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Original Research

EVALUATING THE EFFICACY AND SAFETY OF TS1 - CISPLATIN REGIMEN IN THE FIRST - LINE TREATMENT OF ADVANCED GASTRIC CANCER PATIENTS

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ABSTRACT

Objectives: *To evaluate the efficacy and safety of TS1-Cisplatin regimen in the first - line treatment of metastatic gastric cancer patients.*

Methods: *38 eligible patients were treated with TS1-cisplatin at Hanoi Medical University Hospital from January 2018 to December 2021.*

Results: *Mean age was 57.4. Male: female ratio = 3.2:1. Most patients had good performance status (PS 0 or PS 1 - 84.2%). Most received dose rate from 85% to 100% of standard dose (78.9%). After six cycles, complete response rate was 13.2%, partial response rate was 42.1%. The median progression - free survival was 5.7 months. The median overall survival was 13.5 months. Neutropenia was the most common adverse event (52.6%), of which 13.1% was in grade 3 - 4. Diarrhea accounted for 36.8%, only one of which was in grade 3 (2.6%). Only one patient had hand - foot syndrome (2.6%).*

Conclusion: *TS1-Cisplatin regimen in metastatic gastric cancer had a good response rate while being safe and tolerable.*

Keywords: *Advanced gastric cancer, TS1, cisplatin*

I. INTRODUCTION

Gastric cancer is one of the most common cancers in many countries around the world as well as in Vietnam. According to GLOBOCAN 2020, gastriccancer is the sixth most common cancer in terms of incidence rate and the 5th most common cause of cancer - related death [1]. In Vietnam, gastric cancer ranks 4th in incidence and 4th in mortality [1]. The incidence of gastric cancer has decreased markedly, but this disease remains one of the leading causes of death.

Although many advances in diagnosis have been made, many gastric cancer cases are still detected in locally advanced or metastatic stages. In these settings, systemic chemotherapy has become the cornerstone of treatment. Of all chemotherapy regimens, fluoropyrimidine plus platinum agent is currently considered as the standard regimen in the first-line treatment of advanced - stage gastric cancer worldwide [2,3].

TS-1 is a novel oral fluoropyrimidine derivative, first approved in Japan in 1999. Currently, TS-1 plus Cisplatin has become the standard chemotherapy regimen for gastric cancer in this country. Phase III clinical trials have demonstrated the superiority in efficacy and safety of this combination regimen in the first - line treatment of advanced gastric cancer, significantly improving both progression - free survival up to 6.0 months and overall survival up to 13.0 months [4,5].

In Vietnam, TS-1 plus Cisplatin has been applied in clinical practice to treatmetastatic gastric cancer for the past few years. However, so far, there are still very few studies that fully evaluate the survival outcomes as well as the adverse effects of this regimen in Vietnam. Therefore, we conducted the study to evaluate the treatment results of the TS1-Cisplatin regimen in the first - line treatment ofmetastatic gastric cancer at Hanoi Medical University Hospital.

II. METHODS

A retrospective descriptive study was carried out on 38 metastatic gastric cancer patients treated with TS-1 plus Cisplatin as first - line regimen at Hanoi Medical University Hospital from January 2018 to December 2021. This study was approved by the Director Board of Hanoi Medical Univerisity Hospital. All information was only used for scientific purposes.

Inclusion criteria were: Adenocarcinoma gastric cancer patients; Metastatic gastric cancer patients with measurable target lesions; Patients received TS1-cisplatin as first - line regimen in metastatic setting; ECOG performance status 0, 1, 2; Adequate liver, kidney, and bone marrow function; Patients with adequate information in medical records, including treatment response, progression - free survival, overall survival and toxicities.

Exclusion criteria were: Patients had synchronoussecond cancer; Pregnancy or breastfeeding women.

Medical record of all patients were collected. Patients were evaluated for treatment - related toxicities at the day before the next cycle, and for response after three cycles.

Studyendpoints:Treatmentresponse,progression-free survival, overall survival, hematologictoxicities, and non-hematologic toxicities.

Statistical analysis was performed with the use of SPSS 20.0.

III. RESULTS

Table 1: Clinicopathological characteristics

Characteristics		**N**	**Rate (%)**
Mean age		**57.4 (32-70)**	
Sex	Male	29	76.3
	Female	9	23.7
Performance status	PS 0	11	28.9
	PS 1	21	55.2
	PS 2	7	18.4
Numbers of metastatic sites	1	17	44.7
	≥ 2	21	55.3

Mean age was 57.4. Male:female ratio = 3.2:1. Most patients had good performance status (PS 0,1 - 84.2%).

Table 2: Number of chemotherapy cycles

Number of chemotherapy cycles	**N**	**Rate(%)**
3	8	21.1
4	7	18.4
5	7	18.4
6	16	42.1
Total	38	100

The number of total cycles was 183. All patient was treated with at least 3 cycles. 16 patients received 6 cycles (42.1%).

Table 3: Treatment dose

Treatment dose	**N**	**Rate (%)**
≤ 85% standard dose	8	21.1
> 85% standard dose	30	78.9
Total	38	100

Most patients received doses higher than 85% of the standard dose (78.9%)

Table 4: Response rate after three cycles

		N	**Rate (%)**	**Total (%)**
Response	Complete response	5	13.2	55.3
	Partial response	16	42.1	
Non-response	Stable disease	8	21.1	44.7
	Progression disease	9	23.6	

The response rate was 55.3%, in which 5 patients had complete responses (13.2%). The stable disease rate was 21.1% and 9 patients progressed (23.6%).

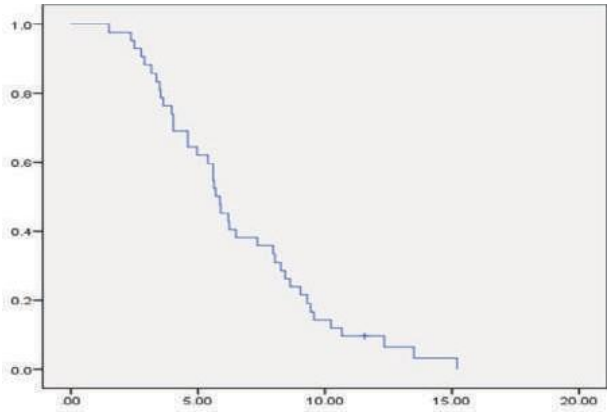

Figure 1: Progression free survival
Median progression - free survival (mPFS) was 5.7 months. Progression - free rates for 3 months, 6 months, and 12 months were 84.2%, 45.2%, and 7.1%.

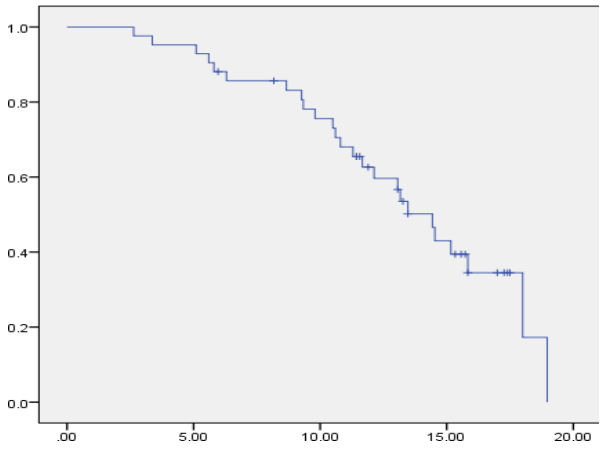

Figure 2: Overall survival
Median overall survival (mOS) was 13.5 ± 1.08 months. Survival rate for 12 months was 47.3%

Table 5: Hematologic toxicities

Toxicities	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%	n	%
Neutropenia	18	47.4	2	5.3	13	34.2	4	10.5	1	2.6
Anemia	12	31.6	14	36.8	12	31.6	0	0	0	0
Thrombocytopenia	31	81.6	4	10.5	3	7.9	0	0	0	0-

52.6% had neutropenia, most were in grade 1-2 (15 patients - 39.5%). 5 patients (13.1%) had grade 3-4 neutropenia. Anemia rate was 68.4%, all of which were in grade 1 (36.8%) or grade 2 (31.6%). Only 7 patients had thrombocytopenia (18.4%); all were in grade 1 or grade 2.

Table 6: Non - hematologic toxicities

Toxicities	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%	n	%
Creatinin	37	97.4	1	2.6	0	0	0	0	0	0
AST	36	94.7	2	5.3	0	0	0	0	0	0
ALT	35	92.1	3	7.9	0	0	0	0	0	0
Nausea, vomiting	19	50	13	34.2	6	15.8	0	0	0	0
Diarrhea	24	63.1	11	28.9	2	5.3	1	2.6	0	0
Hand - food syndrome	37	97.4	1	2.6	0	0	0	0	0	0
Peripheral nervous toxicities	33	86.8	5	13.2	0	0	0	0	0	0

Diarrhea was the most common non - hematologic adverse event (36.8%), but only one patient (2.6%) had grade 3 toxicity. None had grade 3 or grade 4 liver/renal toxicities. 5 patients had peripheral nervous toxicities (13.2%). Only one patient had hand food syndrome (2.6%).

IV. DISCUSSION

In our study, after three cycles of TS1-cisplatin chemotherapy, 21 patients had an objective response (55.3%), of which 5 patients achieved a complete response (13.2%) and 16 patients achieved a partial response (42.1%). This result was similar to the results in the study on Japanese patients of Koizumi et al (2015), with the overall response rate accounting for 54%, while higher than the figure in the study on European patients by Ajani et al (2013) with the overall response rate accounted for 29.1%. [4,6]. This may be attributable to the difference in ethnic characteristics since our participants shared many similarities with Japanese patients in Koizumi's study.

In our study, median progression - free survival (mPFS) was 5.7 months (4.97 - 6.42 months). This result is equivalent to the result of To Nhu Hanh (2012) with ECX regimen (6.04 months); slightly higher than that of Nguyen Van Hung (2017) with the FOLFIRI regimen (5.1 months) and Nguyen Khanh Ha (2019) with the TCX regimen (5.4 months) [7,8,9]. Thus, TS-1 plus cisplatin regimen was comparable with other common regimens in terms of efficacy. Median overall survival was 13.5 ± 1.08 months. Of the 38 patients, 16 were still alive up to now, and the longest follow-up in a living patient was 19.3 months. The results of our study are equivalent to the study of Koizumi et al (2008) with the median overall survival of 13 months in advanced gastric cancer patients treated with the same regimen [4].

In our study, neutropenia was recorded in 52.6% of patients, most of whom were in grades 1-2 (39.5%). Patients with grade 3-4 neutropenia were used G-CSF (Filgrastim 300 mcg/day) subcutaneously daily, check blood count continuously until white blood cell count returns to normal. No patient suffered from febrile neutropenia. According to the study of Koizumi et al(2008), the overall rate of leukopenia is 70%, of which grade 3-4 leukopenia accounts for 11% [4]. Anemia is also one of the common manifestations in patients with advanced-stage gastric cancer. Causes of anemia may result from bleeding in the tumor, poor diet, vitamin B12 deficiency due to previous radical gastrectomy. In our study, anemia accounted for 68.4%, of which 14 patients with grade 1 anemia (36.8%) and 12 patients with grade 2 anemia (31.6%). There were no patients with grade 3 and grade 4 anemia. No patients required blood transfusion or had treatment interruption due to anemia.

Our study did not record any grade 3-4 liver or renal toxicity cases. There was one patient with grade 1 creatinine level elevation. His cisplatin dose was reduced to less than 85% of the standard dose and monitored throughout the course of treatment. No further creatinine level elevation was observed afterward. Besides, there were 2 patients with grade 1 elevation of AST and 3 patients with grade 1 elevation of ALT. All of the above patients had no clinical manifestations and did not need treatment breaks.

Regarding other toxicities, vomiting and nausea were still common side effects, accounting for 50% of cases (n=19), mainly nausea and mild vomiting. No patient had severe vomiting. Diarrhea accounted for 36.8% of cases, mainly in grade 1. According to some studies comparing regimens containing 5-FU intravenously versus TS-1 orally, the proportion of patients experiencing gastrointestinal side effects such as diarrhea was higher in the TS-1 treatment group than in the 5-FU intravenously group [10,11]. This suggests that the gastrointestinal mucosal toxicity of TS-1 is higher than that of infusion 5-FU. However, we did not record any cases of severe diarrhea in our study. Studies also showed that although diarrhea is the main dose-limiting toxicity of TS-1 in Westerners due to their higher activity of cytochrome P-450, TS-1 orally still harbors promising efficacy on this population when carefully monitored and adjusted dose [12].

Our study showed that hand-foot syndrome (HFS) was found in only 1 patient (2.6%) and was mild, causing mild discomfort and little effect on the patient's quality of life. Other studies also showed that HFS occurs in about 50% of patients treated with capecitabine monotherapy, with about 10% in severe severity [7]. Thus, compared with capecitabine - another oral 5-FU derivation, TS-1 is associated with much fewer HFS incidences. Although HFS is not life-threatening, it does cause damage to areas of the skin that contain many sensory nerve endings and are responsible for important daily activities. Therefore, TS-1 is recommended to reduce toxicity on hands and feet while still maintaining the therapeutic effect of the 5-FU chemical group.

V. CONCLUSION

TS1-Cisplatin regimen in metastatic gastric cancer patients has encouraging efficacy with a

response rate of 55.3%, the median overall survival time of 13.5 months, while is safe and well-tolerated. Most patients taking this regimen would benefit from reducing the incidence of hand - foot syndrome.

REFERENCES

1. Sung H, Ferlay J, Siegel RL et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021;71(3): 209-249.
2. Kobayakawa M, Kojima Y. Tegafur/ gimeracil/ oteracil (S-1) approved for the treatment of advanced gastric cancer in adults when given in combination with cisplatin: a review comparing it with other fluoropyrimidine-based therapies. Onco Tagets and Ther. 2011;4:193-201
3. Wagner AD, Grothe W, Haerting J, Kleber G et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006; 24(18): 2903-2909.
4. Koizumi W, Narahara H et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9: 215-221.
5. Boku N, Yamamoto S, Fukuda H et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. The Lancet Oncology. 2009;10(11): 1063-1069.
6. Ajani JA, Buyse M, Lichinitser M et al. Combination of Cisplatin/S-1 in the treatment of patients with advanced gastric or gastroesophageal adenocarcinoma: Results of noninferiority and safety analyses compared with Cisplatin/5-fluorouracil in the First-Line Andvanced Gastric Cancer Study. European Journal of Cancer. 2013;49:3616-3624.
7. Khanh Ha Nguyen. Evaluating the treatment results of TCX regimen in recurrent or metastatic gastric cancer. Medical Thesis. 2019. Hanoi Medical University.
8. Nhu Hanh To. Evaluating the treatment results of EOX regimen in inoperable advanced gastric cancer. Medical Thesis. 2012. Hanoi Medical University.
9. Van Hung Nguyen, Hong Thang Vu, Hai Dang Do, et al. Evaluating the treatment results of FOLFIRI regimen in advanced gastric cancer. Vietnam Medical Journal. 2017;459.
10. Li Y, Qiu M, Xu J. S-1 plus cisplatin versus fluorouracil plus cisplatin in advanced gastric or gastro-esophageal junction adenocarcinoma patients: a pilot study. Oncotarget. 2015;6(33):35107-35115.
11. Boku N, Yamamoto S, Fukuda H et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomized phase 3 study. The Lancet Oncology. 2009;10(11): 1063-1069.
12. He M, Wu W, Wang F et al. S-1-Based Chemotherapy versus Capecitabine-Based Chemotherapy as First-Line Treatment for Advanced Gastric Carcinoma: A Meta-Analysis. PLoS ONE. 2013;8(12): e8279