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Treatment of Vietnamese patients diagnosed with myelodysplastic neoplasms: Practical experience in a developing country

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ABSTRACT

Background: Treatment of patients diagnosed with myelodysplastic neoplasms (MDS) is difficult and the outcome is still limited, especially in developing countries. We conducted this study in order to share some experience in treating patients diagnosed with MDS in developing countries.
Methods: This was a retrospective study that included 32 patients with newly MDS. 13 lower-risk patients, including 2 patients with MDS 5q- were treated with erythropoiesis stimulating agent (ESA). 19 patients with higher risk were treated with hypomethylating agent (HMA), which was decitabine.
Results: In the ESA treatment group, the rate of hematologic improvement-erythroid was 69.2 %, the rate of total hematologic improvement (with 3 lineages improvement) was 61.5 %. In the HMA treatment group, the overall response rate was 52.6 %. The follow-up times were 42 months. The overall survival (OS), leukemic transformation-free survival (LFS), and progression-free survival (PFS) of the ESA treatment group were 30.44, 28.91, and 28.29 months; respectively. The OS, LFS, and PFS of the HMA treatment group were 34.27, 31.45, and 26.83 months; respectively.
Conclusions: Patients with lower risk MDS, including MDS 5q-, may benefit from treatment with erythropoiesis stimulating agent (ESA). Patients with higher risk MDS may have a favorable outcome with decitabine (HMA) treatment.

1. Introduction

Myelodysplastic neoplasms (MDS), previously known as myelodysplastic syndromes, are clonal hematological malignancies characterized by ineffective hematopoiesis, dysplasia of one or more cell lineages, and an increased risk of acute myelogenous leukemia transformation [1]. The fifth edition of the WHO classification of hematolymphoid tumors (WHO 2022) renamed "myelodysplastic syndromes" to "myelodysplastic neoplasms" to emphasize their neoplastic nature [2]. Although there have been several advances and improvements in diagnosis, classification and prognosis, MDS treatment decisions have remained based on risk classification over the past decade. In the lower risk group, supportive care and erythropoiesis stimulating agents (ESAs) are used. For patients with serum erythropoietin (EPO) level >500 mU/mL, or who do not respond, immunosuppressive agents or hypomethylating agents have been shown to be beneficial. For patients with del (5q), lenalidomide is recommended. In the higher risk group, hypomethylating agents (HMAs), chemotherapy and allogeneic stem cell transplantation are the choice [3–6]. Novel drugs such as the *IDH1* inhibitor (ivosidenib), the *IDH2* inhibitor (enasidenib), and the *bcl2* inhibitor (venetoclax) are considered in higher-risk MDS. Luspatercept and other erythroid maturation agents (EMA) have recently been investigated in patients with lower- risk MDS, who lose response to ESA [3–6]. Otherwise, the BSH guideline supported that allogeneic transplantation should be performed in lower and higher risk MDS [5].

However, the results of treatment are still limited, especially in developing countries. Obstacles to access novel drugs, high costs and severe complications (especially in the elderly patient group, which has

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a high rate of MDS) of allogeneic transplantation make the treatment of MDS in these countries even more difficult. Is it possible to develop a guideline for the treatment of MDS that is simpler, more appropriate to the context of a developing country and still beneficial to patients? We conducted this study with the objective of sharing some experience in treating patients diagnosed with MDS in developing countries.

2. Patients and methods

2.1. Patients

The retrospective study was conducted in the National Institute of Hematology and Blood Transfusion (NIHBT), Hanoi, Vietnam. All patients with newly diagnosed MDS who accepted treatment from January 2018 to June 2021 were consecutively recruited in our study.

The study protocol was approved by the Institutional Review Board (IRB) of NIHBT (no. 939/QĐ-HHTM). The patient's consent was waived by the IRB since this study was a retrospective observational study. All details of the patient were deidentified.

2.2. Cytogenetic and gene mutation analysis

The bone marrow samples of the patients were analyzed at the time of diagnosis. Karyotypes were analyzed from G-band staining results. Fluorescence *in situ* hybridization (FISH) technique was applied to detect del(5q). Next-generation sequencing was performed to detect *SF3B1* and *TP53* gene mutations.

2.3. Treatment

The treatment decision was based on the classification of risk according to IPSS-R. Patients with very low and low risk with serum EPO level<500 mU/ml: supportive care, erythropoiesis stimulating agent (ESA). Patients with a high, very high risk: hypomethylating agent (HMA). Patients with intermediate risk: The choice depends on the patient's status.

In the group of ESA treatment, patients were treated with erythropoietin 60.000 UI per week.

In the group of HMA treatment, patients were treated with decitabine 15 mg/m^2 by continuous infusion in 3 h three times a day for 3 days, repeated every 6 weeks. Patients received 4 to 9 treatment cycles.

2.4. Definition

The diagnosis of MDS was determined according to Proposal of minimal diagnostic criteria of MDS [7]. The classification of MDS was based on WHO 2022 [2]. The risk was stratified according to IPSS-R [4]. The response to treatment was based on International Working Group (IWG 2006) [8]. Response of patients with ESA treatment was based on hematologic improvement including: hematologic improvement-erythroid (HI-E), hematologic improvement-platelets (HI-P), hematologic improvement-neutrophils (HI-N). Patients with 3 lineages improvement were considered to achieve a total hematologic improvement (HIs). Response of patients with HMA treatment based on hematologic improvement and reduction of blast. All patients with completed remission (CR), partial remission (PR), bone marrow completed remission (marrow CR) were considered to achieve a overall response.

OS (overall survival) was calculated from the time of diagnosis to death or the last follow-up. LFS (leukemic transformation free survival) was calculated from the beginning of treatment to leukemic transformation or death. PFS (progression free survival) was calculated from the beginning of treatment to relapse or death for patients with HMA treatment. For patients with ESA treatment, PFS was calculated from the start of treatment to progression from hematologic improvement (Prog from HI) or death.

2.5. Statistical analysis

The differences between the ESA and HMA treatment groups were evaluated. Comparison of qualitative variables (clinical characteristic, karyotype, cytogenetic risk, type of MDS, IPSS-R) was analyzed by χ^2 or Fisher's test. The comparison of quantitative variables (hemoglobin, neutrophil count, platelet count, percentage of peripheral blood blast, bone marrow cell count, percentage of bone marrow blast) was analyzed using an independent sample T-test or Mann- Whitney test according to normal or non-normal distribution. The P -value <0.05 was considered statistically significant.

Survival analyzes including OS, PFS and LFS were calculated using the Kaplan-Meier method. The comparison between the ESA and HMA treatment groups was evaluated. The P^{Logrank} value <0.05 was considered statistically significant.

3. Results

3.1. Patients characteristics

In our study, thirty- two patients were recruited, including 20 men (62.5 %) and 12 women (37.5 %). The median age was 66 years (range: 28–81). The median age of the ESA treatment group was 69 years that was older than in the HMA treatment group (64 years). Table 1 shows the characteristics of the patients. Almost all patients had anemia. Other clinical features such as hemorhage, infection, etc. were less common. According to the latest classification (WHO 2022), patients diagnosed with MDS with defining genetic abnormalities (MDS 5q-, MDS *SF3B1*, MDS- bi*TP53*) had a lower rate (6.25 %, 6.25 % and 3.1 %; respectively), while patients diagnosed with MDS with morphologically defined (MDS low blast, MDS-IB1, MDS-IB2) had a higher rate (28.1 %, 31.25 % and 25 %; respectively).

There were statistically significant differences between the ESA and HMA treatment groups. The ESA treatment group included MDS 5q-, MDS *SF3B1* while the HMA treatment groups included MDS-bi*TP53*. The HMA treatment group also had a higher bone marrow cell count. These factors (except for 5q-) were not used to calculate risk score according to IPSS-R.

3.2. Outcome treatment and survival analysis

Table 2 shows that in the HMA treatment group, the overall response rate (including CR, PR, marrow CR) was 52.6 %. In the ESA treatment group, the rate of hematologic improvement-erythroid was 69.2 % and the rate of total hematologic improvement was 61.5 %. The follow-up times were 42 months. Table 2, Figs 1-3 show survival time of the ESA treatment and the HMA treatment groups. In the ESA treatment group, OS, LFS, and PFS were 30.44, 28.91, and 28.29 months; respectively. In the HMA treatment group, OS, LFS, and PFS were 34.27, 31.45, and 26.83 months; respectively. The estimated mean OS and LFS were longer in the HMA treatments group, while PFS was shorter, but there was no statistically significant difference.

3.3. Discussion

Anemia is a major clinical feature in almost patients with MDS, caused by ineffective erythopoiesis due to decreased response to endogenous erythropoeitin (EPO). However, ESAs have been used in patients with MDS with low serum EPO levels for decades and have been shown to improve anemia [6]. ESAs have been widely used for patients with lower-risk MDS without del(5q) as first-line treatment. However, there was no consensus on the serum EPO level. The NCCN and ESMO guidelines recommended for serum EPO level <500 mU/mL while EMA approved for ESA with serum EPO level <200 mU/ml [6]. In our study, the treatment decision was based on the serum EPO level <500 mU/mL. The results indicated that the rate of hematologic

Table 1
Patients characteristics.

Characteristics			Treatment regimen		Total ($n = 32$)	P
			ESA ($n = 13$)	HMA ($n = 19$)		
Clinical characteristics	Anemia		13	18	32 (100 %)	$P > 0.05$
	Hemorhage		3	4	7 (21.8 %)	$P > 0.05$
	Infection		3	4	7 (21.8 %)	$P > 0.05$
	Hepatomegaly		2	2	4 (12.5 %)	$P > 0.05$
	Splenomegaly		1	3	4 (12.5 %)	$P > 0.05$
	Lymphadenopathy		1	1	2 (6.25 %)	$P > 0.05$
Type of MDS	MDS 5q-		2	0	2 (6.25 %)	**$P < 0.001$**
	MDS *SF3B1*		2	0	2 (6.25 %)	
	MDS-bi*TP53*		0	1	1 (3.1 %)	
	MDS low blast		9	0	9 (28.1 %)	
	MDS-IB1		0	10	10 (31.25 %)	
	MDS-IB2		0	8	8 (25 %)	
Karyotype	Normal		9	16	25 (78.1 %)	$P > 0.05$
	Abnormal	Del (5q) isolated	2	0	2 (6.25 %)	
		Complex Karyotype	0	2	2 (6.25 %)	
		Others	2	2	4 (12.5 %)	
Cytogenetics Risk	Very good		1	0	1 (3.1 %)	$P > 0.05$
	Good		12	15	27 (84.4 %)	
	Intermediate		0	0	0 (0 %)	
	Poor		0	2	2 (6.25 %)	
	Very Poor		0	2	2 (6.25 %)	
IPSS-R	Very Low		2	0	2 (6.25 %)	**$P < 0.001$**
	Low		7	0	7 (21.8 %)	
	Intermadiate		4	6	10 (31.25 %)	
	High		0	10	10 (31.25 %)	
	Very High		0	3	3 (9.4 %)	
Cell indices			Treatment Protocol		Total ($n = 32$)	P
			ESA ($n = 13$)	HMA ($n = 19$)		
Hemoglobin (g/L) (Mean ± SD)			80.38 ± 17.30	82.58 ± 14.25	81.69 ± 15.33	$P > 0.05$
Platelet count (G/L) (Median)			71	78	75	$P > 0.05$
Neutrophil count (G/L) (Median)			1.59	0.79	1.3	$P > 0.05$
Peripheral blast (%) (Median)			0	2	1	**$P < 0.001$**
Bone marrow cell count (G/L) (Median)			19	36.9	29.5	**$P = 0.041$**
Bone marrow blast (%) (Mean ± SD)			0.69 ± 1.38	9.79 ± 3.26	6.09 ± 5.25	**$P < 0.001$**

Note: ESA: erythropoietin stimulating agent.
HMA: hypomethylating agent.
MDS: myelodysplastic neoplasms (myelodysplastic syndromes).
IB: increase blast.
IPSS- R: Revised International Prognostic Scoring System.
P: between ESA treatment group and HMA treatment group.

Table 2
Response to treatment, OS, PFS and LFS according to the treatment regimen.

Response		Treatment regimen		P
		ESA ($n = 13$)	HMA ($n = 19$)	
HI-E (n/%)		9 (69.2 %)		
HI-P (n/%)		8 (61.5 %)		
HI-N (n/%)		9 (69.2 %)		
HIs (n/%)		8 (61.5 %)		
CR (n/%)			4 (21.1 %)	
PR (n/%)			5 (26.3 %)	
Marrow CR (n/%)			1 (5.2 %)	
Survival		ESA ($n = 13$)	HMA ($n = 19$)	
OS	Months	30.44	34.27	$P > 0.05$
	CI 95 %	26.41–34.47	28.47–40.1	
LFS	Months	28.91	31.45	$P > 0.05$
	CI 95 %	23.31–34.51	24.69- 38.21	
PFS	Months	28.29	26.83	$P > 0.05$
	CI 95 %	21.83- 34.76	20.08- 33.58	

Note: ESA: erythropoietin stimulating agent.
HMA: hypomethylating agent.
HI-E; hematologic improvement erythroid.
HI-P: hematologic improvement platelets.
HI-N: hematologic improvement neutrophils.
HIs: total hematologic improvement (3 lineages).
CR: completed remission.
PR: partial remission.
Marrow CR: marrow completed remission.

improvement-erythropoeisis was 69.2 %, the rate of hematologic improvement was 61.5 %. In the Balleari et al. study, the rate of hematologic improvement- erythropoeisis was 52.6 %; however, patients with higher risk (such as RAEB2) were included [9]. Castelli et al. showed that 66.7 % of patients with lower-risk MDS achieved an erythroid response [10]. Seventeen % of patients with lower-risk MDS failed ESA treatment in the study by Savill et al. [11]. In our study, 2 patients with MDS 5q- were diagnosed. Although lenalidomide was not used, both achieved hematologic improvement. In fact, for patients with lower risk of del(5q), NCCN guidelines also allow the initial therapy with ESA in cases with serum levels of EPO <500 mU/ml [6]. Our study also demonstrated that patients with ESA treatments had a survival advantage. OS, LFS, and PFS were 30.44, 28.91, and 28.29 months; respectively, (the follow-up time was 42 months).

For patients diagnosed with MDS of higher risk, allogeneic stem cell transplantation is considered first. However, whether or not to pursue transplantation, most patients with higher-risk MDS should receive HMA therapy (azacitidine or decitabine). Xia et al. suggested that azacitidine improved OS and LFS compared to decitabine [12]. According to the BSH guideline, the ESMO guideline, azacitidine is preferred for use [4,5]. Otherwise, only azacitidine is accepted in the UK [5]. However, recently, there have been some studies showing the effectiveness of decitabine [13–15].

Our study also showed that, in the higher risk group with decitabine treatment, the total response rate of decitabine was 52.6 %, higher than in the study by Liu et al. (40 %), Liu H et al. (41.5 %), lower than in the

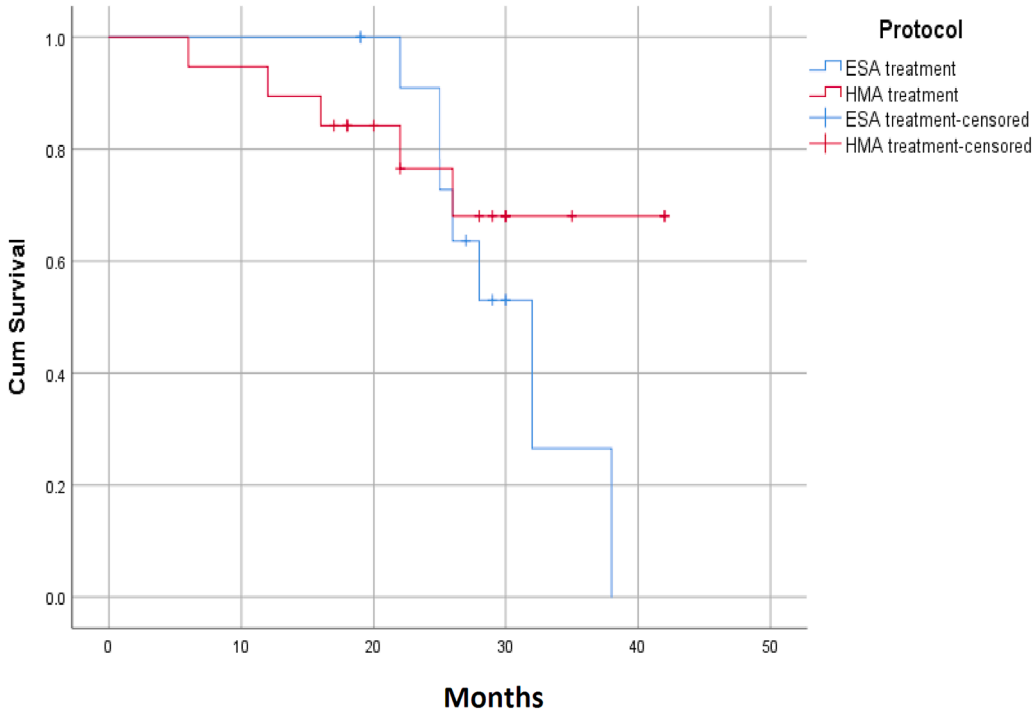

Fig. 1. Overall survival (OS) according to treatment regimen: ESA (erythropoiesis stimulating agent), HMA (hypomethylating agent).

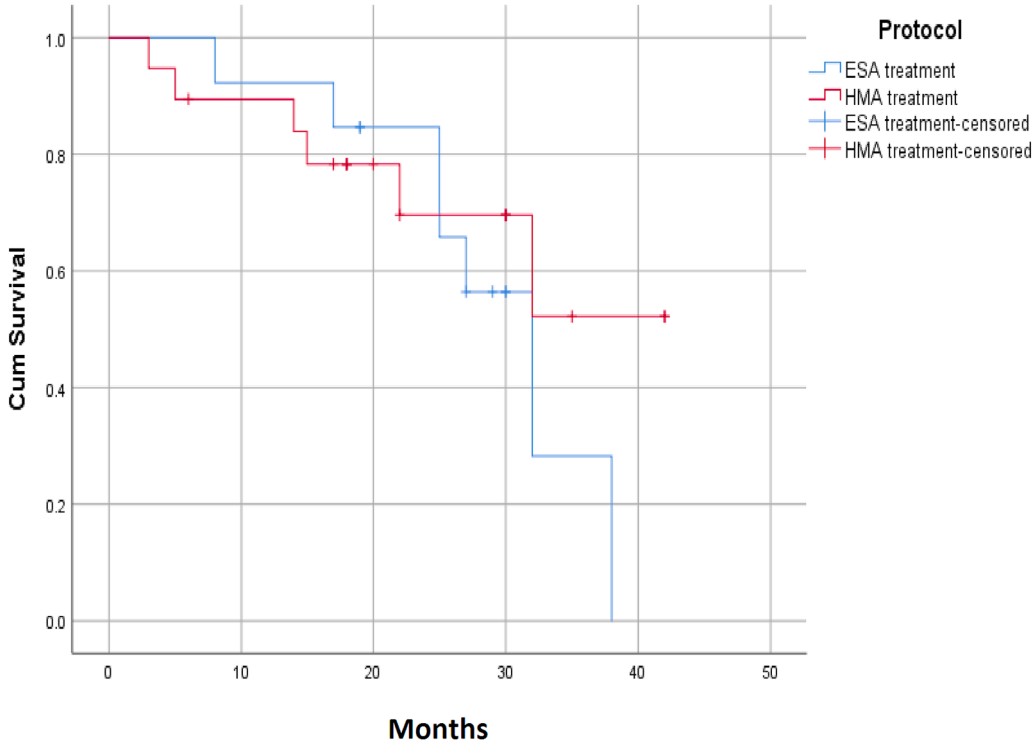

Fig. 2. Leukemic transformation- free survival (LFS) according to treatment regimen: ESA (erythropoiesis stimulating agent), HMA (hypomethylating agent).

study by Feng (55 %) [13–15]. Liu et al. also indicated that the combination of decitabine and chemotherapy increased the effective response rate, but did not affect the survival time (OS, PFS) [13].

Our results indicated that in the HMA treatment group, OS, LFS and PFS were 34.27, 31.45, and 26.83 months; respectively (the follow-up time was 42 months). Similarly to Liu et al., Liu H et al., and Feng et al., whether or not allogeneic transplantation was followed, higher-risk MDS patients would still benefit from treatment with decitabine.

4. Conclusion

Patients with lower-risk MDS, even including MDS 5q-, may benefit from treatment with erythropoeisis stimulating agents (ESAs). Similarly, patients with higher-risk MDS may have favorable outcomes with the

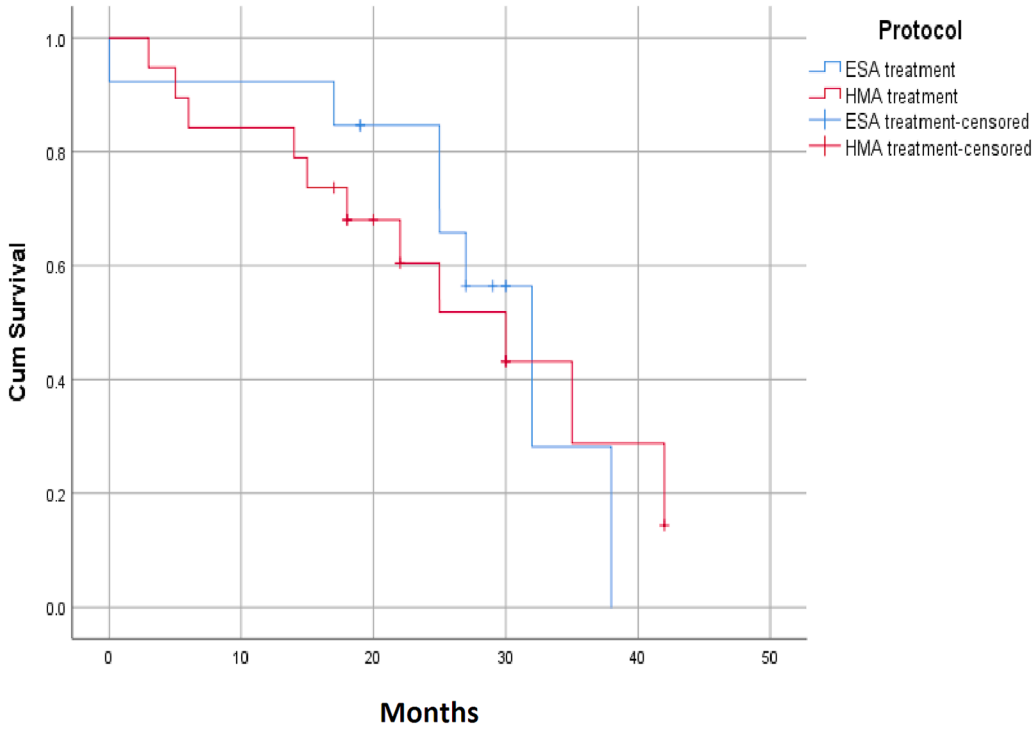

Fig. 3. Progression- free survival (PFS) according to treatment regimen: ESA (erythropoiesis stimulating agent), HMA (hypomethylating agent).

treatment of decitabine (HMA) treated. Thus, it is possible to temporarily apply a simpler protocol with drugs available in developing countries where access to novel or preferable drugs is difficult.

Financial disclosure statement

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Ethics approval and consent to participate

The Review Board of the NIHBT approved the study (no. 939/QĐ-HHTM) and waived informed consent as it was a retrospective observational study.

CRediT authorship contribution statement

Quang Hao Nguyen: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Minh Phuong Vu:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Ha Trang Kieu:** Writing – original draft, Investigation, Formal analysis, Data curation. **Duc Binh Vu:** Writing – original draft, Investigation, Formal analysis, Data curation. **Ha Thanh Nguyen:** Writing – original draft, Formal analysis, Data curation. **Quoc Khanh Bach:** Writing – original draft, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data can be obtained from the corresponding author upon resonable request.

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