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ORIGINAL ARTICLE

Sorafenib therapy for hepatocellular carcinoma prior to liver transplant is associated with increased complications after transplant

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Summary

This study compared post-transplant outcomes of patients with hepatocellular carcinoma (HCC) who took sorafenib prior to orthotopic liver transplantation (OLT) with those patients who were not treated with sorafenib. Thirty-three patients with HCC who were listed for liver transplantation were studied: 10 patients were treated with sorafenib prior to transplantation in an attempt to prevent progression of HCC while awaiting transplant. The remaining 23 patients were considered controls. The mean duration of sorafenib use was 19.2 (SD 25.2) weeks. Overall death rates were similar between the sorafenib group and control group (20% vs. 8.7%, respectively, $P = 0.56$). However, the patients in the sorafenib group had a higher incidence of acute cellular rejection following transplantation (67% vs. 22%, OR = 7.2, 95% CI 1.3–39.6, $P = 0.04$). The sorafenib group also had a higher rate of early biliary complications (67% vs. 17%, OR = 9.5, 1.6–55.0, $P = 0.01$). The use of sorafenib was found to be an independent predictor of post-transplant biliary complications (OR 12.6, 1.4–116.2, $P = 0.03$). Sorafenib administration prior to OLT appears to be associated with an increase in biliary complications and possibly in acute rejection following liver transplantation. Caution should be taken in this setting until larger studies are completed.

Introduction

Liver transplantation is accepted as the best curative option for those with hepatocellular carcinoma (HCC) meeting the Milan criteria (single lesion ≤5 cm or three or less lesions ≤3 cm each) in the setting of advanced liver disease [1,2]. Subsequently, locoregional therapy (LRT) [radiofrequency ablation, transarterial chemoembolization (TACE)] is often used as a bridging therapy in those patients awaiting orthotopic liver transplantation (OLT) to prevent tumor progression and or patient dropout from the waiting list [1]. The efficacy of treatment with LRT for prevention of transplant waitlist dropout is difficult to determine because of the lack of randomized studies [1,2]. There are also significant costs and procedural risks associated with LRT, especially in those patients with advanced liver disease. Now, with the advent of an oral chemotherapeutic agent, sorafenib, as a therapy for HCC, those awaiting OLT have another alternative which alone or in combination with LRT may inhibit tumor growth and decrease dropout rates on the liver transplant waiting list.

Sorafenib is a multikinase inhibitor with inhibitory activity against Raf-1 serine threonine kinase and vascular endothelial growth factor (VEGF) receptor tyrosine kinases which are involved in tumor growth and angiogenesis [3]. These pathways have been implicated in the pathogenesis of HCC [4]. Based on previous findings that single agent sorafenib may have a therapeutic effect for HCC [5] the SHARP trial investigators conducted a large phase 3 randomized double-blind, placebo-controlled trial which showed an improved overall median survival time and time to radiologic progression of almost 3 months [4]. In transplant centers with prolonged waiting time in patients with HCC, this window of tumor growth arrest might allow more patients to proceed to liver transplantation without progression of tumor.

We present a pilot cohort study with controls that reflects our institutional experience regarding complications and outcomes in patients pre and post-transplantation with Child-Pugh class (CP) A, B or C disease treated with sorafenib and or LRT in the pretransplantation time period.

Materials and methods

Patients older than 18 years of age with a diagnosis of HCC and cirrhosis who underwent or were awaiting OLT between September 2007 and November 2009 were included in this study. Follow-up was completed on all study patients to December 2010. Patients who were living donor recipients, recipients of donation after cardiac death, and those who underwent multiorgan transplant were excluded from the analysis. Those patients who were treated with sorafenib and LRT or sorafenib alone in the pretransplantation time period were selected for analysis. Patients were not randomized to treatment arms. The decision for use of sorafenib was left to the patient's medical and transplant team. Once the clinical decision was made to initiate sorafenib, trained study personnel abstracted the medical records using standardized data collection methods to assess for side effects, medical and surgical complications in the perioperative time frame, and post-transplant complications and survival. Pretransplant medication side effects were graded based on the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) [6]. Those with HCC who underwent OLT during the same time period and were not treated with sorafenib prior to transplantation were chosen as a control population to assess post-transplant complications. Surgical teams and techniques were consistent and unchanged during the study period.

Patients receiving sorafenib were initiated at a dose of 400 mg twice daily. By protocol, sorafenib was discontinued on the day of transplantation once a suitable donor organ had been accepted by the transplant team for the recipient. If significant side effects were noted in the pretransplantation period, dose reduction (400 mg daily) and or dose interruption occurred at the discretion of the transplant team. Treatment was continued until the day of transplantation or until unacceptable side effects necessitated discontinuation of the drug prior to transplantation. No patient in this study received sorafenib after transplantation.

Standard definitions of side effects and complications were used. Pretransplant adverse effects of sorafenib treatment were graded using the CTCAE. Post-transplant complications were defined as follows: All episodes of acute rejection were biopsy proven and were considered significant if treatment was required within 30 days of transplantation. Liver biopsies confirming rejection were performed when there was a clinical suspicion of rejection. The hepatopathology team categorized acute rejection into mild, moderate, or severe, based on the Banff histological scoring criteria. Rejection was treated at the discretion of the transplant team with the local standard of care. Typically, mild rejection was treated with an increase in the dose of oral immunosuppression regimen. Moderate or severe rejection was treated with corticosteroid boluses and or with the addition of another immunosuppression agent. All patients in this series started with dual agent immunosuppression utilizing tacrolimus and prednisone during the study period (within the 30 days post-transplant). One patient suffering severe rejection had a steroid pulse and addition of mycophenolate to his regimen. Tacrolimus levels generally were held between 10–12 ng/ml during the first 30 days post-transplant. Wound complications were considered significant if surgical debridement, prolonged antibiotics, or healing by secondary intention were required within 30 days after transplantation. Biliary complications, either bile leaks or anastomotic strictures, were considered significant if a surgical procedure, percutaneous biliary drain, or endoscopic retrograde cholangiographic (ERC) intervention was required in the 30 days after transplantation. Liver transplant waiting list time was defined as the number of days from the time of activation on the liver transplant waiting list until the day of transplantation.

Demographics, tumor characteristics, and surgical characteristics were compared between patients receiving sorafenib and those who did not. Donor risk contributing to post-transplant recipient survival was assessed using the donor risk index [7]. Univariate comparisons were performed using the chi-square, Fisher exact, Student *t*-test, or Wilcoxon sign-rank tests as appropriate. Survival analyses were performed using the Kaplan-Meier technique and the log-rank test. Multivariate analyses were performed on a limited set of independent variables using

logistic regression and the method of least squares to determine independent predictors of biliary complications. Data analysis and dataset management was performed using SAS version 9.2 (Cary, NC, USA). All statistical testing was two-sided and the level of statistical significance for type 1 error was set at ≤0.05. The data-analysis protocol was approved by the University of Virginia Institutional Review Board. All patients were counseled on the potential risks and benefits of this therapy and verbal informed consent for use of the drug was obtained by the clinical provider prior to administration of the medication. This was not a randomized clinical trial and all patients had a labeled indication for the use of sorafenib. The University of Virginia Institutional Review Board for Human Research granted permission to retrospectively collect outcome data from the chart, perform statistical analysis, and publish the results. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and no donor organs were obtained from executed prisoners or other institutionalized persons.

Results

During the period of September 1, 2007 through November 30, 2009, 179 patients' charts were screened. A total of 33 patients met study qualifications: 10 patients who took sorafenib while awaiting OLT and a total of 23 also with a diagnosis of HCC who met OLT criteria who did

Table 1. Study population characteristics. Continuous variables are expressed as mean (SD, 95% CI) and categorical variables are number (percent). The one patient taking sorafenib who was still waiting at the time of publication was included in the pretransplant safety analysis but excluded from the post-transplant analysis.

	Sorafenib (*n* = 10 pretransplant and *n* = 9 post-transplant)	No Sorafenib (*n* = 23)	*P*
Recipient age, mean years	59.3 (7.4, 54.0-64.6)	57.0 (5.4, 54.6–59.3)	0.31
Recipient male	5 (50)	18 (78)	0.10
Recipient Caucasian	8 (80)	20 (87)	0.63
Recipient weight, mean (kg)	88.9 (17.8, 76.1–101.6)	92.2 (16.6, 85.0–99.4)	0.61
Etiology of liver disease			
Viral	6 (60)	14 (61)	0.95
NAFLD	2 (20)	5 (22)	
Alcohol	2 (20)	3 (13)	
Other	0	1 (4)	
Total tumor burden, mean (cm)	2.99 (2.2, 1.43–4.55)	3.12 (1.4, 2.50–3.75)	0.84
Tumor stage			
T3a	1 (10)	2 (9)	0.81
T2	8 (80)	20 (87)	
T1	1 (10)	1 (4)	
Viable tumor in explant	4 (44)	12 (52)	0.99
AFP at diagnosis, mean (ng/ml)	610 (1758, 0–1867)	262.8(935, 0–667)	0.57
Child-Pugh classification			
A	6 (60)	9 (39)	0.34
B	4 (40)	13 (57)	
C	0	1 (4)	
Locoregional therapy			
TACE alone	7 (70)	11 (48)	0.99
TACE and RFA	1 (10)	3 (13)	
TACE and radiotherapy	1 (10)	1 (4)	
Ethanol injection and TACE	0	1 (4)	
RFA alone	0	4 (17)	
No locoregional therapy	1 (10)	3 (13)	
Creatinine at transplant*, mean (mg/dl)	0.84(0.19, 0.70–0.98)	1.11(0.71, 0.81–1.42)	0.10
Albumin at transplant*, mean (g/dl)	3.83(0.77, 3.29–4.37)	3.40(0.35, 3.24–3.55)	0.11
Total bilirubin at transplant*, mean (mg/dl)	1.83(0.87, 1.20–2.46)	2.80(1.63, 2.09–3.50)	0.04
INR at transplant*	1.26(0.17, 1.14–1.38)	1.41(0.33, 1.27–1.56)	0.09
Laboratory MELD at transplant*	10.9 (2.8, 9.1–13.2)	14.6 (5.3, 12.5–17.1)	0.02
Donor risk index	1.52 (0.45, 1.18–1.86)	1.42 (0.28, 1.29–1.54)	0.43
Waiting list time, mean (days)	203 (190, 66–339)	240 (217, 146–334)	0.64

*Or at the time of last follow-up for the nontransplanted patient.
TACE, transarterial chemoembolization

not take sorafenib. Patient characteristics are described in Table 1. All patients were cirrhotic and met transplant listing criteria at our center. The majority of patients had tumors meeting Milan T2 criteria and were therefore eligible for a model for end-stage liver disease (MELD) exception and priority on the transplant list. One patient in each group was staged T1 and did not qualify for MELD exception. Three patients (two in the control group and one in the sorafenib group) had tumors staged T3a and underwent down-staging of their tumor prior to listing for transplantation with a MELD exception.

Although study subjects were not randomly assigned to treatment groups, patient characteristics including age, gender, race, weight, etiology of liver disease, total tumor burden, AFP levels, MELD score and use of LRT pretransplant were similar between groups (Table 1). Viral etiology (predominantly hepatitis C) was the leading cause of liver disease followed by nonalcoholic fatty liver disease and alcohol induced disease. Prior to transplantation, 15 patients were CP A, 17 patients were CP B and 1 patient (control group) was CP C. During the study period, 32 patients underwent OLT and 1 patient was still on the waiting list at the end of the study period. To maximize safety data, the patient still waiting at the end of the study observation period was included in the pretransplant safety analysis but excluded from the post-transplant analysis. As a result of the MELD exceptions related to HCC, the calculated laboratory MELD scores at the time of transplant (or at the date of last follow-up in the nontransplanted patient) were low and clinically similar, although statistically different between groups: 10.9 (SD 2.8, 95% CI 9.1–13.2) in the sorafenib group and 14.6 (SD 5.3, 95% CI 12.5–17.1) in the control group ($P = 0.02$).

The mean duration of sorafenib use was 19.2 (SD 25.2) weeks. There were a total of 192 person-weeks of drug exposure. Side effects because of sorafenib were common in the patient population although only one patient discontinued the medication because of side effects. Five patients receiving sorafenib (50%) had a dose reduction or dose interruption because of side effects, one for skin rash, two for hand–foot skin reaction, and two for diarrhea. These rates of side effects because of sorafenib are consistent with previously published series [4,8]. Table 2 shows the treatment details of the patients treated with sorafenib. Eight of nine (89%) patients stopped sorafenib by protocol on the day of OLT. One patient stopped 5 weeks prior because of diarrhea. No bleeding events were observed in the pretransplantation time frame. There were no dropouts because of progression of HCC in the sorafenib group. The control group for this study was chosen from a cohort of patients who successfully underwent liver transplantation with HCC. However, during the study period there were two patients listed for transplantation (2 of 35, 5.7%) who were not treated with sorafenib and had progression of HCC resulting in exclusion from transplantation and eventual death. No patient in either study cohort died in the pretransplant period.

The mean waiting times were similar between groups (203 days, SD 190, 95% CI 66–339, in the sorafenib group versus 240 days, SD 217, 95% CI 146–334, in the control group, $P = 0.64$). There was a mean follow up time of 938 (SD 403) days in the control group and 678 (SD 304) days in the sorafenib group. There were a total of four deaths, two in the sorafenib group and two in the control group. The overall death rates in the study populations were similar between the sorafenib group and the control group (20% vs. 8.7%, respectively, $P = 0.56$). The pre and post-transplant survival curves by Kaplan-Meier analysis and log-rank comparison showed no statistical difference between groups ($P = 0.46$ for the pretransplant group and $P = 0.25$ in the post-transplant group). There was viable tumor remaining in the liver explant in 12 (52%) controls and in 4 (44%) patients receiving sorafenib ($P = 0.99$).

Table 3 shows the post-transplant complications of interest in the study groups. No transplants involved donation after cardiac death, split grafts, or nationally

Table 2. Details of sorafenib use in the pretransplant setting.

	Duration (weeks)	Start dose (mg)	Dose reduction	End dose	Dose interruption	Sorafenib at time of transplant
Patient 1	23	200 bid	200 daily	200 daily	No	Yes
Patient 2	1	400 bid	–	400 bid	No	Yes
Patient 3	5	400 bid	–	400 bid	No	Yes
Patient 4	15	400 bid	200 bid	200 bid	No	Yes
Patient 5	15	400 bid	200 bid	200 bid	Yes	No
Patient 6	3	400 bid	–	400 bid	No	Yes
Patient 7	39	400 bid	200 bid	400/200	Yes	Waiting
Patient 8	16	400 bid	–	400 bid	No	Yes
Patient 9	18	400 bid	200 bid	200 bid	No	Yes
Patient 10	8	400 bid	200 bid	200 bid	Yes	Yes

Table 3. Post-transplant complications in study groups. See text for definitions of complications. Variables are reported as number (percent).

Complication	Sorafenib (n = 9)	No Sorafenib (n = 23)	P
Biliary	6 (67)	4 (17)	0.01
Acute cellular rejection	6 (67)	5 (22)	0.04
Recurrent HCC	0 (0)	2 (9)	0.99
Other*	1 (11)	9 (39)	0.21

*Other includes cardiovascular, infectious, and non-hepatic thromboembolic events.
HCC, hepatocellular carcinoma

shared organs. There were no significant wound complications in either group. There was one significant bleeding episode related to a hepatic artery aneurysm in the perioperative period which contributed to the patient's eventual death in the sorafenib group; however the investigators deemed this event unrelated to sorafenib therapy. There were 11 episodes of acute rejection in the study, six in patients exposed to sorafenib and five in those who were not. Rejection episodes were mild in three patients, moderate in seven, and severe in one. There were no statistical differences in severity of rejection between those patients exposed to sorafenib and those who were not. As a general policy, prednisone is generally discontinued (tapered) at 6 months post-transplant in patients who have not had a severe rejection episode. At the time of this manuscript, two patients remained on prednisone, one in the sorafenib group and one in the control group. Patients in the sorafenib group had a higher overall incidence of biopsy proven acute cellular rejection requiring treatment within the 30 days immediately following transplantation (67% vs. 22%, OR = 7.2, 95% CI 1.3–39.6, P = 0.04). The sorafenib group also had a higher rate of early biliary complications requiring surgical or endoscopic intervention (67% vs. 17%, OR = 9.5, 1.6–55.0, P = 0.01). This effect was independent of donor factors. Of the six biliary complications in the sorafenib group, five were anastomotic strictures while one was a bile leak. All were treated with endoscopic intervention. There were no statistical differences between groups in the rates of recurrent HCC or other significant complications. As a result of the small sample size, a limited multivariate analysis was undertaken. Table 4 shows the multivariate adjusted analysis, after adjusting for MELD score, donor risk index, and the use of sorafenib. Pretransplant exposure to sorafenib was found to be an independent predictor of post-transplant biliary complications (OR 12.6, 1.4–116.2, P = 0.03) whereas the effect on acute cellular rejection was not independent although there was a statistical trend.

Table 4. Multivariate adjusted analysis of independent risk factors for post-transplant biliary complications and acute cellular rejection.

	Biliary complications			Acute cellular rejection		
Risk factor	OR	95% CI	P	OR	95% CI	P
Pretransplant sorafenib use	12.6	1.4–116.2	0.03	6.06	0.95–38.7	0.06
MELD at transplant	1.03	0.83–1.27	0.81	0.97	0.78–1.19	0.74
Donor risk index	20.4	0.71–588	0.08	2.67	0.20–36.4	0.46

Discussion

Sorafenib is the first molecularly targeted systemic chemotherapeutic agent shown to have a survival benefit in advanced HCC [4]. Sorafenib monotherapy in those patients with CP A and B cirrhosis and advanced HCC is generally well tolerated [3,9]. Diarrhea, hand–foot skin reaction, and fatigue are the most common events reported in major clinical trials [4,8] and are considered manageable side effects [3]. There are reports of the use of sorafenib in the post-transplant time frame [10–12] for the purpose of prevention of tumor recurrence after transplantation. These studies are small pilot studies and conclusions are difficult based on the small sample size. There are currently very little data available regarding additional risks or adverse events attributable to sorafenib in the pre-liver transplantation time periods [13] and the single published series on this topic is without controls for comparison. Given the manageable side effect profile, the use of sorafenib in the pretransplant period as a neoadjuvant treatment option could increase survival time on the liver transplant waiting list by slowing or halting tumor progression, especially when combined with LRT. Some theoretical support for this strategy has been published with respect to cost-effectiveness [14] and prevention of tumor progression [15] but complications of the drug have not been fully explored in this setting. This pilot study, while small in size, showed no progression in tumor size in the sorafenib treated patients requiring removal from the transplant list. However, there were unexpected statistically significant increases in biliary complications and acute cellular rejection after transplantation in the treatment group.

The most commonly occurring adverse events observed in those treated with sorafenib in the pretransplant setting were hand–foot skin reaction and diarrhea, which improved with dose reduction or dose interruption. Initial studies with multikinase inhibitors raised concerns for the risk of bleeding, elevations in blood pressure, and cardiac events [3,4,16]. In this series of cirrhotic patients with HCC, elevations in blood pressure were not observed, possibly in keeping with the peripheral vasodi-

lation of cirrhosis. No episodes of clinically significant bleeding occurred in the pretransplant time period and no intraoperative excess bleeding was observed; however, one postoperative bleeding event related to a hepatic artery aneurysm occurred. Biliary complications and acute cellular rejection were also observed as early post-transplantation adverse events. The estimated incidence of expected biliary complications is between 9 and 15% following transplantation [17]. Typically, early biliary complications such as bile leaks and anastomotic strictures are attributable to technical causes such as ischemia, suturing technique, and method of biliary reconstruction [17,18].

Blood supply to the biliary system is critical to maintain the surgical anastomosis, especially in duct-to-duct reconstruction. The intrahepatic biliary system is supported by the peribiliary vascular plexus (PBP) which is fed by branches of the hepatic artery. There is developing research emphasizing the importance of the PBP in maintaining the health of the biliary tree, especially in the setting of acute injury and regeneration [19–21]. One hypothesis for the increased rate of biliary complications observed in this case series is the role of sorafenib and VEGF receptor inhibition (VEGFR-2, VEGFR-3). Gaudio, *et al.*, have shown that ligation of the bile duct and hepatic artery of rats induced ischemia of the biliary tract, subsequent loss of the PBP, and in cholangiocytes, decreased proliferation, increased apoptosis and decreased VEGF-A secretion [22,23]. However, administration of VEGF-A prevented ischemia induced by the hepatic artery ligation, by restoring cholangiocyte proliferation and therefore maintenance of the PBP [22]. The same group of investigators previously had shown that VEGF modulated cholangiocyte proliferation, likely through an autocrine mechanism, in their rat models of cholestasis [24]. There is recent evidence that sorafenib itself inhibits signal transduction and has a potential to inhibit resistance to apoptosis in human cholangiocyte cell lines [25]. Theoretically, administration of sorafenib until the day of transplantation could hinder PBP integrity, and cholangiocyte recovery by its inhibitory effects on the cholangiocyte VEGF receptors but this effect has not been shown in humans. However, in mice studies, VEGF inhibitors have also been reported to induce capillary regression in those capillaries with increased levels of VEGFR-2 and VEGFR-3 and particularly those with endothelial fenestrations [16]. The amount of drug which induced capillary regression was dose-dependent and variable between organ systems; however, in mouse trachea after regression of capillaries, empty sleeves of basement membrane persisted and served as a scaffold for vascular regrowth [16]. Work by other investigators support the finding that a large number of the PBP capillaries are fenestrated, especially on the sides of the capillary facing the bile duct [26]. Other findings along with the proportion of fenestrations imply a transbiliary endothelial route for excretion and absorption of substances.

With bile ductular damage, venular endothelial inflammation and portal inflammation being the components of acute cellular rejection, perhaps enhanced regression of the cholangiocytes mediated by sorafenib also contributed to the increased percentage of acute cellular rejection noted in our cohort of patients. It has been shown that portal tract microvascular loss preceded bile duct loss seen in acute rejection, and further promoted ischemic injury to the bile duct [27]. Unfortunately, these investigators were unable to accurately identify the PBP through their methods of immunohistochemical staining to further confirm widespread microvascular destruction in acute rejection. It is possible given the mechanisms reported above, that bile duct damage is intensified by sorafenib, therefore making acute rejection more clinically apparent and therefore detectable in this small population of transplant recipients.

The present study has obvious shortcomings. Being a pilot study, the number of patients was limited and statistical considerations make a detailed multivariate analysis difficult. Despite this, there was a statistically significant finding related to biliary complications. Another weakness is the nonrandomized design of the pilot study. There were some differences between the study and the control groups in this analysis but the differences were not clear in the patient and the tumor characteristics reported in Table 1. It is certainly possible that those patients receiving sorafenib were less clinically decompensated than the control group although this would not clearly explain the excess post-transplant complication rate in this group. It is also possible that sorafenib influences the post-transplant liver enzymes and/or bilirubin in a way that would bias the need for liver biopsy (or much less likely, the interpretation of the histopathology specimen showing features of rejection) in one way or another but the sample size in this study precludes a detailed analysis of this possibility. It is also highly probable that type 2 error, because of small sample size, prevents detection of differences in other complications that may be present. A stronger effect in prevention of tumor progression on the transplant list could possibly be revealed if type 2 error could be decreased. Only larger studies can answer these questions. Our post-transplantation findings in those who took sorafenib may be relevant to a current multicenter, randomized German study examining the safety and efficacy of sorafenib in combination with TACE prior to OLT (HeiLivCa) [28]. This study is likely to give more definitive information regarding toxicity and efficacy in this patient population but the results of this study are still forthcoming.

In summary, this pilot study of the use of sorafenib in the pretransplant setting in patients on the transplant waiting list with HCC shows the drug to have comparable side effects with larger published studies. As a result of the small sample size, no statistical conclusions could be made about the ability of sorafenib to prevent tumor progression in patients on the waiting list. However, a statistically significant increase in post-transplant biliary complications raises questions about the practice of using this therapy in the immediate pretransplant time frame until completion of larger randomized controlled trials.

Authorship

AET: designed study, collected data and wrote the paper. SHC: designed the study and contributed to the analysis. NLS: contributed to the analysis and writing the discussion. CKA: contributed to the analysis and writing the discussion. AMSAl-O: contributed to the analysis and writing the discussion. TMS: designed study, contributed to the analysis and writing the discussion. PGN: designed the study, guided the performance of the data collection, performed the analysis and wrote major portions of the paper and revisions.

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