (13). The methylator-resistant xenograft, D-245 MG (PR), was established by serially treating D-245 MG-bearing mice with procarbazine (13).

Subcutaneous Xenograft Transplantation

Xenografts were s.c. transplanted into the right flank of animals with inoculation volumes of 50 μ L.

Tumor Measurements

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

Drug Regimen

Temozolomide was injected i.p. at doses representing fractions of 0.75, 0.50, 0.25, or 0.10 of the dose lethal to 10% of non-tumor-bearing animals (LD₁₀). The LD₁₀ of temozolomide has previously been determined to be 350 mg/kg. D-245 MG tumors were treated with 0.10 or 0.25 of LD₁₀. The resistant xenograft D-245 MG (PR) was treated with temozolomide at a dose of 0.50 or 0.75 of LD₁₀. Temozolomide was dissolved in 30% DMSO and 70% normal saline, and given as a single dose at hour 2 of treatment day. The PARP inhibitor INO-1001 was given at a dose of 100, 150, or 200 mg/kg in a solution of 5% dextrose. INO-1001 was injected i.p. at hours 0, 4, and 8.

Tumor Therapy

Groups of 8 to 10 randomly assigned mice bearing D-245 MG or D-245 MG (PR) tumors were treated i.p. by injection of temozolomide and/or INO-1001 according to the doses described above when tumor volumes reached the size of 100 to 500 mm³, with a median volume exceeding 200 mm³. Control animals were injected with drug vehicle.

Assessment of Response

Xenograft response was assessed by growth delay, calculated as T-C, which represents the difference in days between the median time for tumors of treated (T) and control (C) animals to reach a volume five times greater than the volume at the time of initial treatment. In addition, tumor regressions and toxic deaths were noted during the treatment period. Tumor regressions were defined as a reduction in the tumor volume for at least two consecutive measurements. Toxic deaths included any animal deaths that occurred during the treatment period prior to the animal testing out of the study. Animals tested out of the study when the tumor volume exceeded 1,000 mm³ and tumor volume was greater than five times the tumor volume at the time of initial treatment. Wilcoxon nonparametric statistical analysis was applied to determine statistical significance.

Results

Temozolomide Activation of PARP: Inhibition by INO-1001

A mismatch repair-deficient medulloblastoma cell line (D341 MED; ref. 29) was used to investigate the effects of temozolomide on the activity of PARP in cells. As shown in Fig. 1, 4 hours after treatment with temozolomide, the activity of PARP was elevated >2-fold. If cells were pretreated with the PARP inhibitor, INO-1001, a marked reduction in PARP activity was observed. These results agree with previous experiments using fibroblasts where 100 nmol/L INO-1001 inhibited 70% of the cellular PARP activity and 1 μ mol/L reduced the PARP activity by >95% (22).

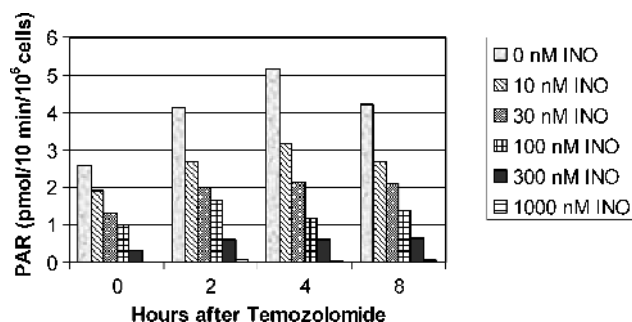


Figure 1. Inhibition of PARP activity in D341 MED cells by INO-1001. D341 MED cells were incubated with the indicated amounts of INO-1001 for 1 h before the addition of 200 μ mol/L temozolomide. PARP activity in the cells was measured by incorporation of [3 H]NAD into poly(ADP-ribose) (27).

Pharmacokinetics Studies of INO-1001

To examine the dose of INO-1001 that would achieve plasma concentrations capable of inhibiting PARP, we injected mice i.p. at 0 and 4 hours and measured the resulting plasma level of the drug at 2 and 8 hours. The results are summarized in Table 1. The lowest dose of INO-1001 used was sufficient to yield plasma levels that would inhibit most of the PARP activity.

Response to Chemotherapy in a Mismatch Repair–Deficient Xenograft

The procarbazine-resistant xenograft, D-245 MG (PR), is tolerant to methylating agents because it does not express the mismatch repair protein MutS α (13); thus, it is deficient in DNA mismatch repair. In an attempt to sensitize these tumors to temozolomide by blocking base excision repair, we investigated different dosing schemes for INO-1001 as shown in Table 2.

The most effective dose of INO-1001 was found to be 150 mg/kg, given i.p. thrice at 4-hour intervals with the first injection in combination with 262.5 mg/kg temozolomide (0.75 LD₁₀, experiments 1 and 2). This dose of temozolomide induced no partial regressions and approximately a 4-day tumor-control (T-C) growth delay in each of two experiments. The combination therapy increased the growth delay by 24.3 and 9.6 days compared with temozolomide alone ($P = 0.001$ and $P = 0.006$) with partial regressions observed in four of eight and three of nine mice, respectively.

Using the same treatment schedule, a higher dose of 200 mg/kg INO-1001 combined with 262.6 mg/kg temozolomide (0.75 LD₁₀) also produced significant growth delays but resulted in considerable toxicity (experiment 3). This combination dose increased the growth delay by 14.9 days when compared with animals treated with temozolomide alone ($P = 0.001$) with partial regressions observed in four of seven animals that survived initial treatment. Animals treated with temozolomide alone had no partial regressions and no significant tumor-control (T-C) growth delays. However, there were three toxic deaths out of a group of 10 animals treated

with combination therapy that occurred within 3 weeks following the treatment day. Subsequently, 9 weeks after treatment, there were two additional delayed toxic deaths. There were no toxic deaths in animals treated with temozolomide alone.

Similar experiments using the same injection schedule combining INO-1001 and temozolomide were completed using either a lower dose of INO-1001 (100 mg/kg, experiment 1) or a lower dose of temozolomide (175 mg/kg-0.50 of the LD₁₀, experiment 4). In both cases, decreasing either the INO-1001 dose or temozolomide dose yielded less significant increases in growth delays (~6 days) when compared with animals treated with temozolomide alone.

Prolonged PARP inhibition was achieved by administering two additional INO-1001 i.p. injections at hours 12 and 16 in addition to the standard schedule. This treatment protocol did not yield any additional growth delay (data not shown) beyond what was observed for animals that received three injections of PARP inhibitor.

Response to Chemotherapy in a Mismatch Repair–Proficient Xenograft

The antitumor activity of the drug combination INO-1001 and temozolomide was also defined in the parent xenograft D-245 MG, which is DNA mismatch repair–proficient (Table 2). Temozolomide alone is highly active, with growth delays of 43.1 and 39.6 days, respectively (experiments 5 and 6). Partial regressions were observed in 10 of 10 and 8 of 8 mice, respectively.

The addition of INO-1001 (200 mg/kg) increased the growth delays by 5.8 ($P = 0.001$) and 6.1 ($P = 0.003$) days, respectively, with only one death in 20 mice.

Discussion

Base excision repair guards cellular DNA against damage caused by metabolism, including that resulting from reactive oxygen species, methylation, deamination, and hydroxylation (20). In the initial step of base excision repair, glycosylases remove the damaged base from the helix; alternatively, the removal of a base can also occur spontaneously through hydrolysis. Next, apurinic/apyrimidinic endonuclease initiates a strand incision at the abasic site. Activated by the DNA strand break, PARP and possibly polynucleotide kinase protect and trim the ends for repair synthesis. DNA pol β then performs a one-nucleotide gap-filling reaction. The remaining nick is sealed by XRCC1-ligase3 complex (20).

Table 1. Pharmacokinetics of INO-1001

INO-1001 dose (mg/kg)	Plasma concentration (2 h)*	Plasma concentration (8 h)*
100	443 \pm 64	484 \pm 116
300	520 \pm 456	1393 \pm 611
500	1258 \pm 45	1036 \pm 54

*Concentrations are expressed in nmol/L \pm SE.

Table 2. Effect of INO-1001 on sensitivity to temozolomide

Xenograft	Temozolomide (fraction of LD ₁₀)	INO-1001 (mg/kg)	T-C (days)	Regressions	Deaths
Experiment 1, D-245 MG (PR)	0.75	0	4.2*	0 of 10	0 of 10
	0	100	0.5	0 of 10	0 of 10
	0	150	1.5	0 of 10	0 of 10
	0.75	100	10.2*	3 of 10	0 of 10
Experiment 2, D-245 MG (PR)	0.75	150	25.8*	4 of 8	2 of 10
	0.75	0	4.3*	0 of 10	0 of 10
	0	150	1.4	0 of 10	0 of 10
	0.75	150	13.9*	3 of 9	1 of 10
Experiment 3, D-245 MG (PR)	0.75	0	-0.4	0 of 10	0 of 10
	0	200	-2.0	0 of 10	0 of 10
	0.75	200	12.9*	4 of 7	3 of 10 (2 delayed deaths)
Experiment 4, D-245 MG (PR)	0.5	0	-1.0	0 of 8	0 of 8
	0	200	3.0	0 of 8	0 of 8
	0.5	200	5.5*	0 of 9	0 of 9
Experiment 5, D-245 MG	0.25	0	43.1*	10 of 10	0 of 10
	0	200	-0.9	0 of 0	0 of 10
	0.25	200	48.9*	9 of 9	1 of 10
Experiment 6, D-245 MG	0.25	0	39.6*	8 of 8	0 of 8
	0	200	2.3	0 of 8	0 of 8
	0.25	200	45.7*	10 of 10	0 of 10

**P* ≤ 0.05.

Base excision repair is responsible for removing the *N*-methylpurine adducts created by temozolomide. Recent attempts to overcome resistance to temozolomide conferred by mismatch repair deficiency have focused on blocking base excision repair. Strategies have included the use of methoxyamine (15), which inhibits base excision repair by preventing apurinic/aprimidinic endonuclease-mediated cleavage, and inhibition of PARP (16–19).

PARPs are a family of enzymes that function in poly(ADP-ribose) anabolism, using NAD⁺ as a substrate to form ADP-ribose polymers (30). The addition of ADP-ribose polymers to target proteins is involved in the regulation of many cellular processes such as DNA repair, gene transcription, cell cycle progression, cell death, chromatin functions, and genomic stability (17, 31). The most well-characterized member of the family is PARP-1, whose structure includes a DNA-binding domain at the NH₂ terminus, an auto-ADP-ribosylation domain, and a catalytic domain at the COOH terminus (17, 31).

When DNA damage is induced by alkylating agents, ionizing radiation, or free radicals, PARP acts as a nick sensor and becomes activated. The DNA-binding domain located at the NH₂ terminus of PARP-1 rapidly binds to DNA single or double strand breaks, undergoes autoribosylation, and adds ADP-ribose polymers to acceptor proteins. This PARP-1-mediated posttranslational modification of cellular proteins provides rapid signals to halt transcription and DNA replication and to recruit DNA repair systems to the site of damage (17, 31).

Our current results clearly show that inhibition of PARP, using the highly potent inhibitor INO-1001, restores some degree of temozolomide sensitivity in a methylator-

resistant human glioblastoma multiforme-derived xenograft we have previously established and characterized. The use of temozolomide at 0.75 LD₁₀ in combination with the optimal dose of INO-1001 (150 mg/kg) produced growth delays of 25.8 and 13.9 days. This degree of tumor activity in the parent xenograft D-245 MG is produced by temozolomide doses of ~0.1 to 0.15 LD₁₀. Therefore, full restoration of sensitivity was not accomplished but a relatively large growth delay with tumor regressions in all animals treated was observed. The clinical significance of this degree of restoration of temozolomide sensitivity is unclear but suggests the translation into the clinic may produce a meaningful therapeutic intervention. As is true of all modulations that target naturally occurring biochemical pathways, inhibition of PARP in combination with temozolomide can be expected to produce additional toxicity. This was observed in our animal setting, particularly at the higher doses of either temozolomide or INO-1001. Nevertheless, this does not preclude the use of this combination in the clinic although phase I studies will need to be conducted.

A recently published study showed that a novel PARP inhibitor, AG14361, was able to restore sensitivity to temozolomide in mismatch repair-deficient cells (32). Consistent with these results, our study showed that PARP inhibitor INO-1001 was also able to restore sensitivity to temozolomide in previously resistant mismatch repair-deficient glioblastoma multiforme tumor cells. Interestingly, the antitumor effect of temozolomide was also modestly enhanced in mismatch repair-proficient cells.

It is hypothesized that PARP inhibition is able to restore temozolomide activity because of a change in the

cytotoxicity locus of temozolomide from O⁶ methylguanine to N⁷ methylguanine and N³ methyladenine. Typically, the cytotoxicity of temozolomide is attributed to futile attempts by the mismatch repair system to process methyl adducts at the O⁶ position of guanine that repeatedly and incorrectly pair with thymine (7). Tumor cells that are mismatch repair-deficient no longer recognize the mispairing that occurs at O⁶ methylguanine, and, thus, do not initiate the cycles of repair, tolerating this methyl adduct in the genome. By blocking base excision repair through PARP inhibition, the methyl adducts at N⁷ guanine and N³ adenine become cytotoxic. In the absence of PARP, DNA strand breaks generated at the initiation of base excision repair are not able to be rejoined leading to eventual cell death.

PARP inhibition may modestly enhance the antitumor effect of temozolomide in mismatch-proficient cells by increasing the number of cytotoxic lesions; in addition to the cytotoxicity attributed to the O⁶ position of guanine, the methyl adducts at N⁷ guanine and N³ adenine also contribute to cell death.

The novel treatment strategy of combining temozolomide with PARP inhibitor INO-1001 may be a promising therapeutic option for patients suffering from malignant gliomas. Previous studies indicated that 16 of 16 glioblastomas showed PARP activity (data not shown). A phase I trial of INO-1001 given 24 and 12 hours prior to craniotomy in patients with newly diagnosed or recurrent glioblastoma is currently under way to define a dose capable of depleting PARP. In the future, possible prescreening of cancer patients could determine the mismatch repair status of tumor cells and therefore determine the benefit of combination therapy. INO-1001 in combination with temozolomide may offer a better prognosis for those suffering from glioblastoma multiforme.

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