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ORIGINAL REPORT

Phase II Trial of Tipifarnib in Patients With Recurrent Malignant Glioma Either Receiving or Not Receiving Enzyme-Inducing Antiepileptic Drugs: A North American Brain Tumor Consortium Study

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ABSTRACT

Purpose
A phase II study was undertaken in patients with recurrent malignant glioma to determine the efficacy and safety of tipifarnib, a farnesyltransferase inhibitor, dosed at the respective maximum-tolerated dose (MTD) for patients receiving and not receiving enzyme-inducing antiepileptic drugs (EIAEDs). Because tipifarnib undergoes extensive hepatic metabolism, MTD is doubled in patients on EIAEDs. The population included 67 patients with glioblastoma multiforme (GBM) and an exploratory group of 22 patients with anaplastic glioma (AG).

Patients and Methods
Patients received tipifarnib (300 and 600 mg bid for 21 days every 4 weeks in non-EIAED and EIAED patients, respectively). All patients were assessable for efficacy and safety.

Results
Two AG patients (9.1%) and eight GBM patients (11.9%) had progression-free survival (PFS) more than 6 months. Among the latter eight GBM patients, six of 36 patients (16.7%; 95% CI, 7% to 32%) were not receiving EIAEDs and two of 31 patients (6.5%; 95% CI, 1% to 20%) were receiving EIAEDs. Four patients had partial responses in group A GBM and one patient had a partial response group B GBM. An exploratory comparison of PFS between GBM groups A and B was statistically significant ($P = .01$). Patients not receiving EIAEDs had a higher incidence and increased severity of hematologic events. However, the incidence and severity of rash (the previously determined dose-limiting toxicity in patients receiving EIAEDs) seemed similar in EIAED and non-EIAED subgroups.

Conclusion
Tipifarnib (300 mg bid for 21 days every 4 weeks) shows modest evidence of activity in patients with recurrent GBM who are not receiving EIAEDs and is generally well tolerated in this population.

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INTRODUCTION

Treatment of malignant glioma remains a major therapeutic challenge. The heterogeneity of molecular pathways and control steps in glioma pathology make the neoplasia difficult to treat.[1,2] Chemotherapeutic treatment of glioma remains limited and novel agents that target aberrant signaling pathways need to be evaluated. *RAS* genes control normal cell growth and differentiation; however, overexpression of the *ras* oncogene is found in a large proportion of human cancers.[3] Amplification of epidermal growth factor receptor (EGFR), platelet-derived growth factor, and the angiogenic factor, vascular endothelial growth factor, can lead to the downstream ras activation: these ras-dependent factors are implicated in the pathogenesis of malignant astrocytomas.[3-5]

Tipifarnib (R115777, Zarnestra; Johnson & Johnson Pharmaceutical Research & Development LLC, Titusville, NJ) is a potent and selective nonpeptidomimetic farnesyltransferase inhibitor (FTI). In pharmacokinetic studies, tipifarnib has demonstrated oral bioavailability with dose-proportional pharmacokinetics.[6,7] In phase I studies, the maximum-tolerated dose (MTD) was established at 300 mg bid administered for 21 days every 4 weeks with myelosuppression as the dose-limiting toxicity (DLT).

Given that glioma patients face limited therapeutic options and FTIs present a new therapeutic modality with a unique mechanism of action that affects multiple tumor-promoting pathways, the investigation of the clinical effectiveness of tipifarnib in patients with recurrent glioma was believed to be warranted.

Commonly, glioma patients are treated with enzyme-inducing antiepileptic drugs (EIAEDs). Patients receiving EIAEDs show decreased plasma levels of several chemotherapeutic drugs when administered at conventional doses.[8-10] Induction of hepatic enzymes by EIAEDs can alter the metabolism of concurrently administered chemotherapeutic agents, which might lead to ineffective dosing.[11-13] Notably, EIAEDs reduced the area under the plasma concentration-time curve (AUC) of irinotecan by 1.5-fold in malignant glioma patients compared with those not receiving EIAEDs.[14] It was therefore considered important to investigate any potential interaction between EIAEDs and tipifarnib in glioma patients. A phase I study using tipifarnib in recurrent glioma patients taking EIAEDs showed that both MTD and DLT were different from previous studies in patients not receiving EIAEDs[15]: MTD was 600 mg bid for 21 days every 4 weeks, which is double that for patients not receiving EIAEDs, and the DLT was rash rather than myelosuppression. Pharmacokinetic evaluation showed that the $AUC_{0\text{ to }12\text{ hours}}$ at MTD was approximately halved in those receiving EIAEDs compared with those not receiving EIAEDs. However, a limited pharmacodynamic evaluation showed the MTD dosing scheme in the patients receiving EIAEDs was adequate to inhibit farnesylation in peripheral blood mononuclear cells.

These results present uncertainty about whether the dosing scheme would be dose equivalent at MTD for patients receiving EIAEDs and not receiving EIAEDs. We therefore performed a phase II study of tipifarnib in patients with recurrent malignant glioma to determine efficacy in anaplastic glioma (AG) and glioblastoma multiforme (GBM). Although not planned prospectively, we also evaluated differences between those with recurrent glioblastoma multiforme either receiving or not receiving EIAED at MTD.

PATIENTS AND METHODS

Patient Population

Eligible patients were ≥ 18 years and had histologically confirmed diagnosis of progressive or recurrent malignant glioma with measurable disease confirmed by magnetic resonance imaging or computed tomography scan. For histologic stratification, GBM was defined as those patients with a primary or secondary GBM including gliosarcoma; AG was defined as patients with primary or secondary diagnosis of anaplastic astrocytoma, anaplastic oligodendroglioma, or anaplastic mixed gliomas. The baseline scan had to be performed within 14 days of entry and with the patient receiving a corticosteroid dose that was stable for more than 5 days. Patients may have had up to two prior relapses. All patients must have experienced treatment failure after radiation therapy; prior surgical resection was not a requirement. Prior irradiation or chemotherapy had to have been discontinued ≥ 4 weeks (≥ 6 weeks if prior therapy was with nitrosourea) before trial entry and patients had to have recovered from the toxic effects of all prior therapies. Patients had to have a Karnofsky performance score (KPS) ≥ 60, and acceptable hematology and biochemistry (WBC ≥ 3,000/μL, absolute neutrophil count ≥ 2,000/μL, platelet count ≥ 120,000/μL, hemoglobin ≥ 10 g/dL, AST and bilirubin < 2× the upper limit of normal, creatinine < 1.5 mg/dL, and creatinine clearance ≥ 60 mL/min).

Dosing was stratified according to EIAED use: group A was not taking EIAEDs and group B was taking EIAEDs. Phase I results for patients receiving EIAEDs have been reported previously in a separate publication.[15] Patients needed to be taking an EIAED for ≥ 2 weeks before entry to be considered for stratification to the EIAED dosing group and had to continue taking their EIAEDs throughout the trial. Patients needed to have discontinued taking EIAEDs ≥ 2 weeks to be considered in the groups not taking EIAEDs. Table 1 lists EIAEDs and non-EIAEDs.

Patients were excluded from the study if they had a concurrent medical illness that, in the judgment of the investigator, would make the patient inappropriate for study entry. Patients were also excluded if they had active infection, were HIV positive, or were taking proton pump inhibitors. Pregnant patients and lactating mothers were ineligible. The protocol and informed consent were approved by the local institutional review board at each participating institution and all patients reviewed, signed, and provided written informed consent before enrollment.

Dosing

Tipifarnib was supplied by the National Cancer Institute as 100-, 200-, and 300-mg tablets. Patients not taking EIAEDs (group A) were treated with oral tipifarnib 300 mg bid on days 1 to 21 every 4 weeks. Patients taking EIAEDs (group B) received oral tipifarnib 600 mg bid on days 1 to 21 every 4 weeks. Tablets were taken after morning and evening meals. Dose reduction/interruption was allowed as predefined according to the protocol.

Patient Evaluation

Pretreatment evaluation included a complete medical history and complete physical examination including neurologic examination. Patients were evaluated clinically every cycle and with laboratory tests at the start and day 7 of every cycle. Magnetic resonance imaging or computed tomography was obtained at baseline and the same type of scan was repeated after every other cycle to assess response. Complete response (CR) was defined as the complete disappearance of all measurable and assessable disease. Complete responders must have discontinued corticosteroid use except if needed for physiologic maintenance. Those with a partial response (PR) must have been taking the same or decreasing doses of dexamethasone and have had stable or improved neurologic examinations. PR was a ≥ 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable lesions. Progressive disease (PD) was defined as a ≥ 25% increase in the sum of the products of all measurable disease over the smallest sum observed, clear worsening of any assessable disease, or the appearance of any new lesion. Stable disease (SD) or no response was defined as those patients with a tumor status that did not qualify for CR, PR, or PD for a minimum of 12 weeks. Failure to return for evaluation because of death or deteriorating condition was considered to represent PD.

Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2 (http://ctep.info.nih.gov/reporting/index.html).

Statistical Considerations

The primary end point for this study was 6-month progression-free survival (PFS). PFS was defined as the time from initiation of therapy to the date of disease progression or death. The intent was to enroll 32 patients with GBM (grade 4) or gliosarcoma in groups A and B (non-EIAED and EIAED)

Table 1. List of Antiepileptic Drugs Considered As EIAEDs and Non-EIAEDs

Non-EIAEDs	EIAEDs
Valproic acid	Carbamazepine
Gabapentin	Oxcarbazepine*
Lamotrigine	Phenytoin
Topiramate	Fosphenytoin
Levetiracetam	Phenobarbital
Tiagabine	Primidone
Zonisamide	
Clonazepam	

Abbreviation: EIAED, enzyme-inducing antiepileptic drug.
*Enzyme induction limited and less potent than carbamazepine.

and a total of 16 patients with AG (grade 3) in each group. AG included patients with anaplastic astrocytoma (predominantly), anaplastic oligodendroglioma, and anaplastic mixed glioma. The initial 32 patients with glioblastoma or gliosarcoma were in group A. The protocol was amended to enroll an additional 32 patients in group B only in an effort to provide exploratory comparisons between the two groups. The significant difference in pharmacokinetic parameters at MTD between groups A and B, and preliminary data showing objective responses in group A emphasized the interest for an exploratory evaluation. No formal comparisons between groups A and B were defined. The sample size was selected to provide an adequate number of patients to have a more than 90% probability of detecting an improvement in 6-month PFS from 15% to 35% using a one-tailed α value of .1 in each of the GBM subgroups.

The sample size for the AG subgroups was intended to provide preliminary information on outcome for patients with grade 3 tumors, and was intended primarily to be descriptive. Accrual was stopped when the planned number of patients was enrolled based on institutional assessment of tumor histology. The final numbers differed somewhat from those planned because of changes in histology based on central pathology review. For the purpose of the primary planned evaluation of 6-month PFS for the two groups (A and B), all treated patients were included and the proportion known to have PFS more than 6 months was calculated separately for the GBM and AG subgroups. In addition, Kaplan-Meier curves were used to describe the results graphically. For these and other time-to-event analyses, patients not known to have progressed were censored at the time of the last known assessment before any nonprotocol therapy.

For the unplanned comparisons between groups A and B, demographic comparisons used the Cochran-Mantel-Hanzel test for ordered or unordered categories, as appropriate for the measure being assessed. The comparison of PFS between groups used the log-rank test. In addition, a Cox proportional hazards model was used including KPS, age, and number of prior chemotherapies, as well as grouping based on anticonvulsant use, to determine if the difference in outcome between the groups remained when adjustment was made for these variables.

RESULTS

Patient Characteristics

A total of 89 patients were enrolled between June 2000 and January 2003 at nine US centers. All patients were assessable for both efficacy and safety. Patient characteristics are summarized in Table 2. There were 46 patients in group A (36 GBM and 10 AG) and 43 patients in group B (31 GBM and 12 AG). All patients had experienced treatment failure after surgery and radiation therapy.

PFS

Among the 46 non-EIAED patients, progression times are defined for all but five patients. Two patients, one with AG and one with GBM, were censored at 9 weeks because alternative therapy was started without documented progression. One GBM patient was without progression at 36 weeks, but was lost to follow-up for progression at that time. This patient subsequently died. Two GBM patients were alive without progression at last contact 147 and 187 weeks after start of study. None of the AG patients achieved the targeted goal of PFS more than 6 months. The median PFS was 8 weeks (95% CI, 4 to 14 weeks). Median PFS for the non-EIAED GBM patients was 9 weeks

Table 2. Patient Demographic and Clinical Characteristics

Characteristic	Total (N = 89)		Tumor Grade: Anaplastic Glioma (n = 22)		Tumor Grade: Glioblastoma Multiforme (n = 67)		EIAED Use: No (group A; n = 46)		EIAED Use: Yes (group B; n = 43)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Sex										
Female	27	30.3	8	36.7	19	28.4	17	37.0	10	23.3
Male	62	69.7	14	63.7	48	71.6	29	63.0	33	76.7
Age, years										
Median	48		46		49		49		47	
Range	24-75		24-69		30-75		30-75		24-70	
Race										
White	86	96.6	21	95.5	65	97.0	44	97	42	98
Other	3	3.4	1	4.5	2	3.0	2	3	1	2
KPS										
Median	80		85		80		85		80	
Range	60-100		60-100		60-100		60-100		60-100	
EIAED use										
No (group A)	46	51.7	10	45.5	36	53.7	46	100	0	0
Yes (group B)	43	48.3	12	54.5	31	46.3	0	0	43	100
Tumor grade										
Anaplastic glioma	22	24.7	22	100	0	0	10	21.7	12	27.9
Glioblastoma multiforme	67	75.3	0	0	67	100	36	78.3	31	72.1
Prior chemotherapy										
None	11	12.4	2	9.1	9	13.4	10	21.7	1	2.3
1 regimen	59	66.3	16	72.7	43	64.2	35	76.1	24	55.8
2 regimens	18	20.2	4	18.2	14	20.9	1	2.2	17	39.5
3 regimens	1	1.1	0	0	1	1.5	0	0	1	2.3

Abbreviations: EIAED, enzyme-inducing antiepileptic drug; KPS, Karnofsky performance score.

(95% CI, 7 to 14 weeks). Six of 36 GBM patients (16.7%; 95% CI, 7% to 32%) were alive and progression free at 6 months. None of these results met the prespecified definition of success.

Among the 43 EIAED patients, all patients have experienced disease progression. Among the 12 AG patients, median time to progression was 8 weeks (95% CI, 7 to 12 weeks). Two patients (16.7%; 95% CI, 3% to 45%) had PFS more than 6 months. Median PFS for the 31 GBM EIAED patients was 6 weeks (95% CI, 4 to 8 weeks). Two patients (6.5%; 95% CI, 1% to 20%) had PFS more than 6 months. There was a high frequency of early treatment failure in this group. Ten of the 31 patients experienced treatment failure in $\leq$ 4 weeks compared with five of 36 among the non-EIAED GBM patients.

As an exploratory analysis, a comparison was made between the efficacy outcomes of GBM patients in groups A and B. The difference in PFS was statistically significant ($P = .01$; Fig 1). Ages were similar for the two groups (median, 49 and 52 years for group A and B, respectively; $P = .24$) as was KPS (median, 80 for both groups; $P = .26$). However, the EIAED group tended to have more prior chemotherapies ($P < .001$); 45% of the EIAED patients had two or three prior chemotherapy regimens compared with only 3% for the non-EIAED group. Although the two groups differed in number of prior chemotherapies, this difference did not seem to be a primary source of the observed difference in outcome. The estimated hazard ratio for the group difference (group B/group A) in a univariate Cox proportional hazards model was 1.9 (95% CI, 1.2 to 3.2). When number of prior chemotherapies was included in the model, the estimated hazard ratio was slightly smaller (1.8; $P = .05$), but there was no indication that the number of prior chemotherapies was predictive of 6-month PFS ($P = .61$). In a multivariate model adding age and KPS as well as number of prior therapies, the results were qualitatively the same, although the estimate was reduced further to 1.7 ($P = .08$). Again, of all the variables included, the group effect (group B/group A) was the strongest (most statistically significant) predictor and is the variable selected if a backward stepwise selection process is used.

Objective Response

The only objective responses were seen in patients with GBM. Four GBM patients had a PR in group A and one patient had a PR in group B. The partial responses were not centrally reviewed. No patient achieved a CR.

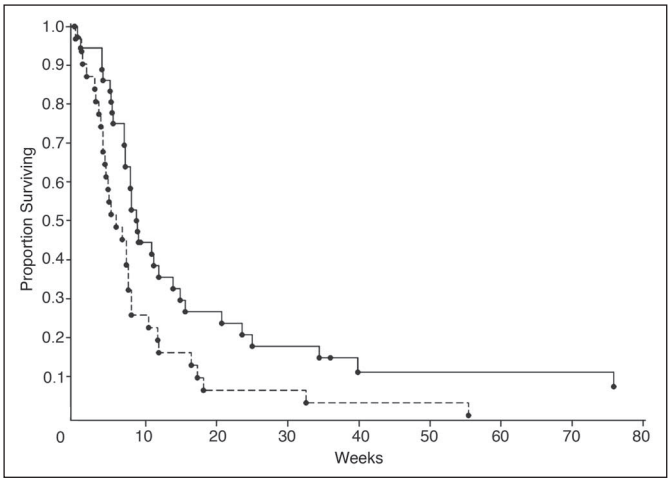

Fig 1. Progression-free survival in group A (non–enzyme-inducing antiepileptic drug [EIAED]; n = 36; [——]) and group B (EIAED; n = 31; [– – –] for patients with glioblastoma multiforme, grade 4. Four patients were censored in group A and none were censored in group B.

Safety

Treatment was relatively well tolerated by the patients in both groups A and B. There were no treatment-related deaths. Treatment-related adverse events are summarized in Table 3. Group A had a higher incidence of hematologic adverse events (grade 1 to 4). There were no grade 3/4 hematologic adverse events in group B. Only two patients experienced grade 4 adverse events: granulocytopenia and leukopenia, respectively, each occurring in patients in group A. Group A patients also had a higher incidence of anorexia, fatigue, and nausea (grades 1 to 2), whereas group B patients tended to have a higher incidence of constipation and alkaline phosphatase increase (grade 1 to 2). Rash and desquamation occurred at a similar incidence in each group. There were no grade 4 nonhematologic adverse events and grade 3 nonhematologic adverse events were infrequent in either group.

DISCUSSION

In the total cohort of 89 patients with recurrent malignant glioma, 10 patients (11.2%) treated with tipifarnib showed 6-month PFS. In the main subgroup with GBM (grade 4 glioma), eight of 67 patients (11.9%) had 6-month PFS as compared with two of 22 patients (9.1%) in the exploratory subgroup with AG (grade 3 glioma). Among the eight GBM patients with PFS more than 6 months, six of 36 (16.7%) were not receiving EIAEDs, compared with two of 31 patients who were receiving EIAEDs. The difference in PFS was statistically significant. The majority of the difference between these subgroups was accounted for by the high frequency of early treatment failure in group B patients (ie, patients who were receiving EIAEDs). In addition, PRs were seen predominately in GBM group A patients.

Tipifarnib was administered at the previously determined MTD doses of 300 and 600 mg bid on days 1 to 21 every 4 weeks in patients receiving and not receiving EIAEDs, respectively.[15] Given that tipifarnib undergoes extensive hepatic metabolism,[7,16,17] it had been anticipated that concomitant dosing with EIAEDs would substantially increase the hepatic clearance of tipifarnib. Our previous phase I study showed that even though the MTD of tipifarnib was doubled in patients receiving EIAEDs, the $AUC_{0\text{ to }12\text{ hours}}$ at MTD was approximately halved in those receiving EIAEDs compared with those not receiving EIAEDs.[15] At the MTD, tipifarnib was well tolerated in patients both receiving and not receiving EIAEDs. Hematologic adverse effects were more frequent and severe in group A (non-EIAED) as were grade 1/2 fatigue, nausea, and anorexia. Grade 1/2 alkaline phosphatase increase and constipation seemed to be more frequent in group B (EIAED). Rash/desquamation of any grade occurred at a similar frequency in groups A and B (15% *v* 16%, respectively) and grade 3 rash/desquamation was relatively rare in each group (one of 46 patients in group A and two of 43 patients in group B).

These observations suggest an enhanced biologic effect in group A (no EIAED) compared with those in group B (EIAED). However, there are concerns regarding defining an enhanced biologic effect in group A from these results. These evaluations were not designed to take into consideration all important prognostic stratification factors that might provide for more definitive efficacy comparisons. For

Table 3. Safety

Adverse Event	Not Receiving EIAEDs (group A; n = 46)						Receiving EIAEDs (group B; n = 43)					
	Grade 1/2		Grade 3/4		Any Grade		Grade 1/2		Grade 3/4		Any Grade	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Hematologic												
Anemia	14	30.4	0	0	14	30.4	7	16.3	0	0	7	16.3
Granulocytopenia	10	21.7	4	8.7	14	30.4	4	9.3	0	0	4	9.3
Leukopenia	15	32.6	3	6.5	18	39.1	6	14.0	0	0	6	14.0
Lymphocytopenia	1	2.2	1	2.2	2	4.3	0	0	0	0	0	0
Thrombocytopenia	13	28.3	1	2.2	14	30.4	0	0	0	0	0	0
Nonhematologic												
AP increase	0	0	0	0	0	0	6	14.0	0	0	6	14.0
Anorexia	5	10.9	0	0	5	10.9	1	2.3	0	0	1	2.3
Constipation	4	8.7	1	2.2	5	10.9	8	18.6	0	0	8	18.6
Diarrhea	4	8.7	1	2.2	5	10.9	4	9.3	0	0	4	9.3
Fatigue	24	52.2	1	2.2	25	54.3	12	27.9	1	2.3	13	30.2
Headache	5	10.9	0	0	5	10.9	4	9.3	2	4.7	6	14.0
Nausea	9	19.6	0	0	9	19.6	4	9.3	0	0	4	9.3
Rash/desquamation	6	13.0	1	2.2	7	15.2	5	11.6	2	4.7	7	16.3

Abbreviations: EIAED, enzyme-inducing antiepileptic drug; AP, alkaline phosphatase.
*Includes only two grade 4 adverse events (granulocytopenia and leukopenia, respectively), each of which occurred in patients not receiving EIAEDs (group A).

instance, group B patients were more heavily pretreated than were those in group A. In addition, one might question whether group B MTD was effectively defined since rash was an unexpected DLT in the phase I study. Moreover, failure to reach the predefined goal for success of 6 month PFS makes it difficult to consider the biologic effect as clinically significant.

Nevertheless, these findings, in total, favor an enhancement in biologic effect at MTD for patients not receiving EIAED (group A). However, the therapeutic benefit from single-agent tipifarnib is modest. Given these data, two opportunities exist for the possible effective use of single-agent tipifarnib in recurrent malignant gliomas. Recently it was found that responsiveness to EGFR kinase inhibitors is increased in a subgroup of glioblastoma patients who coexpress EGFRvIII and phosphatase and tensin homologue deleted on chromosome.[18] EGFR kinase inhibitors previously had been thought to have limited use as a single agent in recurrent glioblastoma, with 6-month PFS ranging from 0% to 17%.[19-21] Similar tissue interrogations on tumor samples from patients treated with tipifarnib might be focused on farnesylated proteins[22] as well as RAS-MAP kinase and PI3 kinase pathways[23] to aid in identifying a subset of patients who are more likely to respond to this agent. Additional dosing strategies may allow for greater drug exposure, potentially leading to a greater clinical effect.[24] In the absence of a defined effective use as a single agent, tipifarnib will likely need to be used in combination with conventional cytotoxic therapies or complementary targeted molecular agents to provide clinically significant benefit in patients with malignant gliomas. A number of glioblastoma trials are ongoing to evaluate the benefit of combining tipifarnib with other therapies in the newly diagnosed and recurrent setting. These trials currently are only evaluating patients not receiving EIAED.

In conclusion, tipifarnib when dosed at MTD shows some evidence of enhanced biologic effect in patients with recurrent GBM (grade 4) who are not receiving EIAEDs, compared with those receiving EIAEDs. Future studies in glioblastoma with tipifarnib should be limited to those patients not receiving EIAEDs.

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