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ORIGINAL RESEARCH

Impact of the SOX Regimen on Immune Function and Tumor Markers in Advanced Gastric Cancer

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Background: Locally advanced gastric cancer presents significant challenges in treatment, often limiting the effectiveness of surgical interventions. Chemotherapy, especially the SOX regimen (combining oxaliplatin and tegafur/gimeracil/oteracil), has been explored as a potential alternative in the management of advanced gastric cancer. While studies on SOX have been conducted in other regions, its impact on immune function and tumor markers remains inadequately evaluated, particularly in China.

Objective: This study aimed to assess the toxicological profile, immune function modulation, and tumor marker reduction of the SOX regimen in patients with advanced gastric cancer.

Methods: A retrospective analysis was conducted on 100 patients diagnosed with advanced gastric cancer, excluding eight ineligible cases. Based on clinical records, patients were grouped into either the oxaliplatin monotherapy group (reference group) or the SOX regimen group (observation group), with 50 patients in each group. The primary endpoint was clinical effectiveness, while secondary endpoints included immune function, tumor marker levels, and chemotherapy-related toxicity.

Results: The SOX regimen demonstrated significantly higher disease control and objective remission rates compared to oxaliplatin monotherapy ($P<0.05$). In the SOX group, immune function was enhanced, with increased levels of immunoglobulins (IgA, IgG, IgM) and lymphocyte subsets (CD3+, CD4+, NK cells), and a decrease in CD8+ levels ($P<0.05$). Additionally, tumor markers such as CA125, CEA, MRP14, SDF-1, FSP-1, and CXCR4 showed a significant reduction ($P<0.05$). The SOX regimen also exhibited a more favorable safety profile, with lower incidences of chemotherapy-related nausea, vomiting, and leukopenia ($P<0.05$).

Conclusion: The SOX regimen is an effective and promising treatment option for advanced gastric cancer, offering significant improvements in clinical outcomes, immune function, and tumor marker reduction, with fewer chemotherapy-related toxicities. This study provides valuable insights into the application of the SOX regimen in Chinese patients with advanced gastric cancer.

Keywords: oxaliplatin, tegafur/gimeracil/oteracil, advanced gastric cancer, immune function, tumor markers, chemotherapy toxicity

Introduction

Gastric cancer ranks as the fifth most prevalent malignancy globally and is the third leading cause of cancer-related deaths worldwide.[1] Epidemiological data indicate a five-year survival rate of approximately 20% among gastric cancer patients. Radical gastrectomy remains the most effective treatment; however, even with curative intent, the tumor recurrence rate remains high at around 30%. For advanced cases, systemic chemotherapy is primarily utilized,[2] with two-drug chemotherapy regimens preferred based on balancing toxicity and clinical efficacy. The primary chemotherapeutic agents for advanced gastric cancer currently include fluorouracil, oxaliplatin, and paclitaxel.[3] According to the National Comprehensive Cancer Network (NCCN)[4] and the European Society for Medical Oncology (ESMO)[5] guidelines, the standard first-line chemotherapy for gastric cancer is a platinum-fluoropyrimidine doublet, with oxaliplatin and cisplatin being the most commonly used platinum drugs. Recommended combination regimens often involve fluorouracil with either oxaliplatin or paclitaxel.[6] Oxaliplatin, a third-generation platinum compound, is favored for its tolerability and ease of administration, while tegafur/gimeracil/oteracil (S-1)—an oral formulation combining tegafur (a prodrug of 5-fluorouracil or 5-FU) with two modulators—delivers potent therapeutic effects against gastrointestinal tumors, making it a cornerstone of modern gastrointestinal cancer therapy.[7,8]

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The SOX regimen, a combination of S-1 and oxaliplatin (OX), has been explored in several studies as a first-line treatment option.[9,10] Notably, two clinical trials by the Japan Clinical Oncology Group (JCOG) established the non-inferiority and even superiority of S-1 over 5-FU, leading to its recommendation as a standard first-line treatment for advanced gastric cancer in Japan. However, despite its success in Japan, detailed clinical research on the SOX regimen remains limited within China, particularly in evaluating its impact on immune function and tumor marker dynamics.[11] Therefore, this study aims to address this gap and investigate the therapeutic effects of the SOX regimen in Chinese patients with advanced gastric cancer.

Globally, the standard first-line chemotherapy regimen for advanced gastric cancer typically involves a platinum-based drug and a fluoropyrimidine drug combination, such as oxaliplatin or cisplatin with fluorouracil (5-FU). The SOX regimen, a combination of S-1 and oxaliplatin, has shown clinical benefits, particularly in enhancing immune function and reducing tumor marker levels, with a favorable safety and tolerability profile.[12] It is thus considered a promising alternative in treatment strategies for gastric cancer.

In the SOX regimen, oxaliplatin, a third-generation platinum chemotherapeutic agent, exerts its anti-tumor effects by binding to DNA and inhibiting DNA repair, while S-1, an oral formulation of 5-FU's prodrug, exerts potent therapeutic effects by modulating two enzymes that enhance 5-FU's anti-cancer activity, particularly against gastrointestinal tumors.[13] These mechanisms have contributed to its widespread application in the treatment of gastrointestinal malignancies. This study aims to investigate the safety, immune modulation, and tumor marker reduction associated with the SOX regimen in patients with advanced gastric cancer.

Materials and Methods

Study Participants

A total of 100 patients diagnosed with advanced gastric cancer were recruited, excluding 8 ineligible cases. The patients were retrospectively grouped into either the oxaliplatin monotherapy group (reference group) or the SOX regimen group (observation group) based on clinical records. Group allocation was based on the treatment decisions made by the clinicians at the time of treatment, without randomization. The final analysis included 50 patients in each group. The study received ethical approval from the Hengshui People's Hospital's ethics committee, and all participants provided informed consent. This study complies with the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Inclusion Criteria

1) It conforms to the diagnostic criteria for advanced gastric cancer in the "Gastric Cancer Diagnosis and Treatment Guidelines (2018 Edition)"[14] and the "Introduction and Interpretation of the TNM Staging System for Gastric Cancer (8th Edition) by the International Union Against Cancer and the American Joint Committee on Cancer",[3] and has been pathologically confirmed through gastroscopy., normal ECG, and standard results in routine blood, liver, and kidney function tests. 2) Patients included in this study were diagnosed with advanced gastric cancer, and none had received prior curative surgery. 3) Adults, irrespective of gender. 4) Expected survival of more than 6 months. 5) Karnofsky Performance Status (KPS) score greater than 60.

Exclusion Criteria

1) Allergy history or intolerance to study drugs. 2) History of organ transplantation. 3) Pregnancy or lactation. 4) Brain metastases or impaired consciousness. 5) Pulmonary fibrosis.

Treatment Methods

Drug Sources

1) Oxaliplatin: Approval No. H20133247, Shandong New Age Pharmaceutical Co. 2) Capecitabine: Shanghai Roche Pharmaceutical Co. 3) Tegafur/gimeracil/oteracil (S-1): Approval No. H20080802, Lunan Pharmaceutical Group Co.

Reference Group

Patients received diphenhydramine and cimetidine 30 minutes before treatment for allergy prevention. Oxaliplatin was administered at 130 mg/m² via intravenous infusion over more than 2 hours on Day 1, followed by oral capecitabine at 1000 mg/m² daily from Days 1 to 14. Treatment comprised two cycles, with each cycle lasting 21 days.[15]

Observation Group

Patients received 130 mg/m² of oxaliplatin via intravenous infusion over more than 2 hours on Day 1, followed by oral S-1 at 40 mg twice daily from Days 1 to 14. Treatment consisted of two cycles, each lasting 21 days. Patients were advised to avoid exposure to cold and contact with cold objects during drug administration.[16] All patients in this study received palliative chemotherapy as part of their treatment regimen, as they were diagnosed with advanced-stage gastric cancer.

Clinical Endpoints

Efficacy Evaluation

After treatment, lesion size (total length and width) was assessed using magnetic resonance imaging (MRI) and gastroscopy. Response categories included: Complete Remission (CR): Complete disappearance of lesions for over 28 days. Partial Remission (PR): Reduction of ≥30% in lesion length and width, sustained for over 28 days. Stable Disease (SD): Reduction in lesion size lasting less than 28 days. Progressive Disease (PD): Lesion reduction inferior to the criteria for SD.

Objective remission rate (ORR)=(CR+PR)/total number of cases×100%, disease control rate (DCR)=(CR+PR+SD)/total number of cases×100%.

Immunological and Tumor Marker Assessment

Before and after treatment, 5 mL of fasting venous blood was collected from patients to measure serum levels of immunoglobulins A (IgA), G (IgG), and M (IgM) by flow cytometry. T lymphocyte and natural killer (NK) cell ratios, along with tumor markers relevant to gastric cancer, were quantified using enzyme immunoassay. Key tumor markers included cancer antigen 125 (CA125), carcinoembryonic antigen (CEA), migration inhibitory factor-related protein 14 (MRP14), stromal cell-derived factor 1 (SDF-1), fibroblast-specific protein 1 (FSP-1), and C-X-C Motif Chemokine Receptor 4 (CXCR4).

Toxicity Assessment

Chemotherapy-related toxicity was evaluated according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC).

Statistical Analysis

Data analysis was conducted using SPSS 26.0 software. Continuous data were presented as mean ± standard deviation (x ±s) and analyzed using *t*-tests. Categorical data were expressed as percentages (%) and analyzed using the chi-square (X2) test. Statistical significance was defined as $P<0.05$. To evaluate the statistical power of the study, a sample size calculation was performed using a significance level of 0.05 and a power of 0.80. Based on previous studies and the expected effect sizes, a sample size of 100 patients (50 in each group) was considered adequate to detect meaningful differences in clinical outcomes, immune markers, and tumor markers between the two treatment groups.

Results

Patient Characteristics

In the observation group, there were 28 male and 22 female patients, aged between 44 and 73 years (mean age 60.58 ± 7.35), with a KPS score >60 (76.98 ± 5.23). Tumor staging included 19 cases of TNM stage IIIb and 31 cases of stage IV, with histopathology showing 30 cases of adenocarcinoma, 5 cases of mucinous adenocarcinoma, and 15 cases of indolent cell carcinoma. In the reference group, there were 26 male and 24 female patients, aged between 47 and 78 years (mean age 60.88 ± 7.17), with a KPS score >60 (76.24 ± 5.05). This group included 21 cases of TNM stage IIIb and 29 cases of stage IV, with 33 cases of adenocarcinoma, 6 cases of mucinous adenocarcinoma, and 11 cases of indolent cell carcinoma. Both groups were comparable in baseline characteristics ($P>0.05$) (Table 1).

Table 1 Patient Characteristics ($\overline{X} \pm S$)

		Observation Group	Reference Group	*t*	*P*
n	–	50	50	–	–
Sex	Male	28 (56.00)	26 (52.00)	–	–
	Female	22 (44.00)	24 (48.00)	–	–
Age (years)	–	44–73	47–78	–	–
	Mean	60.58±7.35	60.88±7.17	0.207	0.837
KPS scores	–	>60	>60	–	–
	Mean	76.98±5.23	76.24±5.05	0.719	0.474
TNM stage	IIIb	19 (38.00)	21 (42.00)	–	–
	IV	31 (62.00)	29 (58.00)	–	–
Pathological type	Adenocarcinoma	30 (60.00)	33 (66.00)	–	–
	Mucinous adenocarcinoma	5 (10.00)	6 (12.00)	–	–
	Indocellular carcinoma	15 (30.00)	11 (22.00)	–	–

Clinical Efficacy

In the observation group, there were 20 cases of CR, 18 cases of PR, 9 cases of SD, and 3 cases of PD, yielding a DCR of 94.00% and an ORR of 76.00%. In contrast, the reference group reported 16 cases of CR, 15 cases of PR, 12 cases of SD, and 7 cases of PD, with a DCR of 86.00% and an ORR of 62.00%. The SOX regimen demonstrated significantly higher clinical efficacy compared to oxaliplatin monotherapy, as reflected in the superior DCR and ORR (P<0.05) (Figure 1).

Immune Function

Immunoglobulins

Post-treatment levels of immunoglobulins in the observation group were IgA (2.07 ± 0.58), IgG (7.56 ± 2.01), and IgM (0.53 ± 0.13), whereas in the reference group, IgA was (1.53 ± 0.44), IgG (6.03 ± 1.88), and IgM (0.45 ± 0.18). The SOX regimen led to significantly greater immune recovery compared to oxaliplatin monotherapy, as indicated by the higher levels of IgA, IgG, and IgM in the observation group (P<0.05) (Table 2).

T-Cell Subsets and NK Cells

In the observation group, the post-treatment levels were CD3+ (61.99 ± 4.52), CD4+ (39.54 ± 2.28), CD8+ (28.14 ± 2.21), and NK cells (8.46 ± 0.56). In the reference group, CD3+ was (58.41 ± 4.33), CD4+ (36.25 ± 2.37), CD8+ (35.01 ± 2.66), and NK cells (6.15 ± 0.81). The SOX regimen enhanced serum levels of T-cell subsets and NK cells more effectively than oxaliplatin alone (P<0.05) (Table 3).

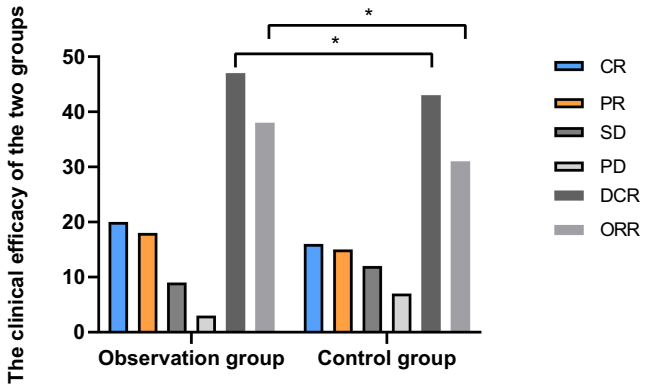

Figure 1 Clinical efficacy.
Note: *indicates P<0.05.

Table 2 Immunoglobulins $(\overline{X} \pm S)$

		Observation Group	Reference Group	t	P
n	–	50	50	–	–
Before treatment	IgA (g/L)	1.16±0.33	1.18±0.34	0.298	0.766
	IgG (g/L)	5.11±1.39	5.09±1.48	0.070	0.945
	IgM (g/L)	0.39±0.08	0.38±0.11	0.022	0.983
After treatment	IgA (g/L)	2.07±0.58	1.53±0.44	5.345	<0.001
	IgG (g/L)	7.56±2.01	6.03±1.88	3.931	<0.001
	IgM (g/L)	0.53±0.13	0.45±0.18	2.628	0.010

Table 3 T-Cell Subsets and NK Cells $(\overline{X} \pm S)$

		Observation Group	Reference Group	t	P
n	–	50	50	–	–
Before treatment	CD3+	57.15±3.68	57.34±3.55	0.249	0.804
	CD4+	46.14±3.08	46.22±3.35	0.125	0.901
	CD8+	37.85±2.78	37.74±2.94	0.193	0.848
	NK cells	9.41±1.01	9.52±1.03	0.542	0.589
After treatment	CD3+	61.99±4.52	58.41±4.33	4.042	<0.001
	CD4+	39.54±2.28	36.25±2.37	7.088	<0.001
	CD8+	28.14±2.21	35.01±2.66	14.095	<0.001
	NK cells	8.46±0.56	6.15±0.81	16.696	<0.001

Tumor Markers

Post-treatment tumor marker levels in the observation group were CA125 (48.89 ± 7.65), CEA (40.56 ± 8.41), MRP-14 (8.14 ± 1.18), SDF-1 (2.64 ± 0.96), FSP-1 (4.35 ± 1.14), and CXCR4 (0.48 ± 0.08). In the reference group, these values were CA125 (101.84 ± 10.51), CEA (68.56 ± 9.12), MRP-14 (11.74 ± 1.33), SDF-1 (4.97 ± 1.35), FSP-1 (8.56 ± 1.94), and CXCR4 (0.82 ± 0.13). The SOX regimen offered markedly higher anti-tumor efficacy compared to oxaliplatin monotherapy, as shown by significantly lower serum concentrations of CA125, CEA, MRP14, SDF-1, FSP-1, and CXCR4 ($P<0.05$) (Table 4).

Table 4 Tumor Markers $(\overline{X} \pm S)$

		Observation Group	Reference Group	t	P
n	–	50	50	–	–
Before treatment	CA125 (U/mL)	247.56±19.55	247.88±19.68	0.082	0.935
	CEA (ng/mL)	125.26±14.35	124.98±13.97	0.099	0.922
	MRP-14 (mg/L)	30.56±4.15	30.88±4.03	0.384	0.702
	SDF-1 (ng/L)	9.56±2.08	9.47±2.05	0.242	0.809
	FSP-1 (ng/L)	18.56±2.41	18.94±2.17	0.829	0.409
	CXCR4 (pg/L)	1.53±0.21	1.55±0.19	0.762	0.448
After treatment	CA125 (U/mL)	48.89±7.65	101.84±10.51	28.788	<0.001
	CEA (ng/mL)	40.56±8.41	68.56±9.12	15.960	<0.001
	MRP-14 (mg/L)	8.14±1.18	11.74±1.33	14.263	<0.001
	SDF-1 (ng/L)	2.64±0.96	4.97±1.35	9.987	<0.001
	FSP-1 (ng/L)	4.35±1.14	8.56±1.94	13.230	<0.001
	CXCR4 (pg/L)	0.48±0.08	0.82±0.13	16.456	<0.001

Table 5 Toxic Side Effects (%)

	Observation Group	Reference Group	x^2	*P*
n	50	50	–	–
Anemia	19 (38.00)	20 (40.00)	0.042	0.838
Nausea and vomiting	6 (12.00)	14 (28.00)	4.000	0.046
Thrombocytopenia	10 (20.00)	17 (34.00)	2.486	0.115
Leukopenia	18 (35.00)	28 (56.00)	4.026	0.045
Mucositis of the oral cavity	5 (10.00)	3 (6.00)	0.543	0.461
Liver function impairment	4 (8.00)	4 (8.00)	0.000	1.000
Hand-foot syndrome	9 (18.00)	10 (20.00)	0.065	0.799
Peripheral neurotoxicity	8 (16.00)	7 (14.00)	0.078	0.779

Toxic Side Effects

The SOX regimen displayed a more favorable safety profile than oxaliplatin monotherapy, with a reduction in occurrences of nausea, vomiting, and leukopenia (P<0.05) (Table 5).

Discussion

The main findings of the current study are that the SOX regimen significantly improves clinical efficacy, immune function, and tumor marker reduction in patients with advanced gastric cancer. Specifically, patients treated with SOX exhibited superior disease control and objective remission rates compared to those treated with oxaliplatin monotherapy. Additionally, the SOX regimen led to a significant improvement in immune recovery, as evidenced by increased levels of immunoglobulins and T lymphocyte subsets, and decreased tumor marker levels. These findings align well with existing studies highlighting the potential of oxaliplatin-based regimens and S-1 combination therapies in enhancing treatment outcomes in advanced gastric cancer.

Research has demonstrated that chemotherapy significantly improves quality of life and extends mean life expectancy in patients with advanced gastric cancer. Systemic chemotherapy remains the primary therapeutic approach, yet there is ongoing debate over the optimal regimen. Oxaliplatin, a third-generation platinum-based drug, exerts its anticancer effects by forming intra- and interstrand DNA alkylation complexes, thereby inhibiting DNA synthesis and replication. It is highly effective against a broad spectrum of cancers, exhibits strong anticancer activity, and does not display cross-resistance with cisplatin or carboplatin, enhancing its efficacy across various tumor types. Currently, regimens incorporating 5-FU, docetaxel, and calcium folinic acid are among the most recommended options for chemotherapy in advanced gastric cancer.[17,18]

The S-1 therapy, comprising tegafur/gimeracil/oteracil, is a modified form of 5- FU widely used in clinical practice due to its synergistic effects and reduced toxicity. Studies have indicated that replacing 5-FU with S-1 in treating advanced gastric cancer can significantly enhance clinical outcomes and minimize adverse drug reactions.[19,20] In this study, the SOX regimen demonstrated notably higher clinical efficacy and safety compared to oxaliplatin monotherapy, evidenced by superior disease control and objective remission rates, along with a lower incidence of adverse events (P<0.05), aligning with prior findings.Research highlights the efficacy of oxaliplatin-based regimens, where oxaliplatin's central platinum atom, enclosed by the 1,2-diaminocyclohexane ring of oxalic acid in an anti-configuration, provides potent antitumor activity. S-1, as an oral 5-FU-based antitumor agent, includes tegafur (FT) with cytotoxic properties, gimeracil (CDHP) to inhibit dihydropyrimidine dehydrogenase, and oteracil (OXO) to selectively inhibit orotate-ribosyltransferase in intestinal mucosal cells, preventing 5-FU phosphorylation. This combination enhances clinical efficacy while reducing chemotherapy-related toxicities. It is also noted that patients with advanced gastric cancer commonly experience immune dysfunction and immunosuppression, which can facilitate tumor cell invasion and proliferation.[21]

In this study, the SOX regimen demonstrated superior immune recovery compared to oxaliplatin monotherapy, as indicated by significantly higher levels of IgA, IgG, IgM, CD3+, CD4+, and natural killer (NK) cells, along with lower CD8+ levels in the observation group (P<0.05). Advanced gastric cancer is often associated with immune dysfunction,

primarily reflected by an imbalance in T lymphocyte subsets and heightened suppressive immune responses, which can exacerbate the disease.[22–24] Findings from this study suggest that the combination of oxaliplatin and S-1 exerts synergistic anti-tumor effects, enhancing blood circulation and balancing T-cell subsets and NK cells in vivo, thereby improving patients' immune function.Previous studies have shown that certain tumor markers contribute to cancer progression: MRP-14 promotes gastric cancer cell growth and metastasis while reducing chemotherapeutic efficacy, SDF-1, predominantly in mesenchymal cells, mediates oncogenic inflammatory responses that intensify tumor cell proliferation, FSP-1 binds cytoskeletal elements like microtubulin to activate cytoskeletal dynamics and foster cancer cell infiltration, and CXCR4 enhances cancer cell proliferation and angiogenesis, promoting metastasis.[25,26] Consequently, these markers—MRP-14, SDF-1, FSP-1, and CXCR4—are closely linked to gastric cancer development, and changes in their levels can indicate chemotherapy's antitumor effects. Additionally, CA125 and CEA are well-established indicators for assessing therapeutic efficacy in gastric cancer.

Studies have demonstrated the clinical importance of serum tumor marker levels in assessing treatment efficacy for tumors. In this study, the SOX regimen offered significantly greater anti-tumor effects compared to oxaliplatin monotherapy, as evidenced by notable reductions in serum concentrations of key tumor markers, including CA125, CEA, MRP14, SDF-1, FSP-1, and CXCR4 ($P<0.05$). These results support the hypothesis that the SOX regimen can positively impact cellular immune function, reduce tumor marker levels, inhibit tumor progression, and lower malignancy in patients with advanced gastric cancer.[27] In line with the European Society for Medical Oncology (ESMO) guidelines, which recommend the use of oxaliplatin and S-1 combination therapy for advanced gastric cancer,[4] our study's results support the clinical efficacy of the SOX regimen in this patient population.

This study, being retrospective, has certain limitations. The sample size was relatively small, and uniform inclusion/exclusion criteria and randomization were not implemented, which could introduce selection bias. Additionally, the follow-up period was limited, as the study assessed the short-term clinical efficacy of the two-cycle treatment regimen. Future research with longer follow-up periods would be necessary to evaluate the long-term effects of the SOX regimen. Furthermore, the retrospective design may also introduce biases in patient selection, and the lack of stratified randomization could affect the comparability of the groups. To address these limitations, future prospective studies with stratified randomization and larger sample sizes would provide a more robust foundation for validating these findings and refining treatment strategies for gastric cancer patients.

Conclusion

The SOX regimen presents a promising treatment option for managing advanced gastric cancer, demonstrating significant clinical efficacy. It enhances immune function, reduces tumor marker levels, minimizes chemotherapy-related toxicities, and offers notable prognostic benefits. However, it is important to note that the study's relatively short follow-up period and its retrospective design may limit the ability to assess long-term outcomes. Future studies with larger sample sizes and prospective designs are needed to validate these findings and evaluate the sustained efficacy of the SOX regimen in a broader patient population.

Disclosure

The authors report no conflicts of interest in this work.

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