Multifaceted end points in brain tumor clinical trials: Cognitive deterioration precedes MRI progression

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Current treatments for brain cancer have, for the most part, equivocal survival benefit. However, clinical trials of new anticancer agents do not adequately assess potential clinical benefits for patient function other than survival and time to tumor progression.We evaluated 56 patients with recurrent brain tumors who were recruited on phase 1 and phase 2 clinical trials and given assessments of cognitive function, quality of life (QOL), and ability to perform activities of daily living (ADL) prior to receiving treatment and at intervals coinciding with MRI scans, generally monthly. Meaningful change on the cognitive and functional assessments was determined by the reliable change index. Cognitive or functional deterioration was then used as a time-dependent covariate in a Cox proportional hazards regression model with tumor progression, as defined by standard criteria, as the end point. Cognitive deterioration occurred 6 weeks prior to radiographic failure (median 7.4 weeks vs. 13.4 weeks). In contrast, median time for QOL to deteriorate was not achieved. Median time for instrumental ADL to decline was 43 weeks, long after tumor progression. For patients with brain cancer, brain function began to worsen before MRI evidence of tumor progression. QOL and ADL function were not strongly tied to cognitive decline or to time to tumor progression, suggesting that these measures may not be sufficiently sensitive to change in clinical trials of new anticancer agents, although they are important measures in terms of patient care. This study also demonstrates the feasibility of performing neurocognitive testing in this patient population. New drugs that slow the cognitive decline of brain tumor patients may be of clinical benefit regardless of the impact on overall survival. *Neuro-Oncology 5, 89–95, 2003 (Posted to Neuro-Oncology [serial online], Doc. 02-026, February 20, 2003. URL http://neuro-oncology.mc.duke.edu)*

Primary malignant brain cancer is characterized by short-term survival and significant morbidity as the disease progresses (Meyers, 1997). Therefore, entering patients in clinical trials of new agents is critical. To date, however, existing treatments have not significantly altered overall survival except in the case of anaplastic astrocytoma, which now has a median survival of 3 years (Levin et al., 1997). The minimal survival benefit of existing treatments highlights the need for other measures of patient outcome, including ability to function and quality of life (QOL).[3] As defined by a working group composed of members of the Food and Drug Administration, the National Cancer Institute (NCI), and the NCI Division of Cancer Treatment Board of Scientific Counselors, net clinical benefit of cancer therapy includes (a) survival benefit, (b) time to treatment failure and disease-free survival, (c) complete response rate, (d) response rate, and (e) *beneficial effects on disease-related symptoms and/or quality of life* (authors' italics) (O'Shaughnessy et al., 1991). In the case of brain cancer, which is characterized by progressive impairments of mental function, a beneficial treatment may be one that stabilizes or slows the pro-

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[2] Abbreviations used are as follows: ADL, activities of daily living; COWA, Controlled Oral Word Association; FACT-Br, Functional Assessment of Cancer Therapy with brain tumor-specific module; FIM, Functional Independence Measure; HVLT, Hopkins Verbal Learning Test; KPS, Karnofsky performance scale; NCI, National Cancer Institute; QOL, quality of life; RCI, reliable change index; TTP, time to tumor progression.

gression of worsening symptoms, whether or not overall survival is extended.

Brain dysfunction caused by brain cancer is manifested by neurologic and cognitive impairment. Impairments due to the tumor itself are related to the site of the lesion and thus vary among individuals (Scheibel et al., 1996). Treatment, particularly radiation therapy, tends to affect the subcortical white matter, causing impairments in cognitive speed, frontal lobe executive functions (apathy, perseveration, etc.), memory, sustained attention, and motor coordination (Archibald et al., 1994; Grant et al., 1994; Hochberg and Slotnick, 1980; Imperato et al., 1990; Lieberman et al., 1982; Salander et al., 1995; Scheibel et al., 1996; Taphoorn et al., 1994). Some patients develop an outright treatment-related dementia that may even lead to death (DeAngelis et al., 1989).

Most brain tumor treatment trials include assessment of performance status such as the Karnofsky performance scale (KPS) (Karnofsky and Burchenal, 1949). Assessment of QOL using various questionnaires is also increasingly common in clinical trials. Analysis of QOL data from patients with brain involvement needs to consider the potential effect of neurocognitive impairment. Since many cognitively impaired patients cannot complete QOL instruments, there may be substantial amounts of missing data. Information that is collected only on those patients who are cognitively more intact may bias the interpretation of results. The use of proxy reports of patient QOL by caregivers or health care providers when the patient is unable to respond reliably is problematic since QOL is subjective by definition (Browne et al., 1994; Osoba, 1994), and the results may be of questionable meaning in a person who cannot appreciate his or her circumstances. Proxy assessments have been performed with relatively poor agreement obtained between patient and proxy, even while the patient is still able to respond (60%) (Sneeuw et al., 1997).

In addition, the KPS does not address domains considered essential for measuring QOL, nor does it address cognitive impairment (Aiken, 1994; Wade, 1992). Although the KPS is most sensitive to patient age (Mackworth et al., 1992) and has questionable validity and reliability (Hutchinson et al., 1979), it continues to be used as the primary tool for assessing QOL in many brain tumor trials (Kleinberg et al., 1993; Leibel et al., 1989; Sachsenheimer et al., 1992; Scerrati et al., 1994; Trojanowski et al., 1989). Some groups have improved on the KPS by using assessments that combine survival with the length of time patients have adverse effects of disease and treatment (Murray et al., 1995). This approach (quality-adjusted survival analysis) provides information on patient function beyond that obtained from KPS scores and allows for better assessment of the benefits of different therapeutic strategies (Scott, 1997). Other groups are instituting more comprehensive and objective assessments of the patients' ability to perform activities of daily living (ADL) to supplement the KPS score (Brazil et al., 1997).

The World Health Organization (1980) has proposed a 3-tiered system for classifying the effects of neurologic disease on the patient: (1) *Impairment* is the effect of the disease process (in this case the tumor and treatment) on the function of the brain, which is assessed by neurologic and neurocognitive evaluations; (2) *disability* refers to the effect of the impairment on the patient's ability to function in ADL, often assessed by performance status measures; and (3) *handicap* refers to the impact of the impairment and disability on the patient's function in social and vocational roles and on life satisfaction, often captured by QOL measures. A multifaceted assessment of these 3 components can be used to document patient response to treatment, to distinguish the effects of tumor and treatment on brain function, and to provide a basis for implementing intervention strategies in patients with neurologic compromise. The multifaceted approach has the potential to better define the relative risks versus benefits of different treatment regimens, particularly when they exhibit small differences in terms of survival benefit. It may also provide additional helpful information in the drug approval process as well as improving survival and time to tumor progression (TTP) (Meyers et al., 1996).

In order to be practical, an assessment of patient function that addresses impairment, disability, and handicap must be brief, inexpensive, sensitive to change, and able to be completed by most patients, even those with significant neurologic compromise. The assessment must be comprehensive enough to be sensitive to the focal effect of tumors in various locations. Formal assessment of neurocognitive function has unfortunately been characterized as burdensome to the patient, and brief assessments of global cognitive function are considered most practical (Choucair et al., 1997). However, a brief assessment such as the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) may not be sensitive to mild cognitive impairments or focal lesions (Lezak, 1995), which could reduce the sensitivity and specificity of these measures in assessing neurocognitive impairment and changes in function over time in brain tumor patients (Wade, 1992).

In this study we have proposed a model that uses objective measures of neurocognitive function (impairment), patient function in ADL (disability), and subjective QOL (handicap) in brain tumor patients undergoing phase 1 and phase 2 clinical trials for recurrent tumor. The time to complete these assessments is on average 23 min (Meyers et al., 1999), and the test battery has demonstrated practicality in terms of cost, repeatability, and burden to patient. In this study we examined the relationship between time to cognitive deterioration and time to radiographic tumor progression.

Methods

Patients

A total of 80 patients with recurrent glioblastoma or anaplastic astrocytoma were seen for baseline evaluations prior to beginning the specific clinical trial for recurrent/relapsed tumor. All protocols were approved by the Institutional Review Board, and all patients gave

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Table 1. Demographic characteristics of patients (N=56)

Characteristic	Patients No.	%	Median	Range
Age, years			49.5	(25, 67)
Sex				
Male	36	65		
Female	20	35		
Tumor type				
Glioblastoma	36	65		
Anaplastic glioma	20	35		
Side of tumor				
Right	23	41		
Left	29	52		
Bilateral	4	7		
Location of tumor				
Frontal	23	41		
Temporal	16	29		
Parietal	8	14		
Occipital	1	2		
Multiple lobes	8	14		
KPS scores			90	(70, 100)
No. of previous surgeries				
One	21	38		
Two	25	45		
Three	9	16		
Four	1	2		
Extent of previous surgery				
Biopsy	6	11		
Subtotal resection	25	45		
Total resection	24	43		
Unknown	1	1		
No. of disease recurrences				
One	49	88		
Two	7	13		
Interval from Diagnosis to 1st test (months)			7.0	(3.7, 226)

Abbreviation: KPS, Karnofsky Performance Scale.

written informed consent to participate. All patients had previously undergone surgical resection, radiation therapy, and front-line chemotherapy. All of the protocols had similar eligibility and exclusion criteria (e.g., KPS score ≥60). The demographic characteristics of the patients are listed in Table 1. Evaluations of cognitive function, QOL, and ADL were conducted as a part of 9 different treatment protocols. Twenty-four of the patients were excluded from analysis because only their baseline evaluation was obtained. Some of those patients had undergone rapid progression of their disease, but there was not a statistical difference in the median time to MRI progression (Kaplan-Meier estimate) between patients with only baseline assessments and the 56 patients with multiple assessments (10 months vs. 13 months, respectively, $P > 0.05$). Thus, data from the 56 patients are presented.

Neuropsychological Test Battery

Patients received a pretreatment baseline evaluation and on-treatment follow-up prior to the next course of therapy (usually monthly; range, 3–8 weeks) until going off-study for progressive disease. MRI scans and neurocognitive testing were always performed within 1 to 2 days of each other. The tests used are standardized psychometric instruments for assessing cognitive functions known to be affected by brain tumors and treatment, testing a fairly broad range of cognitive functions in a nonredundant manner and as briefly as possible. All have published evidence of validity and reliability, as well as normative data that take into account age and, where appropriate, education and gender. Tests resistant to the effect of repeated administration were used whenever possible. The memory test has 6 alternate forms, and the verbal fluency test has 2. The other tests measure motor and cognitive speed and other functions that are less resistant to the effects of practice. One would expect in the normal population that performance would typically improve somewhat on subsequent evaluations; however, our experience is that brain tumor patients remain stable or decline because of the effects of their disease and treatment. We have successfully used this test battery in a number of multisite clinical trials with good success. The tests were as follows: *attention span*, Digit Span (Wechsler, 1981), which requires the repetition of numbers forward and backward; *graphomotor speed*, Digit Symbol (Wechsler, 1981), which requires the patient to code symbols for numbers as rapidly as possible; *memory*, Hopkins Verbal Learning Test (HVLT) (Benedict et al., 1998), which is a list of 12 words in 3 semantic categories that measures immediate recall across 3 trials, recognition of the words from distractors, and delayed recall; *verbal fluency*, Controlled Oral Word Association (COWA) (Benton and Hamsher, 1989), which requires the production of words beginning over a specific letter for three 1-min trials; *visual-motor scanning speed,* Trail Making Test Part A (Lezak, 1995), which requires the subject to connect dots in numerical order as rapidly as possible; *executive function*, Trail Making Test Part B (Lezak, 1995), which requires the subject to connect dots with alternating numbers and letters as rapidly as possible; *motor speed and dexterity*, Grooved Pegboard (Lezak, 1995), which requires the subject to place slotted pegs into holes as rapidly as possible, separately for the dominant and nondominant hands; *QOL*, Functional Assessment of Cancer Therapy with brain tumor-specific module (FACT-Br) (Cella et al., 1993; Weitzner et al., 1995); *ADL*, Functional Independence Measure (FIM) (Linacre et al., 1994).

Response Criteria

MRI scans were evaluated for response and progression by using established criteria that also incorporate patient neurologic function and steroid use (Macdonald et al., 1990). The criteria for progressive disease include ≥25% increase in the area of enhancing tumor, the appearance of any new tumor, and frank neurologic deterioration. No patients in this study, however, progressed on only neurologic grounds. All were declared to have tumor progression on radiographic grounds.

Statistical Analysis

The inherent error in test scores is known for tests with published test-retest reliability, and a change in score that

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is clinically as well as statistically meaningful can be determined. We used the reliable change index (RCI) (Jacobson and Truax, 1991). This index is derived from the standard error of measurement of each test, and it represents the 90% confidence interval for the difference in raw scores from baseline to follow-up that is expected if no real change has occurred. The difference from baseline to follow-up for each test was coded as 1 if the score deteriorated beyond the RCI for that test, 2 if there was no change and the score fell within the RCI, and 3 if the score improved beyond the RCI. Patients were then divided into two groups: those who were stable or improved and those who experienced a significant decline. The minimum time to the first significant decline for all 9 tests and for the 3 most sensitive tests was computed. The most sensitive tests were those on which patients were most likely to fail. We used the 3-test rule to control for the possible oversensitivity of defining failure as a decline in 1 of 9 tests. Kaplan-Meier curves were used to estimate the probabilities of remaining free from neurocognitive decline.

To assess the association between neurocognitive failure and radiographic failure, we used neurocognitive failure as a time-dependent covariate in a Cox proportional hazards regression model with radiographic failure as the end point. We assessed neurocognitive failure in 2 ways: (1) failure on any of 9 tests and (2) failure on 1 of the 3 most sensitive tests. The Cox model estimates the ratio of hazard rate of radiographic failure with and without neurocognitive failure. In essence, we used a 3-state model in which patients start in an initial, nonfailed state and can move to 1 of 2 failure states: neurocognitive or radiographic. Patients in the neurocognitive failure state can move into the radiographic failure state. The hazard rate of radiographic failure measures the rate at which patients move to the radiographic failure state. Thus, we are comparing whether they are moving faster to this state or to the neurocognitive failure from the initial state. The statistical issues relevant for comparing neurocognitive failure with MRI progression are discussed by Hess et al. (1999).

Results

Table 2 displays the mean baseline scores for the tests, the normative range for the test scores, and the raw number of points for each test that determined the RCI used to determine failure. As can be seen from this table, overall the patients were performing well below the normal population on all of the cognitive tests at baseline, and were not fully independent in their ADL. However, their overall QOL (measured by the FACT-Br) was comparable to the brain tumor population sample used to validate the instrument. Figure 1 shows the event chart comparing time to failure on any 1 of 9 cognitive tests versus MRI progression. Patients had evidence of tumor recurrence on MRI at a median of 13.4 weeks (95% confidence interval, 11.0–19.0). Figure 2 shows the hazard function for deterioration on cognitive testing compared to MRI progression. The median time for patients to deteriorate cognitively on any 1 of the 9 assessments was 7.4 weeks (95% confidence interval, 5.0–9.6). In terms of individual performance, 6 patients (11%) never declined on cognitive testing while undergoing assessment, 34 patients (61%) declined prior to radiographic progression, 14 patients (25%) failed at the time of progression, and 2 patients (4%) failed after progression. When only the 3 tests most sensitive to cognitive decline were used (HVLT recall, HVLT recognition, Grooved Pegboard), the median time to failure was 8.9 weeks (95% confidence interval, 6.0–12.9). The hazard ratio (95% confidence interval) for any of the 9 tests was 3.4 (1.6–7.7, $P = 0.0008$). For the best 3 of the tests, the hazard ratio was 2.0 (1.1–3.7, $P = 0.024$). Thus, cognitive decline, as revealed by a battery of tests, occurred approximately 50% earlier than MRI evidence of tumor progression. Even the use of only 3 tests showed that cognitive decline occurred more than a month earlier than MRI evidence of progression. This decline occurred in the setting of expected improvement in performance due to practice effect. In contrast, the median time for QOL to worsen was not achieved, as only 3 patients declined beyond the RCI. Similarly, the median time for patients to worsen in terms of their ability to perform ADL was 43 weeks (95% confidence interval, 14 weeks–not reached), well after radiographic progression.

Table 2. Baseline test scores

Test	Mean	(SD)	Normative Mean	(SD)	RCI score
Digit Span*	8.2	(3.7)	10.0	(3.0)	3
Digit Symbol*	7.7	(3.1)	10.0	(3.0)	3
HVLT Recall†	18.9	(8.0)	28.8	(3.8)	5
HVLT Recognitionff	9.6	(2.7)	11.2	(1.1)	2
COWA§	25.5	(11.9)	37.0	(10.0)	13
Trails A¶	67.9	(60.0)	29.7	(8.4)	12
Trails B¶	170.0	(107.4)	73.6	(19.4)	24
Pegboard right hand¶	111.0	(63.9)	68.1	(9.4)	11
Pegboard left hand¶	136.3	(75.8)	74.7	(10.5)	12
FIM#	115.2	(13.3)	126.0	(—)	9
FACT-Br‡	138.1	(22.7)	136.0	(26.0)	28

Abbreviations: ADLs, activities of daily living; COWA, Controlled Oral Word Association; FACT-Br, Functional Assessment of Cancer Therapy with brain tumor specific module; FIM, Functional Independence Measure; HVLT, Hopkins Verbal Learning Test; QOL, quality of life; RCI, reliable change index.

* Age-corrected scaled scores (range, 1–19).

† Number of words recalled over 3 trials (maximum, 36).

ff Number of words accurately recognized minus false alarms (range, -12 – +12).

§ Number of words produced during 3 min.

¶ Time in seconds to complete task.

Raw score (range, 18–126; higher scores mean greater independence in ADL).

‡ Raw score (range, 0–188; higher scores mean better QOL; norms based on brain tumor patients).

Discussion

In this study, cognitive decline in patients with recurrent malignant glioma preceded radiographic evidence of tumor progression by approximately 6 weeks. Because

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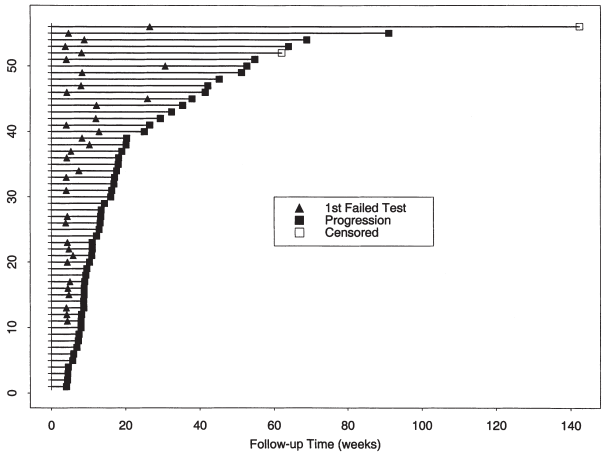

Fig. 1. Event chart comparing time to neurocognitive failure on any of the tests (▲) and radiographic tumor progression (■) for each subject (y axis). "Censored" (□) indicates the individual had not yet progressed.

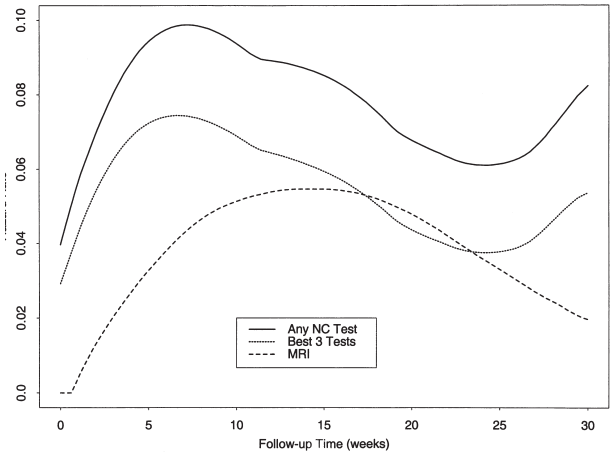

Fig. 2. Hazard function for test failure on any test, test failure on the 3 most sensitive tests, and radiographic failure. The peak cognitive test failure rates occur earlier and are higher than the peak MRI failure rate. The fact that the peak is higher for any test failure than for the 3 best tests reflects the larger number of events.

patients had tumors in differing locations, different patients declined on different tests, and this variation highlights the need to use a battery of tests when evaluating the cognitive function of brain tumor patients. However, tests of memory and fine motor coordination were the most sensitive to decline in this group. In contrast, QOL and ability to perform basic ADL (bathing, feeding, etc.) were less strongly related to cognitive decline and tumor progression.

Cognitive function can be affected by a number of factors in this population, including adjuvant medications, impaired motor or sensory function, and mood disturbance. However, these factors do not appear to have had a substantial influence on cognitive decline in our study. All patients were receiving similar medications (including anticonvulsants and steroids) at the time of the baseline assessment, with no significant changes in medication regimen over the course of the study. Primary motor or sensory loss would have indicated neurologic worsening and would thus have identified the patient as having tumor progression, suggesting that cognitive decline in advance of radiographic tumor progression was not related to neurologic worsening. Finally, mood disturbance and adverse symptoms such as pain and fatigue were captured on the QOL assessment, which in fact did not correlate well with either cognitive decline or tumor progression. These findings bring up several interesting questions for further study.

The assessment of subjective QOL in patients with neurologic deterioration is difficult. In fact, 37% of the patients who filled out a baseline questionnaire had become unable to complete it at their first follow-up assessment because of their declining status. Thus, in comparison to the neurocognitive assessment, fewer patients were able to complete the FACT-Br because of difficulty understanding the questions and how to respond to them.

The ability to perform basic ADL (as assessed by the FIM) did not appear to change much, despite cognitive decline and frank tumor progression. One possibility is that patients had low function at their baseline. The median baseline FIM was 119 (out of a possible 126), and 46% had scores equal to or below 117, which is in the impaired range. Sixteen percent of the patients had values between 60 and 100, indicating significant impairments in independent functioning, 35% had values between 101 and 120, and only 48% had values in the normal range (121–126). This indicates that about half the patients were not totally independent in ADL at baseline, and that change in performance status was not closely related to change in cognitive function or radiographic evidence of tumor progression.

There are several limitations to the analysis we present here. For one, the ways in which MRI progression and neurocognitive progression are determined are not equivalent. Although both are standard ways of determining clinically significant change, they use a different metric (an increase in tumor size on the MRI vs. a change in a cognitive test score that exceeds the inherent test-retest error). In addition, the RCI is based upon the psychometric characteristics of the tests in normal healthy control populations. Brain tumor patients in general have more variable test findings than control populations and in general also score much worse at baseline. However, the point of using the RCI is to use test-retest reliability data to gauge levels of chance variation, the random component of measurement error. In addition, change that exceeds the RCI is still clinically meaningful, even in a patient with a low level of function.

These results indicate that performance on cognitive tests, which assess the function of the brain, is more sensitive than MRI evidence of TTP and predicts tumor recurrence more than a month in advance of MRI confirmation. In contrast, declines in subjective QOL or ability to perform ADL tended to occur after tumor progression. Prospective assessment of QOL is not sufficient by itself to track change in patients who are experiencing neurologic deterioration, and change in the ability to per-

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form ADL is resistant to effects of disease until a late stage. We have previously reported that cognitive function at the pretreatment baseline assessment, but not QOL or ADL, is an independent predictor of survival in these patients after accounting for the usual prognostic variables (patient age, KPS score, tumor histopathology, time since diagnosis) (Meyers et al., 2000).

Tests of cognitive function may be extremely informative in brain tumor clinical trials. Although less informative for trial outcome, assessment of QOL and patient function are important clinical tools for overall patient care. The development of multiple markers of outcome in brain tumor clinical trials, to better assess the neurotoxicity of new therapies in addition to facilitating more accurate assessment of therapeutic response, has been deemed a research priority in the report of the Brain Tumor Progress Review Group cosponsored by NCI and the National Institute of Neurological Disorders and Stroke (2000). In fact, a recent study found delayed time to neurocognitive progression in patients with brain metastases from non–small-cell lung cancer treated with a radiosensitizer in addition to whole-brain radiation, compared to those receiving whole-brain radiation alone (Meyers et al., 2002), and it is likely more such studies will be performed to supplement survival as an outcome.

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