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TREATMENT EFFICACY AND SOME ADVERSE EFFECTS OF CHEMOTHERAPY REGIMENS CONTAINING TS-1 IN INOPERABL GASTRIC CANCER

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ABSTRACT

Objectives: *To evaluate the effectiveness and associated adverse effects of chemotherapy regimens containing TS-1 in patients with inoperable gastric cancer.*

Subjects and methods: *Prospective study, cross-sectional description, longitudinal follow-up in 68 patients with inoperable gastric cancer treated with systemic chemotherapy using the chemical regimens TS-1 alone, TS-1 combined with Oxaliplatin and TS-1 combined with Cisplatin at Central Military Hospital 108 from 10-2019 to 6-2023. Treatment response was assessed using the RECIST, adverse effects were evaluated using the CTCAE v.3.0. while survival time was estimated via the Kaplan-Meier method.*

Results: *The average age of patients was 63.5 ± 10.68. Common metastatic organs included peritoneum (47.1%), liver (36.8%) and lymph nodes (29.7%). Most patients (89.7%) had metastases in multiple organs, with 47.1% affecting two or more sites. The partial response rates and disease control rates were 38.2% and 82.3%, respectively, with no patients achieving complete response. The median progression-free survival was 6.5 months. The median overall survival was 10.9 months. The most common adverse effect was neutropenia in 55.9% (22.1% grade 3 or higher). Hand-foot syndrome and neuropathy were uncommon and mostly mild.*

Conclusions: *The treatment 68 patients of inoperable gastric cancer with chemotherapy containing TS-1 had disease control rates and progression-free survival times comparable to those in published phase 3 trials, and controlled adverse events.*

Keywords: Stomach cancer, metastatic, TS-1, inoperable gastric cancer.

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1. INTRODUCTIONS

Gastric cancer is one of the most common cancers. In Vietnam, the new incidence rate ranks 5th and the death rate from stomach cancer ranks 3rd [1]. The main primary of death in gastric cancer is metastasis. According to an examination of SEER data from 1973 to 2014, at the time of diagnosis, 24.6% of the 157,258 gastric cancer patients were diagnosed with local stage, 37.9% with regional stage, and 34.4% with metastatic stage [2].

Thanks to the development of diagnostic methods, the detection rate of metastatic stomach cancer is increasing. In the Netherlands, the proportion of patients presenting with metastatic disease at the time of diagnosis increased from 24% in 1990 to 44% in 2011 [3]. In Jing Xu et al's study, out of 300 patients who experienced relapse following cured treatment, 191 individuals (63%) developed distant or peritoneal metastases [4].

Treatment guidelines recommend combining targeted therapy and systemic chemotherapy for metastatic gastric cancer [5], [6], [7]. The proportion of gastric cancer patients receiving targeted therapy or immunotherapy is significant (Her-2 (+) rate ranges from 3.8% to 36.6% [8]; CPS rate ≥ 5 is about 29.1% [9]; the MSI rate is high at about 6.74% [10]). The adoption of this treatment in Vietnam remains limited due to several cause, including high costs, insufficient testing facilities, and medicine supply issues, resulting in a significantly low number of patients receiving the therapy. Systemic chemotherapy remains the mainstay of treatment for most patients with metastatic gastric cancer. Treatment guidelines recommend combining a cisplatin chemical (cisplatin, carboplatin) with a Fluouracin chemical (5-FU, Xeloada, Tegafur...) [5], [6], [7].

TS-1 is an oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2,4-dihydropyrimidine (CDHP) and potassium oxonate (Taiho Pharmaceutical Company, Tokyo, Japan). CDHP reversibly antagonizes the activity of dihydro pyrimidine dehydrogenase (DPD), the rate-limiting enzyme that degrades fluorouracil, causing fluorouracil to maintain high concentrations in serum and tumors for long periods of time. Potassium oxonate inhibits fluorouracil phosphorylation in the gastrointestinal tract, lowering the harmful effects of fluorouracil on the gastrointestinal tract, which is the most dose-limiting toxicity of fluorouracil [11]. While numerous phase 3 clinical trials have highlighted the benefits of TS-1 in treating gastric cancer [11], [12], [13]. TS-1 contributes to increasing disease-free survival, overall survival and reducing adverse events (especially hand-foot syndrome and neuropathy). Limited reports exist in Vietnam on this problem.

We conducted this study to evaluate the effectiveness and some adverse effects of the TS-1 regimens alone (TS1-DT), TS-1 combined with Oxaliplatin (SOX) and TS-1 combined with Cisplatin (Cis-TS1) in the treatment of patients with inoperable gastric cancer.

2. SUBJECTS AND METHODS

2.1. Subjects

68 patients with inoperable gastric cancer treated with regimens TS-1 alone, SOX and Cis-TS1 at Central Hospital 108 from October 2019 to June 2023.

- Patient selection criteria: age ≥ 18; No chemotherapy treatment for metastatic recurrence; ECOG = 0-2 points; Ensure the function of major organs (white blood cell count ≥ 3.5 G/L; neutrophil count ≥ 2.000/L; platelet count ≥ 100.000/L; hemoglobin concentration ≥ 9.0 g/dL; serum creatinine concentration ≤ 106,8 µol/l; serum AST and ALT concentration ≤ 150 U/L); consent to participate in the study.

- Exclusion criteria: active infection; active infection; serious complications of gastric cancer; severe chronic diseases (such as diabetes, uncontrolled hypertension...), and other cancers..

2.2. Methods

- Study design: prospective, cross-sectional description, longitudinal follow-up study.

- Sampling and sample size*:* choose the entire sample, convenient sample size.

- Procedure:

+ Ask questions, examine patients, do tests and collect information about clinical and laboratory characteristics.

+ Choice of treatment regimens: based on the performance of status (PS), Co-morbidity, side effect of the regimen and the patient's wishes and desires, one of the regimens was choosen: TS-1 alone, SOX, Cis-TS1. In particular, no therapy in conjunction with Cisplatin or Oxaliplatin was chosen in patients with renal failure; PS = 2 points; numerous co-morbidities. No treatment in combination with Cisplatin in patients over 65 years of age. No treatment in combination with Oxaliplatin in patients over 75 years of age. Chemotherapy treatment:

* TS-1 regimen alone: The TS1 dose was 80 mg/day for body surface area (BSA) < 1.25 m^2, 100 mg/day for BSA ≥ 1.25 to < 1.5 m^2, and 120 mg/day for BSA ≥ 1.5 m^2. TS-1 was given orally twice daily for 2 consecutive weeks, 3-week cycle. The treatments were continued until progressive disease, unacceptable toxicity, the patient refused treatment.

* SOX regimen: TS-1 dose was similar to TS-1 dose in TS-1 regimen alone. Oxaliplatin: dose 100 mg/m2, mixed with 5% Glucose solution, intravenous infusion on day 1 of each cycle. The cycle was every 3 weeks. The treatments were continued until progressive disease or the patien experiences unacceptable toxicity.

* Cisplatin-TS1 regimen: TS-1 was given orally twice daily for the first 3 weeks of a 5-week cycle. TS-1 dose is similar to TS-1 dose in TS-1 regimen alone.

Cisplatin was administered at 60 mg/m^2 as an i.v. infusion with adequate hydration on day 8 of each cycle. The treatments were continued until progressive disease, unacceptable toxicity, the patient refused treatment.

+ Handling situations during treatment:

Treatments were temporarily suspended if leukocyte < 2.0 G/l; granulocytes < 1.0 G/l; platelets < 70 G/l; grade 3 or higher rash.

TS-1 was temporarily stopped if Creatinine > 1.5 mg/ml; diarrhea or grade 2 or higher stomatitis.

Stop chemotherapy completely if there is no improvement after 4 weeks of temporarily suspend treatment.

In patients experiencing febrile neutropenia, neutropenia; leukopenia, thrombocytopenia, or grade 3 or higher rash when recovering in the next treatment, dose was reduced to 80%.

Patients with febrile neutropenia, neutropenia; leukopenia, thrombocytopenia, creatinine > 1.5 mg/ml; grade 3 or higher stomatitis when recovering in the next treatment, TS-1 was decreased by 20 mg/day.

+ Palliative care (symptomatic treatment) were provided for all study patients. In the first line (study regimens), patients do not receive any specific treatment other than the study protocol.

+ When the disease progressed, patients received second line treatment or palliative care depending on the specific patient.

- Research variables: patient characteristics (gender, age, co-morbidities, perfomance status, histopathology); Treatment plan results (number of chemotherapy cycles); inoperable status (extensive invasion, synchronuos metastasis, metachronous distant metastasis), response rate, overall survival time, progression-free survival time and some adverse events.

- Evaluation: record clinical symptoms, blood test results before each treatment cycle or when the patient has abnormalities. Computed tomography or magnetic resonance imaging every 6 weeks until the disease progresses.

- Assessments: general health conditions were assessed using ECOG [14]. Histopathological classification was completed using WHO 2019 and the 3-tier grading system [15]. The treatment response was assessed using the response assessment criteria in solid tumours (RECIST, version 1.0) [16]. Undesirable effects were assessed using Common Terminology Criteria for Adverse Events, version 3.0. (CTCAE 3.0) [17]. Diagnosis of gastric cancer is based on histopathological results. Determination of inoperable gastric cancer according to the recommendations of the American Cancer Network [6]. Assessment of the extent of invasion when the tumor has invaded the mesenteric root or the lymph nodes around the aorta, invading or enveloping major vascular structures. Assessment of synchronous metastasis when metastasis is detected within 6 months from the detection of primary cancer. Assessment of metachronous metastasis when metastasis is detected more than 6 months after the detection of primary cancer.

- Analysis of research data: data pertaining to the research disease were collected and entered into Excel software, with subsequent analysis conducted using SPSS 20.0. Results were presented as mean ± standard deviation and percentage values. Survival estimates were determined using the Kaplan-Meier method.

- Ethical issues: The study complies with the World Medical Association Declaration of Helsinki for ethical principles for medical research involving human subjects. The treatment protocols used in the study complied with the treatment guidelines of the Vietnamese Ministry of Health, which are widely used in clinical practice. All patient personal information will only be used for the purpose of improving the quality of care and treatment and will be kept confidential. All research subjects clearly understand the purpose of the research and agree to participate in writing and can withdraw from the research at any time.

3. RESULTS

3.1. Patient's characteristics

Table 1. Patient's characteristics (n = 68)

Characteristics		N°. of patient	Percentage
Gender	Male	55	80.9
	Female	13	19.1
Age	Range	31 - 81	
	Median	63.5 ± 10.68	
Comorbidity	No	42	61.7
	Yes	26	38.3
	Cardiovascular disease	12	17.6
	Diabetes	7	10.3
	Other	17	25
Performance status (ECOG)	0	17	25
	1	45	66.2
	2	6	8.8
Histology (adeno-carcinoma)	Well differentiated	1	1.5
	Moderately differentiated	24	35.3
	Poorly differentiated	26	38.2
	Other	17	25.0

Characteristics		Nº. of patient	Percentage
Inoperable condition	Locoregionally advanced	2	2.9
	Synchronuos	48	70.6
	Metachronuos	18	26.5
Number of metastatic locations	1	7	10.3
	≥ 2	61	89.7
Metastatic organs	Peritoneal	32	47.1
	Liver	25	36.8
	Lung	13	19.1
	Lymph	27	29.7
	Other	16	23.6
Number of metastatic organs	1	36	52.9
	≥ 2	32	47.1

Male/female ratio = 4.2/1, the average age of disease was 63.5 ± 10.68, common co-morbidities were: diabetes (10.3%), hypertension (17.6%). Synchronuos metastases accounted for 70.6% and 75% of patients having a perfomance status of 1-2 points. Common metastatic organs were: peritoneum (47.1%) and liver (36.8%). Patients often had metastasis to multiple sites (89.7%) with 47.1% having metastasis to 2 or more organs.

3.2. Treatment plan results

Table 2. Results of implementing the treatment plan

Number of treatment cycles	TS-1 alone		SOX		Cis-TS1	
	n	%	n	%	n	%
1-3 cycles	4	44.4	19	34.6	1	25.0
3-6 cycles	3	33.3	10	18.2	1	25.0
6-9 cycles	1	11.5		27.2	1	25.0
> 9 cycles	1	11.5	11	20	1	25.0
Total	9	100	55	100	4	10

The result of implementing the treatment plan in 68 patients studied showed that the number of treatment cycles implemented was at least 1 cycle, the maximum was 25 cycles. Of which, 35.3% (24 patients) received 1 to 3 cycles, 20.6% (14 patients) received 3 to 6 cycles, 25% (17 patients) received 6 to 9 cycles and 19.1% (13 patients) received more than 9 cycles.

3.3. Treatment response and adverse effects

Table 3. Response to treatment

Response	TS-1		SOX		Cis-TS1		Total	
	n	%	n	%	n	%	n	%
Complete respone	0	0	0	0	0	0	0	0
Partial respone	0	0	24	43.6	2	50	26	38.2
Stable disease	5	55.6	24	43.6	1	25	30	44.1
Progressive disease	4	44.4	07	12.8	1	25	12	17.7
Total	9	100	55	100	4	1	68	100

No patient achieved a complete response. The disease control rate (partial response + stable disease) was 82.3%, disease progression was 17.7%.

Table 4. Adverse effects

Adverse effects	All grade		Grade 3 or more	
	n	%	n	%
Treatment-related deaths	0	0	0	0
Febrile neutropenia	13	19.1	10	14.7
Leukopenia	31	45.6	2	2.9
Neutropenia	38	55.9	15	22.1
Anemia	41	60.3	5	7.3
Thrombo-cytopenia	5	7.3	0	0
Hand-foot syndrome	5	7.3	2	2.9
Sensory neuropathy	7	10.3	2	2.9

No patient deaths were related to treatment. The main hematological adverse effects were neutropenia (55.9%), with 22.1% grade 3 or higher and 19% febrile neutropenia (14.7% grade 3 or higher). The rate of hand-foot syndrome was 7.3% and sensory neuropathy was 10.3%.

3.4. Survival time

The shortest patient follow-up was 3 month, the longest follow-up patient was 21 months, and the

average follow-up time was 9 months. Progression-free survival (RFS) and overall survival (OS) are shown in Figures 1 and 2.

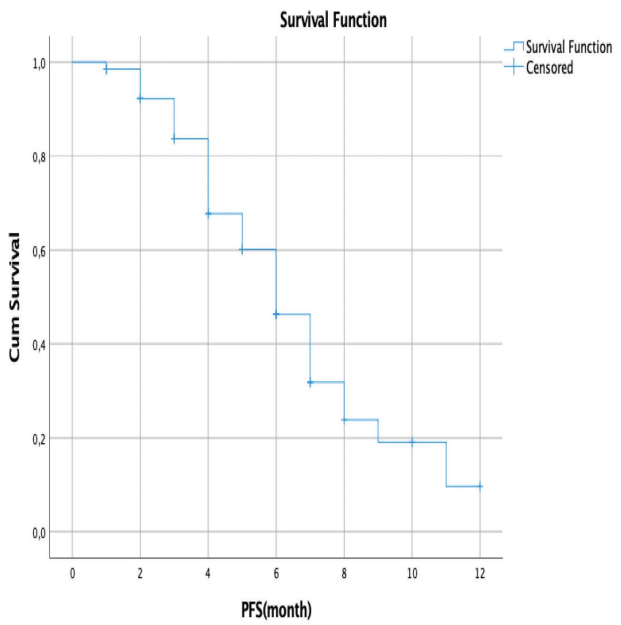

Figure 1. Kaplan-Mayer curve that estimates the Progression-free survival.

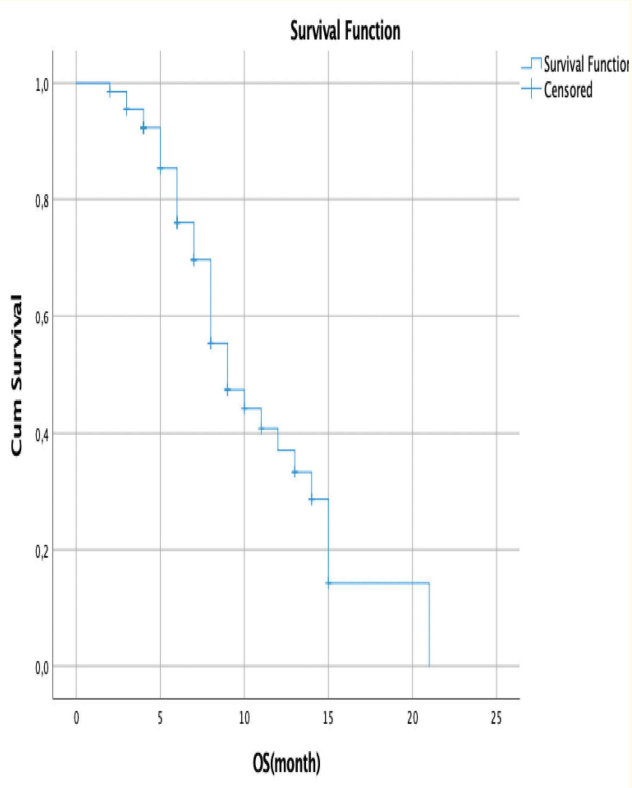

Figure 2. Kaplan-Mayer curve that estimates the overall survival.

Medians free-progressive survival was 6.5 month and medians overall survival was 10.9 month.

4. DISCUSSIONS

4.1. Participant characteristics

Male/female ratio = 4.2/1, the mean age of patients was 63.5 ± 10.68 years (range 31 to 81 years). This result is consistent with some published studies, As in the SPIRIT study 2008 (the male/female ratio was 3.0/1, from 28 to 74 years old, the average age was 62 [11]), in the study conducted by Y. Yamada (the male/female ratio = 2.9/1, from 21 to 85 years old, the average age was 65 [18]).

In 68 patients, the number of patients with co-morbidities accounted for 38,2% (cardiovascular disease was 17.6%, diabetes was 10.3%). Co-morbidities affected the perfomance status (PS), thereby affecting the treatment process. Most patients had a PS of 0-1 points (91.2%), which was suitable for chemotherapy indications (patients had a PS of ≤ 2 ECOG points) and was similar to the results of the SPIRIT study in 2008 (patients with a PS of 0-1 ECOG points accounted for 97% in the TS-1 monotherapy group and 98% in the TS-1 combined with Cisplatin group [11]).

In the study of Vu Van The (2015), the poorly differentiated and undifferentiated types accounted for the highest proportion (72.9%), the moderately differentiated type accounted for 25%, and the well differentiated type accounted for 2.1% [13]. In our study, the well differentiated type also accounted for a low proportion (1.5%) but the poorly differentiated type (38.2%) was lower than in the study of Vu Van The. This difference may be due to the small size of our study' sample.

In the SPIRIT study, 80% of patients had metastases (synchronous metastasis) + extensive invasion, and 20% had metastatic recurrence (metachronous metastasis). These characteristics in our study were 75% and 26.5%, respectively. The common metastatic sites were: peritoneum (47.1%), liver (36.8%), lymph nodes (29.7%), and lungs (19.1%). Up to 47.9% of patients had metastases in 2 or more organs, and up to 89.7% had metastasis in 2 or more locations. Peritoneal metastasis and liver metastasis were two common metastatic sites in the late stage, with significantly poor prognosis in the pooled analysis of Ian Chau et al. (2004) [19]. Research by Nguyen Minh Phuong (2020) also showed that in patients with metastatic gastric cancer, the most common metastatic sites were the peritoneum (47.6%), liver (31%) and lungs (23.8%) and there are 53.7% of patients had metastases in 2 or more locations [12].

4.2. Implementing the treatment plan

In general, if a patient cancer with distant metastasis that can not be cured, systemic therapy is continued until the disease progresses or the patient can not tolerate the side effects. In the SPIRIT study (2008), the number of cisplatin-TS1 cycles was from 1 to 11 cycles (average 4 cycles), the number of TS1 monotherapy cycles was from 1 to 12 (average 3 cycles) [11]. In the Yamada study (2015), the number of SOX was from 1 to 43 (average 7 cycles), the number of CS cycles was from 1 to 19 (average 7 cycles) [18]. In this study, 22.3% of patients in the TS-1 monotherapy group, 47.2% of patients in the SOX group and 50% of patients in the Ci-TS1 group received more than 6 chemotherapy cycles. We believe that patients in the TS1-alone group often have the weakest physical condition so the number of chemotherapy cycles received is also the least. On the other hand, the most adverse events in patients receiving regiment have TS1 is hematological side effects. There are more and more hematopoietic stimulating factors as well as new generations of antibiotics to prophylaxis and treatment of febrile neutropenia has made the use of chemotherapy more easy.

4.3. Response to treatment

Our study showed that: in 9 patients were treated with TS1 alone, 5 patients achieved stable disease, no patients achieved complete response and and partial response while disease control rate was 55.6%. In 55 patients who were treated with SOX regimen, no patients achieved complete response, 24 (43.6%) patients achieved partial response, 24 (43.6%) patients had stable disease, disease control rate was 87.2%. In 4 patients treated with Cis-S1 regimen, 2 patients had partial response (50%), 1 patient had stable disease, disease control rate was 75%. In the SPIRIT trial, the S-1 + cisplatin group had a overall response (complete response + partial response) of 54% (from 43 to 65), the S-1 monotherapy group had a overall response of 41% (23 to 41) [11]. In the G-SOX study by Y. Yamada, SOX was the first-line treatment for advanced gastric cancer in Japan. The SOX group had a overall response of 54.2%, the disease control rate was 85.2%. The cisplatin + TS1 group had a overall response of 52.2%, the disease control rate was 81.8% [18].

Thus, in our study, the overall response rate of the Cis-S1 group was similar to that of the SPIRIT study, the S-1 group was lower than the SPIRIT study, and that of the overall response rate of the SOX group was lower than the G-SOX study (43.6% vs. 54.2%), this difference might be attributed to the small number of patients in our study. However, the disease control rate in our study was comparable to the results of the above two trials.

4.4. Treatment-related adverse events

In the SPIRIT study, the most common adverse event were hematopoietic events. In the TS-1 + Cisplatin group, the rate of neutropenia was 74% (40% had grade 3 or higher and 3% had febrile neutropenia), hand-foot syndrome occurred in 9% (no grade 3 or higher), and peripheral neuropathy was 4% (no grade 3 or higher). In the TS-1 group, the rate of neutropenia was 42% (11% had grade 3 or higher and 1% had febrile neutropenia), hand-foot syndrome occurred in 12% (no grade 3 or higher), and peripheral neuropathy was 0.7% (no grade 3 or higher) [11]. In our study, the main hematological adverse events were neutropenia (55.9%), with 22.1% grade 3 or higher and 19% febrile neutropenia (14.7% grade 3 or higher). The incidence of hand-foot syndrome was 7.3% and sensory neuropathy was 10.3%. The incidence of febrile neutropenia grade 3 or higher and sensory neuropathy was higher in the study than in the SPIRIT study, however, within the manageable range, there were no treatment-related deaths.

4.5. Survival time

In this study, the median progression-free survival (PFS) was 6.5 months (95% CI 5.6-7.4). Similarly in the SPIRIT study, the median progression-free survival time in the S-1 group plus cisplatin was 6 months [3.3 to 12.9], the S-1 group alone was 4 months [2, 1 to 6.8]. In the G-SOX study, the median progression-free survival was 6.9 months [5.5 to 8.3]. The progression-free survival time in our study was comparable to the two published phase 3 studies.

Overall survival (OS): the median OS in our study was 10.9 months (95% CI; 9.1-12.6). In the SPIRIT study, the median OS in the S-1 plus cisplatin group was 13 months (7.6-21.9 months), and the S-1 monotherapy group was 11 months (5.1-19.8 months) [11]. In the study by Y. Yamada et al., the median OS in the SOX group was 14.1 months (13.0-15.8) [18]. The overall survival in our study was slightly lower than the results in the above two trials. However, the overall survival depends on subsequent treatment (second line, third line, etc.)

5. CONCLUSIONS

The treatment of inoperable gastric cancer with chemotherapy containing TS-1 (TS-1 alone, TS-1 combined with Oxaliplatin and TS-1 combined with Cisplatin), in the 108 Hospital achieved disease control rates and progression-free survival times comparable to those in published phase 3 trials, and controlled adverse events.

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