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BRIEF ARTICLE

Therapeutic effects of combined oxaliplatin and S-1 in older patients with advanced gastric cardiac adenocarcinoma

She-Gan Gao, Rui-Nuo Jia, Xiao-Shan Feng, Xuan-Hu Xie, Tan-You Shan, Li-Xian Pan, Na-Sha Song, Yu-Feng Wang, Kai-Li Ding, Li-Dong Wang

She-Gan Gao, Rui-Nuo Jia, Xiao-Shan Feng, Xuan-Hu Xie, Tan-You Shan, Li-Xian Pan, Na-Sha Song, Yu-Feng Wang, Kai-Li Ding, Department of Oncology, First Affiliated Hospital, Cancer Institute, Henan University of Science and Technology, Luoyang 471003, Henan Province, China
Li-Dong Wang, Henan Key Laboratory for Esophageal Cancer, Laboratory for Cancer Research, Basic Medical College, Zhengzhou University, Zhengzhou 450052, Henan Province, China
Author contributions: Gao SG and Feng XS designed the study; Jia RN, Xie XH, Shan TY, Pan LX, Song NS, Wang YF and Ding KL performed the research; Gao SG and Jia RN carried out the analyses and wrote the article; Feng XS, Gao SG and Wang LD approved the final version of the manuscript.
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Correspondence to: Dr. Xiao-Shan Feng, First Affiliated Hospital, Cancer Institute, Henan University of Science and Technology, Luoyang 471003, Henan Province, China. samfeng137@hotmail.com
Telephone: +86-379-64820811 Fax: +86-379-64820811
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Abstract

AIM: To evaluate the effects and safety of combination chemotherapy with oxaliplatin (L-OHP) and S-1 (SOX regimen) in older patients with advanced gastric cardiac adenocarcinoma (GCA).

METHODS: Seventy patients with advanced GCA were classified according to age into an older group (≥ 75 years) and a control group (< 75 years). The SOX regimen was administered to the two groups as follows: S-1 (40 mg/m^2 po bid) on days 1 to 14 followed by a 7-d off period, plus L-OHP (65 mg/m^2 iv) for 2 h on days 1 and 8 of a 21-d cycle. This regimen was repeated for four to six cycles. Response and swallow statuses were evaluated after two cycles (6 wk). Effects and toxicity were evaluated four weeks after chemotherapy was completed.

RESULTS: The response rate was 65.6% (21/32) in the older group and 68.4% (26/38) in the control group (χ^2 = 0.062 and P = 0.804). Improvement in swallowing was 78.1% (25/32) in the older group and 76.3% (29/38) in the control group (χ^2 = 0.032 and P = 0.857). Efficacy was 68.8% (22/32) in the older group and 65.8% (25/38) in the control group (χ^2 = 0.069 and P = 0.793). Toxicities were reversible and similar in both groups (P > 0.05).

CONCLUSION: The SOX regimen is an effective, safe and well-tolerated regimen for older patients with advanced GCA.

Key words: Gastric cardiac adenocarcinoma; Oxaliplatin; S-1; Treatment effect

Peer reviewer: Damian Casadesus Rodriguez, MD, PhD, Calixto Garcia University Hospital, J and University, Vedado, Havana City 999075, Cuba

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INTRODUCTION

With constant improvement in the quality of life in modern

society, people's life span has been prolonged. However, the incidence of elderly patients with gastric cardiac adenocarcinoma (GCA) is gradually increasing, and the majority of these patients have advanced disease when they are diagnosed. Thus, these patients have few opportunities for surgery[1]. The only available treatment choice for advanced GCA patients is systemic chemotherapy[2-4]. Although chemotherapy for advanced gastrointestinal cancer has been proven to be superior to best supportive care (BSC) in terms of survival and quality of life[5-7], there has been evidence supporting more serious adverse events observed among older patients than younger patients[8]. For these reasons, most older patients with metastasis are usually offered BSC and not chemotherapy[9]. However, patients who are 75 years old can still have a considerable number of years to survive (perhaps more than 10 years)[10]. Therefore, it is important to find a highly effective and minimally toxic chemotherapy regimen for elderly patients with advanced GCA.

In the last decade, 5-fluorouracil (5-FU) has been considered a cornerstone of therapy for advanced gastrointestinal cancer. Therefore, combining 5-FU with oxaliplatin (L-OHP) is logical because there is considerable evidence of preclinical synergy between the two agents[11]. S-1 is an orally active prodrug of 5-FU which is a fourth generation oral fluoropyrimidine[12]. Recent clinical studies have reported that S-1 in combination with L-OHP has a high response rate ranging from 53% to 59% and an excellent toxicity profile in the treatment of advanced gastric cancer[13-15]. In these studies, however, there were only a few patients of 75 years of age or older. Furthermore, few studies on the outcome of the S-1 and oxaliplatin (SOX) regimen in patients with GCA have been reported. Therefore, we designed this study to determine the response rate and toxicity profile of SOX regimen in GCA patients over the age of 75 years.

MATERIALS AND METHODS

Patients

GCA was confirmed in 70 patients by pathologic diagnosis in the First Affiliated Hospital, Henan University of Science and Technology from March 2008 to October 2010. All patients were treated with chemotherapy for the first time in this study, and they were experiencing symptoms such as difficulty in drinking, difficulty in eating, vomiting mucus, anemia, and emaciation. The degree of cardia stenosis was assessed using the Stooler Classification System[16] and the barium meal examination. The results of the barium meal examination are shown in Table 1. There were 54 cases of grade Ⅲ, 14 cases of grade Ⅳ, and 2 cases of grade Ⅴ dysphagia. All patients were classified as stage Ⅲ or Ⅳ according to the TNM staging, and they had Karnofsky Performance Status (KPS) scores greater than or equal to 60 points, predicted life spans greater than three months, no contraindications to chemotherapy, and no previous treatment with chemotherapy. Their routine blood examinations, electrocardiograms (ECGs), liver function, and kidney function were also normal. All patients were examined with a computed tomography (CT) before and after chemotherapy, and they were evaluated by the same physician.

Table 1 Degree of cardia stenosis

Clinical classifications	Diet conditions	Cardia diameters in the barium meal exam (mm)
Ⅰ	Ordinary diet	8-10
Ⅱ	Semi-liquid diet	6-8
Ⅲ	Liquid diet	4-6
Ⅳ	No drinking	2-4
Ⅴ	Saliva refluxing	0-2

According to the most recent World Health Organization (WHO) definition of aged people, people who are 65 to 74 years old are categorized as "young aged", and people who are 75 to 90 years old are classified as "older people". All the patients were divided into two groups as follows: patients older than 75 years were classified in the older group, and the remaining patients were classified in the control group. Of the 32 participants in the older group (ranging in age from 75 to 89 years old), 24 patients were male and 8 patients were female, with a median age of 79.5 years. Of the 38 participants in the control group (ranging in age from 55 to 74 years old), 29 patients were male and 9 patients were female with a median age of 64 years (Table 2).

Methods

The following chemotherapy program was used: L-OHP (65 mg/m^2 iv) was administered for 2 h on days 1 and 8; S-1 was orally administered at a dose of 40 mg/m^2 bid for 14 d (from the evening on day 1 until the morning on day 15); and a 7-d rest period followed the L-OHP and S-1 treatments in the 3-wk schedule. Treatment was repeated for four to six cycles. In every cycle, both omeprazole (40 mg iv bid) and tropisetron (5 mg iv qd) were administered before chemotherapy. Furthermore, large doses of oral vitamin B tablets were used to reduce side effects, and low doses of megestrol enhanced appetite and nutrition. Moreover, reconstituted cell colony-stimulating factor was given if needed. Participants were advised to avoid cold food, drinks and water. Blood, urine and stool routine examinations were carried out weekly, and ECG, liver function and kidney function were also checked weekly. Furthermore, a KPS score was determined weekly.

If patients had dysphagia to an extent greater than grade Ⅳ due to cardia stenosis, the stenosis was dilated with a conical Savary-Gilliard silica gel dilator one week before chemotherapy followed by insertion of a gastric canal. High protein and high vitamin liquid nasal feeds were then started. If the patient could swallow food after two chemotherapy cycles, the gastric canal was removed.

The sensitivity of the tumor to chemotherapy and improvement of dysphagia were evaluated after two cycles (6 wk). The effects and toxicity were evaluated at

Table 2 Patient characteristics at baseline, case (%)

Characteristics	Older group (n = 32)	Control group (n = 38)
Demography		
Male/female	24 (75)/8 (25)	29 (76.3)/9 (23.7)
Median age, yr (range)	79.5 (75-89)	64 (55-74)
Karnofsky performance status		
Median	80%	80%
100%	1 (3.1)	2 (5.3)
90%	10 (31.2)	13 (34.2)
80%	17 (53.2)	18 (47.4)
60%-70%	4 (12.5)	5 (13.1)
Weight loss > 5%	11 (34.4)	13 (34.2)
Cardia stenosis status		
Ⅰ-Ⅱ	0	0
Ⅲ	25 (78.1)	29 (76.3)
Ⅳ	6 (18.8)	8 (21.1)
Ⅴ	1 (3.1)	1 (2.6)
Histological grade		
G1-2	17 (53.1)	19 (50)
G3	12 (37.5)	14 (36.8)
Others (grade not stated)	3 (9.4)	5 (13.2)
Extent of disease		
Metastatic	10 (31.3)	12 (31.6)
Locally advanced	22 (68.7)	26 (68.4)
Metastatic site		
Lymph nodes	10 (31.3)	12 (31.6)
Liver	3 (9.4)	3 (7.9)
Peritoneum	1 (3.1)	2 (5.3)
Lung	0	1 (2.6)
Others	0	0
No. of metastatic sites		
1	6 (18.8)	6 (15.8)
⩾ 2	4 (12.5)	6 (15.8)

four weeks with a repeat CT and barium meal examination after the chemotherapy was completed.

Evaluation criteria

Evaluation criteria for chemotherapy sensitivity: The evaluation criteria for chemotherapy sensitivity we used were proposed in 1998 by the European Association of Cancer Research and Treatment, United States National Cancer Institute, and National Cancer Institute of Canada. These evaluation criteria are called the Response Evaluation Criteria In Solid Tumors[17]. Participants had a repeat CT scan with contrast two weeks after the completion of chemotherapy to evaluate the therapeutic effects of the chemotherapy according to the maximum diameters of each tumor. A complete response (CR) was defined as the complete disappearance of all lesions after treatment. A partial response (PR) was defined as a decrease greater than or equal to 30% in the maximum diameters of all tumors after treatment. Progressive disease (PD) was defined as an increase greater than 20% in the maximum diameters of tumors or the emergence of more than one new lesion after treatment. When the tumor diameters were between the diameters found in the PR and PD classifications (< 30% decrease or ⩽ 20% increase) after treatment, the effect was classified as stable disease.

Evaluation criteria for improvement of dysphagia: The evaluation criteria for symptom improvement were based on diet intake and the increase/decrease in cardia diameter. The symptoms were assessed using the barium meal examination[18] with the following classifications: CR, post-treatment cardia diameter two times greater than or equal to the pre-treatment cardia diameter with the patient capable of eating ordinary food; PR, post-treatment cardia diameter one time greater than the pre-treatment cardia diameter with the patient capable of eating semi-liquid food; no change (NC), an increase in the cardia diameter by less than 6 mm with the patient capable of eating only liquid food; and PD, a decrease in the cardia diameter with the patient unable to eat liquid food.

Evaluation criteria for short-term effects: Participants had CT scans in the first and fourth week after the chemotherapy session ended. The area of each tumor (referring to the product of the two longest vertical diameters) was measured before and after chemotherapy. The following evaluation criteria were used[19]: CR, complete disappearance of visible lesions for more than one month; PR, a decrease greater than 50% in the tumor for more than one month; NC, a decrease less than 50% or an increase less than 25% in the tumor for more than one month; and PD, one or more lesions increased by greater than 25% or the emergence of a new lump.

Evaluation criteria for side effects: Toxicities were divided into degrees from 0 to Ⅳ according to the WHO criteria for acute and subacute toxic reactions of antineoplastic agents[19].

Statistical analysis

SPSS 10.0 statistical software (SPSS Company, Chicago, Illinois, United States) was used to perform the χ^2 test to evaluate the data. P values less than 0.05 were considered statistically significant.

RESULTS

Chemotherapy sensitivity

A repeat CT of the epigastrium two weeks after starting chemotherapy with the SOX program measured changes in the diameter of the largest tumor and evaluated the sensitivity to chemotherapy of the older group and control group (Table 3).

Symptom (dysphagia) improvement

After two cycles of chemotherapy with the SOX program, an upper gastrointestinal barium meal examination was repeated. Changes in cardia diameters were measured and calculated, and patients were asked about their diets. Symptom improvement was evaluated and compared between groups (Table 4).

Short-term therapeutic effects

After one week and four weeks of chemotherapy with

Table 3 Comparisons of chemotherapy sensitivity, case (%)

Clinical groups	CR	PR	SD	PD	CR + PR
Older group (n = 32)	3 (9.4)	18 (56.2)	11 (34.4)	0	21 (65.6)[a]
Control group (n = 38)	4 (10.5)	22 (57.9)	12 (31.6)	0	26 (68.4)

[a]χ^2 = 0.062, P = 0.804 *vs* control group. CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

Table 4 Comparisons of symptom (dysphagia) improvement, case (%)

Clinical groups	CR	PR	NC	PD	CR + PR
Older group (n = 32)	5 (15.6)	20 (62.5)	7 (21.9)	0 (0)	25 (78.1)[a]
Control group (n = 38)	5 (13.2)	24 (63.2)	9 (23.7)	0 (0)	29 (76.3)

[a]χ^2 = 0.032, P = 0.857 *vs* control group. CR: Complete response; PR: Partial response; NC: No change; PD: Progressive disease.

Table 5 Comparisons of short-term chemotherapy effects, case (%)

Clinical groups	CR	PR	SD	PD	CR+PR
Older group (n = 32)	5 (15.6)	17 (53.2)	8 (25)	2 (6.2)	22 (68.8)[a]
Control group (n = 38)	5 (13.2)	20 (52.6)	10 (26.3)	3 (7.9)	25 (65.8)

[a]χ^2 = 0.069, P = 0.793 *vs* control group. CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

the SOX program, abdominal CTs were repeated. The maximum diameters of the tumors were measured, and the short-term therapeutic effects in both groups were evaluated (Table 5).

Side effects

The most frequent toxic therapy effects were hematological effects in both groups [grade 3 toxicity found in 13 patients (6 in the older group and 7 in the younger group)]. No grade 4 toxicity was reported. The L-OHP-related peripheral neuropathy appeared to be mild and reversible in the majority of cases. No severe cardiac toxicity or death was recorded among these patients during the study. Details of the side effects are shown in Table 6.

DISCUSSION

The health of the elderly varies from the health of younger patients. Older people are prone to having multiple organ dysfunctions, lower immunity, lower resistance to disease, and lower resistance to senile diseases, leading to reduced tolerance to chemotherapy and increased sensitivity to side effects of these drugs. Generally, caution is required when administering chemotherapy to older patients because they may not be able to tolerate a routine dose or may experience serious side effects. However, a suboptimal dose may not achieve the desired therapeutic effect. Therefore, many experts avoid treating elderly patients with chemotherapy[20].

Table 6 Comparisons of chemotherapy side effects, case (%)

Side effect	Older group (n = 32)			Control group (n = 38)			P[1] value
	I -IV	III	IV	I -IV	III	IV	
Leukopenia	25 (78.1)	3 (9.3)	0	28 (73.7)	4 (10.5)	0	0.666
Anemia	24 (75.0)	2 (6.2)	0	27 (71.1)	2 (5.3)	0	0.900
Thrombocytopenia	23 (71.9)	1 (3.1)	0	27 (71.1)	1 (2.6)	0	0.940
Fever	2 (6.3)	0	0	3 (7.9)	0	0	1.000
Oral mucositis	13 (40.6)	0	0	14 (36.8)	0	0	0.746
Nausea/vomiting	10 (31.3)	0	0	11 (28.9)	0	0	0.834
Diarrhea	14 (43.8)	0	0	16 (42.1)	0	0	0.890
Fatigue	21 (65.6)	2 (6.3)	0	23 (60.5)	1 (2.6)	0	0.660
Sensory neuropathy	18 (56.3)	0	0	21 (55.3)	0	0	0.934
Liver function (ALT/AST)	4 (12.5)	0	0	3 (7.9)	0	0	0.810
Renal function (BUN/Cr)	1 (3.1)	0	0	0	0	0	-
Hand-foot syndrome	0	0	0	0	0	0	-
Myocardial ischemia	0	0	0	0	0	0	-
Anaphylaxis	0	0	0	0	0	0	-

[1]P value for grade I -IV between older group and control group. ALT: Alanine transaminase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; Cr: Creatine.

There is evidence[9,21], however, that older patients with advanced gastroesophageal carcinoma may benefit from chemotherapy. Tougeron *et al*[9] reported that palliative treatment is superior to BSC (6.7 ± 2.1 mo *vs* 1.8 ± 0.4 mo) in older patients (> 70 years of age) with advanced esophageal cancer. The effect of S-1 and cisplatin combination therapy in an 80-year-old patient with gastric carcinoma has been reported in a case study, and the histopathological examination of this patient revealed CR of the disease with no cancer cells[21]. Nevertheless, data regarding GCA is limited.

In this study, the SOX program was used to treat elderly people with advanced GCA to achieve the following goals: (1) to enhance the efficacy of treatment by using a new drug; (2) to reduce toxicity and improve tolerance; and (3) to create an opportunity for treatment in elderly patients with poor health.

S-1 is an effective derivative that combines tegafur with the following two modulators of 5-FU metabolism in a 1:0.4:1 molar ratio: 5-chloro-2,4-dihydroxypyridine (CDHP), a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), and potassium oxonate[12]. Tegafur, an oral prodrug of 5-FU, is gradually converted to 5-FU and is rapidly metabolized by DPD in the liver. The maximum concentration (Cmax) and area under the concentration-time curve (AUC) of 5-FU in plasma during S-1 treatment have been found to be higher than the steady state concentration and AUC of 5-FU in plasma during protracted intravenous infusion of 5-FU at a dose of 250 mg/m^2 per day[22]. Potassium oxonate is an orotate phosphoribosyl transferase inhibitor, which is primarily distributed to the gastrointestinal tract. This component of S-1 decreases incorporation of 5-fluorouridine triphosphate into RNA in the gastrointestinal mucosa, and it reduces the incidence of diarrhea. F-b-alanine (FBAL) is the main metabolite of 5-FU. FBAL and fluorocitrate are thought to cause the neurotoxic and

cardiotoxic effects of 5-FU by inhibiting the tricarboxylic acid cycle[22]. The CDHP component of S-1 inhibits DPD, which is the rate-limiting enzyme in the catabolic pathway of 5-FU. Consequently, the plasma FBAL concentration after oral administration of S-1 is significantly lower than the concentration after continuous infusion of 5-FU[12]. Therefore, the use of S-1 may decrease the incidence of neurotoxicity and cardiotoxicity. Ajani *et al*[23] reported significant safety advantages in the S-1/cisplatin treatment as compared with the infusional fluorouracil/cisplatin treatment for advanced gastric or gastroesophageal adenocarcinoma. They reported the following frequencies resulting from the two treatments: grade 3/4 neutropenia (32.3% and 63.6%, respectively), stomatitis (1.3% and 13.6%, respectively), and hypokalemia (3.6% and 10.8%, respectively).

L-OHP[24-25] is a third generation platinum anticancer drug developed to improve tolerability and ease of administration when compared to cisplatin. The rate at which L-OHP combines with DNA in the body is more than 10 times faster than cisplatin. L-OHP adheres more strongly to DNA, and it has a stronger cytotoxic effect than cisplatin and carboplatin. In addition, the unique diaminocyclohexane group in oxaliplatin avoids some of the resistance mechanisms developed against cisplatin, such as the mismatch repair defect and bypass replication mechanism. A phase Ⅲ trial[26] for metastatic gastroesophageal adenocarcinoma has been conducted, with a treatment of fluorouracil and leucovorin combined with either oxaliplatin [fluorouracil, leucovorin and oxaliplatin (FLO)] or cisplatin [fluorouracil, leucovorin and cisplatin (FLP)] every two weeks. The results of this trial demonstrated that serious adverse events associated with FLO are significantly less than the events associated with FLP (9% and 19%, respectively) and that the median progression-free survival (PFS) improves with FLO when compared to FLP (5.8 mo and 3.9 mo, respectively). This trial also demonstrated that treatment with FLO results in significantly superior response rates (41.3% and 16.7%, respectively), improved median PFS (6.0 mo and 3.1 mo, respectively) and improved overall survival (13.9 mo and 7.2 mo, respectively) when compared to treatment with FLP in patients older than 65 years.

Studies have shown that L-OHP and S-1 are highly active against cancer and that they have a favorable toxicity profile. Furthermore, studies have also shown that L-OHP and S-1 are expected to replace cisplatin and fluorouracil, respectively, as a first-line treatment for advanced gastric cancer[13-15]. Moreover, the SOX program may be considered for treatment of older people because of the greater efficacy and low toxicity of this regimen when compared to cisplatin and fluorouracil.

The SOX regimen in this study resulted in no significant differences between the older and control groups with regard to chemotherapy sensitivity (65.6% and 68.4%, respectively, $P = 0.804$), symptom improvement (78.1% and 76.3%, respectively, $P = 0.857$), and short-term therapeutic effects (68.8% and 65.8%, respectively, $P = 0.793$). More severe side effects caused by the SOX regimen were not detected among the elderly patients when compared to the younger patients, and these side effects did not have a significant effect on treatment administration or quality of life. Therefore, these results suggest that there are treatment options available for elderly patients with cardia obstruction who cannot eat and that there is still an opportunity for these patients to survive if they can get adequate nutrition through nasal feeds.

In summary, the SOX regimen for advanced GCA has high efficacy and mild toxicity, and it can increase the survival and life span of patients with GCA. Moreover, the SOX regimen is a safe chemotherapy program for elderly patients in poor health. Therefore, it is not necessary to entirely avoid chemotherapy in elderly patients with advanced GCA because of their age. Instead, treatment recommendations should consider physiological age and standard KPS score. It is also reasonable to initiate chemotherapy if the patient can obtain sufficient nutrition (e.g., through nasal feeding). However, chemotherapy should not be administered to patients with KPS scores less than 60 points.

In this study, the therapeutic effects of the SOX regimen in both groups were higher than those reported in previous studies of patients with gastric cancer[13-15], which may have been due to the fact that this combination therapy was the first time any of the patients in this study were treated with chemotherapy, resulting in a higher sensitivity and minimal resistance to treatment. Other studies have included patients who had relapsed or failed treatment. Moreover, most of the patients in this study were classified as having stage Ⅲb GCA with only locally advanced cancer. In this study, there were only a few extensive cases of metastasized cancer. Additionally, the SOX program may be more effective at treating GCA than other types of gastric cancer.

COMMENTS

Background

The morbidity of gastric cardiac adenocarcinoma (GCA) in elderly people is gradually increasing, and most elderly GCA patients suffer from advanced carcinoma. Therefore, the opportunity for surgery is low, and only systemic chemotherapy is available for these patients. However, many experts disagree with treating elderly patients with chemotherapy because more serious adverse events have been observed in older patients than in younger patients.

Research frontiers

In the last decade, 5-fluorouracil (5-FU) has been considered a cornerstone for treating advanced gastrointestinal cancers. S-1 is a new orally active prodrug of 5-FU, and clinical studies with S-1/L-OHP (SOX regimen) have reported a high response rate ranging from 53% to 59% and an excellent toxicity profile in the treatment of advanced gastric cancer. In these clinical studies, however, there were only a few patients who were 75 years of age or older. Moreover, only a few studies on the outcome of the SOX regimen in patients with GCA have been reported.

Innovations and breakthroughs

This is the first study to evaluate the effects and safety of the SOX regimen in older patients with GCA. The study showed that the SOX regimen is a safe chemotherapy program for elderly patients with advanced GCA and that this regimen provides a treatment option for elderly patients with GCA.

Applications

The SOX regimen may be an ideal strategy in the future for treatment of older patients with advanced GCA.

Peer review

It is a very interesting topic for the readers.

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