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ORIGINAL ARTICLE

Fotemustine as second-line treatment for recurrent or progressive glioblastoma after concomitant and/or adjuvant temozolomide: a phase II trial of Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO)

Alba A. Brandes · A. Tosoni · E. Franceschi · V. Blatt · A. Santoro · M. Faedi · P. Amistà · M. Gardiman · R. Labianca · C. Bianchini · M. Ermani · M. Reni

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Abstract
Background Standardized salvage treatment has not yet proved effective in glioblastoma multiforme (GBM) patients who receive prior standard radiotherapy plus concomitant and adjuvant temozolomide.
Methods Patients with progressive GBM after radiotherapy plus concomitant and/or adjuvant temozolomide received three-weekly doses (100–75 mg m^2) of fotemustine followed, after a 5-week rest, by fotemustine (100 mg m^2) every 3 weeks for ≤1 year.
Results Forty-three patients (29 M, 14 F; median age 51 years, range 34–68; median KPS 90) were enrolled. Progression-free survival at 6 months (PFS-6) was 20.9% (95% CI: 9–33%); three patients (7.1%) had partial response (PR); 15 (34.9%), disease stabilization (SD). The median survival was 6 months (95% CI: 5–7). *MGMT* promoter status was methylated in 8 (18.6%) and unmethylated in 26 (60.5%) and not assessable in 9 (20.9%) patients, respectively. Disease control was 75% versus 34.6% in methylated and unmethylated *MGMT* patients ($P = 0.044$); no significant difference was found between groups for PFS-6 and survival. Grade 3 and 4 thrombocytopenia and neutropenia were observed in 20.9 and 16.3% of patients, during the induction phase, and in 0 and 9.5% patients during the maintenance phase, respectively.
Conclusions The findings of the present trial, that evaluate fotemustine in a homogeneous population, may represent a new benchmark for nitrosourea activity. Moreover, this is the first study to evaluate correlation between *MGMT* promoter status and outcome of fotemustine for relapsing GBM previously treated with radiotherapy and temozolomide.

A. A. Brandes (✉) · A. Tosoni · E. Franceschi
Department of Medical Oncology,
Ospedale Bellaria-Maggiore, Via Altura 3,
40139 Bologna, Italy
e-mail: alba.brandes@yahoo.it

V. Blatt
Research and Development Unit,
Azienda Ospedale-Università di Padova, Padova, Italy

A. Santoro
Department of Medical Oncology,
Istituto Clinico Humanitas, Rozzano, Italy

M. Faedi
Department of Medical Oncology,
Ospedale Bufalini, Cesena, Italy

P. Amistà
Department of Neuroradiology,
Ospedale Santa Maria della Misericordia, Rovigo, Italy

M. Gardiman
Department of Pathology,
Azienda Ospedale-Università di Padova, Padova, Italy

R. Labianca
Department of Medical Oncology,
Ospedali Riuniti, Bergamo, Italy

C. Bianchini
Scientific Department, Italfarmaco, Milan, Italy

M. Ermani
Department of Neurosciences, Statistics and IT Unit,
Azienda Ospedale-Università di Padova, Padova, Italy

M. Reni
Department of Oncology,
San Raffaele Scientific Institute, Milan, Italy

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Introduction

Worldwide, glioblastoma multiforme (GBM) is the most frequent primary brain tumor in adults, accounting for 15–20% of intracranial tumors and 50% of gliomas [6]. The standard treatment for newly diagnosed GBM with temozolomide (TMZ), concomitant, and adjuvant to radiotherapy provides a significant increase in overall survival with respect to radiotherapy alone [27]. However, nearly all patients treated for GBM faced recurrence. None of the several drug regimens reported in literature substantially delays disease progression [2]. However, promising results have recently been obtained using novel agents, and new schedules or synergic combinations [23, 29, 30]. However, the findings reported following these new approaches require further confirmation based on results obtained in patients who have a longer follow-up.

Nitrosoureas, used alone or in combination with other agents, are still used as standard second-line chemotherapy, and are considered the standard arm in randomized phase II studies for experimental therapy. Moreover, it has not been demonstrated that nitrosourea-based polychemotherapy is anymore effective against GBM than single agent chemotherapy. Fotemustine (FTMS), a third generation chloroethylnitrosourea containing a phosphoalanine carrier group, is grafted to the nitrosourea radical. Thanks to the phosphoalanine group contained, the drug is highly lipophilic; its octanol/water partition coefficient being within a range that is more satisfactory than the ranges obtained with other nitrosoureas, such as carmustine (BCNU) and lomustine (CCNU). FTMS is able to cross the blood-brain barrier [16, 18]; in vitro and in vivo studies have shown that FTMS has a marked anti-neoplastic activity on human GBM and medulloblastoma cell lines [9, 10]. In their phase I study on 22 GBM patients, Khayat et al. [14] specified the dose of FTMS to be used in clinical practice: 100 mg m^2 for 1-h infusions, conducted on days 1, 8, and 15 (induction), to be repeated after 4–5 weeks (hematological recovery) every 21 days (maintenance). However, in the literature, there is little information on activity and toxicity of this regimen.

The aim of the present phase II study on patients with recurrent or progressive GBM, who were uniformly treated with prior radiotherapy and TMZ, was to evaluate the effect of FTMS on progression-free survival at 6 months (PFS-6), response, toxicity and any correlation with O6-methylguanine–DNA methyltransferase (*MGMT*) gene promoter methylation status.

Patients and methods

Eligibility

The criteria for eligibility were GBM recurrent or progressive after surgery and TMZ concomitant with and/or adjuvant to radiotherapy, proven by MRI or CT scans at least 3 months following the radiotherapy end or by two consecutive tests. Measurable disease with contrast enhancement using MRI or CT scans, tested within 2 weeks before study treatment start. In case of re-surgery before chemotherapy start, residual measurable disease with contrast enhancement must be proven by MRI or CT scans, performed within 3 days after surgery. At least one unidimensionally measurable lesion of $\geq$2 cm in diameter by MRI. Stable or decreasing dose of corticosteroids for at least 2 weeks before patient's enrollment. At least 4 weeks following chemotherapy with TMZ. Other inclusion criteria were age $\geq$18 and $\leq$70 years; Karnofsky performance status $\geq$60; adequate bone marrow reserve (absolute neutrophils count $>1.5 \times 10^9\ L^{-1}$; platelets $>100 \times 10^9\ L^{-1}$; hemoglobin $>10\ g\ dL^{-1}$); normal renal and liver function (serum creatinine <1.25×, upper limit of the normal range (ULN); BUN $<25\ mg\ dL^{-1}$; serum bilirubin $\leq$1.25× ULN; AST and ALT $\leq$ 1.5× ULN; alkaline phosphatase $\leq$2× ULN; remaining life expectancy $\geq$3 months. Patients with active infections or other uncontrolled diseases, psychiatric disturbances and/or a previous history of cancer (except for resected non-melanoma skin cancer or carcinoma—in situ of the uterine cervix), were considered ineligible.

All the histological specimens obtained at first diagnosis were reviewed by the coordinating center of Azienda Ospedaliera of Padova (M.G. Department of Pathology) and the diagnosis of GBM was confirmed according to the criteria specified in 2007 WHO central nervous tumor classification.

The study, approved by the Institutional Ethics Committees of all participating centers, was conducted according to the principles of the declaration of Helsinki and the rules of good clinical practice.

All patients signed a form giving their fully informed consent to participate in the study.

Treatment schedule

In line with phase I study protocol and with licensing instructions of the drug, FTMS 100 mg m^2 was administered i.v. over 1 h weekly for three consecutive weeks (induction therapy), followed after 5 weeks by one infusion of FTMS 100 mg m^2 every 3 weeks (maintenance therapy) for up to 1 year, unless disease progression or unacceptable toxicity was observed. If, due to toxicity, treatment suspension was prolonged by more than 2 weeks beyond the next scheduled cycle of treatment planned, the patient was

permanently withdrawn from the study. Based on the most severe toxicity experienced since the last cycle, the subsequent dose was reduced to 75% in the presence of grade 3 or 4 platelet toxicity, grade 4 neutrophils or white blood cells or hemoglobin toxicity. In cases of non-hematologic toxicity, chemotherapy was delayed until recovery to grade 1, for a maximum of 2 weeks (after which the patient was withdrawn from the study). In cases of recovery to grade 1 after grade 3 or 4 toxicity, a dose of 75% the treatment dose was administered.

After the inclusion of the first three patients who experienced grade 4 thrombocytopenia following induction therapy, the protocol was amended to reduce FTMS dosage during induction therapy to 75 mg m^2. In fact, this life-threatening toxicity was considered unacceptable in the palliative setting of salvage therapy of GBM patients.

Efficacy measures and toxicity monitoring

Progression-free survival (PFS) was measured as from the initiation of FTMS to progression or death due to any cause or last follow-up assessment, whichever comes first. Overall survival (OS) was measured as from the start of FTMS to death for any reason, or last follow-up assessment. In this intent to treat study, data on all registered patients who met the main inclusion criteria were included in the statistical analysis.

Evaluation of response, conducted in all patients, included clinical and neurological examinations and MRI or CT neuro-imaging according to Macdonald's criteria [17]. The first evaluation was made after the induction phase (7 weeks after the first study drug administration); thereafter evaluations were made every two cycles during the study treatment (6 weeks) and every 3 months during the follow-up period, or earlier if indicated. Neurological status was assessed by considering signs and symptoms possibly correlated with progression, as compared to the previous examination; each variation in daily corticosteroids dosage was recorded.

Responses were confirmed as complete (CR), partial (PR) and stable (SD) if they were constant at subsequent scans obtained at least 4 weeks apart from each other. An independent central review of CT and MRI scans was made for all patients.

All adverse events were recorded and graded according to the common toxicity criteria of the National Cancer Institute, version 3.0. (http://ctep.cancer.gov/forms/CTCAEv3.pdf).

DNA extraction and methylation-specific polymerase chain reaction

MGMT promoter methylation analysis was performed on tissue taken from the primary surgery specimen before radiotherapy and TMZ.

DNA from 10 μm paraffin sections of cerebral lesion was modified by sodium bisulfite, which converts unmethylated cytosine to uracil, according to the procedure of Herman et al. [13]. Modified DNA was submitted for methylation-specific PCR (MSP) following a nested-PCR protocol [21]. Since the quality of DNA obtained from formalin-fixed paraffin-embedded tumor tissue affects the success rate of MSP, in some cases *MGMT* methylation status was determined by a different nested-MSP approach, with a first pair of primers to obtain smaller amplicons (129 bp), for which forward and reverse primers have been described [21, 28].

End points and statistical analysis

Data from all patients, who received at least one drug delivery and for whom at least one tumoral evaluation was performed, were included in the response analysis.

The primary efficacy endpoint of the study was the percentage of patients free from disease progression at 6 months (PFS-6). Drug activity was evaluated following a one-stage Fleming study design for determination of response rates based on a single-treatment group. A sample size of 40 patients was estimated using exact binomial method and assuming: one-tailed α equal to 0.1, (1-β) equal to 0.9 and π<0.1 (null hypothesis) versus $\pi \geq 0.25$ (alternative hypothesis), where π was the observed 6-month disease progression-free probability. If seven or more patients were evaluated as PFS-6, it was assumed that the drug was active.

Secondary objectives were the rate of best observed response, defined as the best response during the treatment and evaluated with Macdonald's criteria [17]; duration of objective response and stabilization; duration of complete response; time to disease progression, overall survival, toxicity, and evaluation of *MGMT* methylation and the correlation with clinical outcome. All patients receiving the study drug were included in the safety analysis. Median time to progression (mTTP) and median survival were also estimated with associated 95% CI. PFS-6 and OS were calculated using the Kaplan–Meier method; differences in PFS-6 and OS were compared using the log rank test for statistical significance.

Results

Patients' characteristics

From April 2005 to May 2006, 43 patients (29 males; median age: 51 years, range: 34–68 years; median: KPS 90) were enrolled in the study. The demographic and clinical characteristics of patients are outlined in Table 1. Each

Table 1 Patients' characteristics

	Number of patients	%
Sex		
Male	29	67
Female	14	33
Age		
Median years (range)	51 (34–68)	
Karnofsky performance status (KPS)		
Median (range)	90 (70–100)	
Extent of resection		
Macroscopically radical	28	65
Partial	12	28
Biopsy	3	7
Radiotherapy/TMZ	43	100
MGMT status		
Methylated	8	18.6
Unmethylated	26	60.5
Unknown	9	20.9
FTMS initiation and time to TMZ treatment completion		
Within 3 months	30	69.8
Beyond 3 months	13	30.2

patient had completed external-beam radiation therapy (60 Gy/30 F) concurrent and/or followed by adjuvant TMZ. Median number of TMZ cycles was 5 (range 1–23). No patient underwent a second surgical procedure at the time of progression following TMZ administration. Median time between TMZ treatment completion and FTMS start was 1.5 months (range 1–43). Thirty patients (69.8%) started FTMS within 3 months from TMZ last administration. At time of FTMS initiation 26 patients (60.5%) were on enzyme-inducing antiepileptic drugs (EIAEDs), while 11 patients (25.6%) were on non-EIAEDs and 6 patients (13.9%) were not on antiepileptic drugs. The median duration of follow-up was 7.4 months (range 1.2–22.7). In 39 of the 43 patients enrolled in the trial, enough histological material was obtained for evaluation of MSP. MSP was assessable on 34 of these 39 patients. *MGMT* promoter status was methylated in 8 (18.6%) and unmethylated in 26 (60.5%) and not assessable in 9 (20.9%) patients, respectively.

Progression-free survival

Nine patients (20.9%; 95% CI: 9–33%) were PFS-6 and the median PFS was 1.7 months.

The percentages of PFS-6 with *MGMT* promoter methylated or unmethylated status were 25% (95% CI: 7.5–83%) and 19.2% (95% CI: 8.7–42.3%), respectively. PFS-6 in the population ($n = 40$) treated after the amendment was 22.5%, not significantly different with the entire population of 43 pts.

No significant differences were found between median PFS, evaluated using the log rank test, in relation to age ($P = 0.89$), KPS ($P = 0.33$), and *MGMT* promoter methylated or unmethylated status ($P = 0.15$). No significant influence of type of antiepileptic drug was seen, being PFS-6 26.9% and 11.7% in patients on EIAEDS and on non-EIAEDS plus not on antiepileptic drugs, respectively ($P = 0.28$).

Patients that initiated FMTS at least 3 months after TMZ completion showed a significantly higher PFS-6, (30.7 vs. 16.7%) than patients who initiated FTMS immediately after TMZ completion ($P = 0.034$).

Response

Among the 43 assessable patients, 3 had partial responses (7.1%, 95% CI: 0–15%), and 15 stable disease (34.9%, 95% CI: 21–49%). Disease control rate (SD+PR) in the population treated after the amendment was 42.5%, not significantly different with the entire population. All responses were confirmed by an independent centralized review, and stable or decreased steroid dosage was confirmed in all patients at the time of recording response. Median duration of response was 9.1 months (95% CI: 1.7–16.4), and median duration of disease stabilization was 5 months (95% CI: 1.2–8.9). Disease control rate was significantly greater in methylated and unmethylated *MGMT* patients, 75 and 34.6% ($P = 0.044$), respectively; and in patients who started FTMS at least 3 months after TMZ administration had been concluded (76.9 vs. 26.7%, $P = 0.002$).

No significant influence of type of antiepileptic drug was seen, being disease control rate 42.3 and 41.2% in patients on EIAEDS and on non-EIAEDS plus non on antiepileptic drugs, respectively ($P = 0.98$).

Overall survival

The median overall survival was 6 months (95% CI: 5–7). The median overall survival of the population treated after the amendment was 6 months. No statistical difference has been found between patients with methylated and those with unmethylated *MGMT* promoter status: being 6 months (95% CI: 0–14.2) versus 5.5 months (95% CI: 4.2–6.8).

The median overall survival for patients who started FTMS at least 3 months after TMZ administration had been concluded was 8.4 months (95% CI: 2.6–14) versus 5.4 months (95% CI: 4.2–6.5) for patients who initiated FTMS immediately after TMZ completion ($P = 0.022$).

The percentage of patients alive at 6 months was 51% (95% CI: 38–68%), without difference between patients with methylated or unmethylated *MGMT* promoter status

62.5% (95% CI: 36.5–100%) versus 46% (95% CI: 30.5–70%). Only disease control rate obtained with FTMS was significantly correlated with survival ($P = 0.002$).

Treatment and toxicity

All 43 patients completed the induction phase as planned. After induction phase grade 3–4 thrombocytopenia and neutropenia were documented in 9 (20.9%) and 7 out 43 patients (16.3%), respectively; grade 3–4 lymphopenia was found in four patients (9.3%). The study was emended after the first three patients by decreasing the FTMS induction dose from 100 mg m^2 once a week for 3 weeks to 75 mg m^2. Of note, the first three patients that received induction therapy at the dosage of 100 mg m^2 aged 48, 51, and 62 years, had a KPS of 100, 100, and 80, started FTMS 30, 40, and 95 days after TMZ completion, respectively, and did not have significant comorbidities to justify increased toxicities.

The grade 3–4 thrombocytopenia reported for the induction phase in the 40 patients treated after this amendment was 15%.

Twenty-one (49%) patients started maintenance chemotherapy and received a median of two cycles (range 1–14). The main reason for not beginning maintenance therapy after the induction part was disease progression. Only one patient, with prolonged grade 2 neutropenia, discontinued therapy due to toxicity after the induction phase. The toxicity of the maintenance phase was grade 3 leukopenia and grade 4 neutropenia in 14 and 9.5% of the patients, respectively; no patient experienced grade 3–4 thrombocytopenia (Table 2). The most commonly reported grade 3–4 non-hematological toxicity were nausea and vomiting in two (4.6%) patients and transaminase elevation in four patients (9.3%). Pneumonia was reported in one patient (2.3%).

Table 2 Hematological toxicities during and after induction and during the maintenance phase

Adverse Event	Induction ($n = 43$) [% (Pts/Total)]	Induction after amendment ($n = 40$) [% (Pts/Total)]	Maintenance ($n = 21$) [% (Pts/Total)]
Thrombocytopenia			
Grade 3	11.6 (5/43)	12.5 (5/40)	0.0 (0/21)
Grade 4	9.3 (4/43)	2.5 (1/40)	0.0 (0/21)
Leukopenia			
Grade 3	7.0 (3/43)	5.0 (2/40)	14.3 (3/21)
Grade 4	2.3 (1/43)	2.5 (1/40)	0.0 (0/21)
Neutropenia			
Grade 3	9.3 (4/43)	10.0 (4/40)	0.0 (0/21)
Grade 4	7.0 (3/43)	5.0 (2/40)	9.5 (2/21)
Lymphopenia			
Grade 3	7.0 (3/43)	7.5 (3/40)	14.3 (3/21)
Grade 4	2.3 (1/43)	2.5 (1/40)	0.0 (0/21)

Discussion

TMZ concomitant and adjuvant to radiotherapy, which has become the standard treatment for newly diagnosed GBM patients, prolongs overall and progression-free survival more effectively than radiotherapy alone [27]. Consequently, first-line chemotherapy has become more homogeneous than it was in the past. However, while the outcome of patients with newly diagnosed GBM has improved worldwide, recurrence continues to be virtually inevitable. The choice of second-line chemotherapy is therefore of utmost importance in the large number of patients who continue to have a satisfactory PS and are willing to receive further treatment, nitrosourea being the most widely used therapeutic option. However, the real impact of this salvage chemotherapy in terms of activity, disease control, and toxicity after TMZ failure is still largely unknown. The present study is the first trial to evaluate correlation between *MGMT* methylation status (assessable in 79% of patients) and outcome of nitrosourea-based chemotherapy for progressing/relapsing glioblastoma previously treated with radiotherapy and TMZ in the adjuvant setting. Data on the outcome of fotemustine administration, used as second-line treatment in GBM patients were reported by Scoccianti et al. [26], and Fabrini et al.[8]; the authors reported a similar PFS-6 rates (48 and 52%, respectively), disease control rate (48 and 62%, respectively), grade 3–4 hematological toxicities (14.8 and 10%, respectively).

The results from these series seem to be better than ours both in terms of outcome and of toxicity. However, comparison across trials is always challenging. Moreover, the lack of *MGMT* methylation status data in the other FTMS studies and the small number of patients included in these three studies might justify the differences, and highlight the relevance of performing larger prospective trials in this patient population.

We decided to modify the fotemustine dose recommended in a prior phase I trial [14] and in other studies on glioma or melanoma patients [1, 15, 19, 20, 25], as grade 4 thrombocytopenia was observed after induction therapy in the first three patients and this life-threatening toxicity was considered unacceptable in the palliative setting of salvage therapy of GBM patients. This is consistent with the previous observation that hematological toxicity is increased by prior chemotherapy [24]. Moreover, the following 40 patients, treated with the reduced dosage of FTMS during induction phase, experienced a 15% of grade 3–4 thrombocytopenia and neutropenia.

Maintenance fotemustine showed hematological toxicities similar to those showed by BCNU delivered at first-relapse (grade 3–4 neutropenia and thrombocytopenia in 10 and 8% of patients, respectively) [3]. However, no cumulative dose limit for fotemustine was found by us, whereas the use of BCNU is complicated by pulmonary toxicity (G4 toxicities occurring in 5% of cases [3]), which severely compromises quality of life, and life expectancy and leads to discontinuation of therapy (10%).

Fotemustine administration was found to be more feasible and tolerable than PCV treatment, incurring fewer cases of discontinuation due to toxicity (2.3 vs. 43%) [5]. In terms of disease control, fotemustine yielded a PFS-6 of 21%, which met the primary efficacy end point of the study by confirming the drug activity.

Apparently promising results (response rate, 57%; PFS-6, 46%; 6-month overall survival, 77%) were recently reported following the use of combined irinotecan and bevacizumab [29]. However, these drugs have not yet been registered by FDA or EMEA and nor are they available worldwide, nitrosoureas continuing to be the most commonly used second-line standard therapy.

Other interesting approaches include TMZ re-challenge, which was recently investigated by Perry et al. In their retrospective analysis, the authors showed that TMZ re-challenge with a continuous 50 mg m^{-2} daily schedule is an intriguing approach, especially for patients with recurrence after completion of TMZ administration concurrent with and adjuvant to radiotherapy: GBM patients failing during the first 3–6 months of adjuvant therapy (B1); GBM patients failing after more than 6 months of therapy (B2); GBM patients who recurred after stopping treatment (B3). PFS-6 rates were 28.6% (B1), 9.5% (B2), 30.4% (B3) [22]. Our findings are in line with these observations: patients in our series who initiated FMTS at least 3 months after completion of TMZ administration had a significantly higher PFS-6, (30.7 vs. 16.7%) than patients who initiated FTMS while still on TMZ, $P = 0.034$).

MGMT promoter methylation was found to be an independent favorable prognostic factor, irrespective of treatment, in newly diagnosed GBM patients [12]. Conversely, little information is available on the trend of *MGMT* expression during tumoral progression, and after different chemotherapeutic treatments. In the present study, an analysis was made of the correlation between clinical outcome after fotemustine and *MGMT* promoter methylation status; to our knowledge, ours is the first study to analyze the correlation between *MGMT* promoter methylation status and second-line treatment. Adequate paraffin embedded tumor tissue was available in a higher percentage of patients than in other MSP studies (79 vs. 59–67%) [11, 12]. The percentage of methylated patients found in our study was clearly smaller than those reported in other series given upfront and/or salvage therapy (24 vs. 40–47%) [7, 12]. Moreover, we found that disease control rate was 75 and 34.6% in methylated and unmethylated patients ($P = 0.044$). On the other hand, no significant difference was found between groups for PFS-6 and survival; this finding, which is in line with that reported in other series of heterogeneously pre-treated patients who underwent salvage therapy [4], may reflect or a different pattern of resistance at progression, or a change in *MGMT* status at progression. A trend toward prolonged PFS-6 was observed, the lack statistical significance probably reflecting limited statistical power due to the relatively small number of cases in the present study, which precluded the demonstration of this secondary endpoint. It is important to bear in mind that *MGMT* methylation analysis was not made in trials that reported more favorable results [29]. For a reliable assessment of the role of this variable at the time of salvage, a prospective report should be undertaken to evaluate *MGMT* methylation status and, hopefully, to stratify patients enrolled in second-line treatment future trials. The findings made in the present trial may thus represent a new benchmark of nitrosourea activity in a homogeneously pre-treated population that failed to respond to the new standard treatment.

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