Regorafenib treatment outcome for Taiwanese patients with metastatic gastrointestinal stromal tumors after failure of imatinib and sunitinib: A prospective, non-randomized, single-center study

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Abstract. The present study aimed to conduct a prognosis analysis of Taiwanese patients with metastatic gastrointestinal stromal tumors (GISTs), who are resistant to or were unable to tolerate imatinib or sunitinib, and were subsequently treated with regorafenib. The study considered the survival, potential prognostic factors and safety of these Taiwanese patients. A total of 28 patients with pre-treated metastatic GIST, receiving regorafenib treatment, were analyzed between April 2014 and December 2017. Data were collected prospectively, and patients were followed up for a median of 14.8 months. It was reported that 50% (10/20) of male patients and 50% (4/8) of female patients demonstrated response and clinical benefit to regorafenib. The median progression-free survival (PFS) and overall survival (OS) time in all patients receiving regorafenib were 4.4 and 29.3 months, respectively. Good performance status and disease control mediated by regorafenib were independently associated with a more favorable PFS time. Good performance status, higher pre-treated albumin level, lower neutrophil:lymphocyte ratio (NLR) and lower platelet:lymphocyte ratio (PLR) were independent favorable predictors of OS time. Overall, poor performance status and poor disease control predicted a less favorable PFS time in Taiwanese patients with GISTs, who were pre-treated with regorafenib. Meanwhile poor performance status, high NLR, PLR and low albumin level predicted a less favorable OS time.

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Abbreviations: GIST, gastrointestinal stromal tumor; PFS, progression-free survival; OS, overall survival; NLR, neutrophil:lymphocyte ratio; PLR, platelet:lymphocyte ratio; PDGFR, platelet-derived growth factor receptor; IM, Imatinib mesylate; PR, partial response; SD, stable disease; TKI, tyrosine-kinase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors; ECOG, Eastern Cooperative Oncology Group; TTR, time to response; TTP, time to progression; HFSRs, hand-and-foot skin reactions

Key words: regorafenib, treatment outcome, GISTs

Introduction

Gastrointestinal stromal tumors (GISTs) are the leading mesenchymal neoplasms of the gastrointestinal system, with an annual incidence rate of 13.7 per million individuals in Taiwan (1). Effective systemic treatments for GISTs were not available globally until 2001 (2). However, identification of the involvement of constitutively active transmembrane receptor KIT and platelet-derived growth factor receptor A (PDGFRA) signaling in GIST oncogenesis justified the use of small-molecule tyrosine-kinase inhibitors for the treatment of GIST (3). Imatinib mesylate (IM) selectively inhibits several protein tyrosine kinases, such as the intracellular ABL kinase, the chimeric BCR-ABL fusion oncoprotein of chronic myeloid leukemia, KIT and PDGFRs (4-7). The expression of the cell-surface transmembrane receptor KIT, with tyrosine kinase activity, is a major diagnostic biomarker of GIST. The current understanding is that frequent gain-of-function mutations of KIT occur in GISTs (3), causing constitutive activation of KIT signaling and resulting in uncontrolled cell proliferation and resistance to apoptosis (3). For advanced GIST, IM treatment also exhibited favorable results in terms of progression-free survival (PFS) and overall survival (OS) time (8), and several clinical trials have also reported promising effects of this targeted therapy in increasing PFS and OS time (6,9-11).

Although IM has been known to result in notable improvements in the PFS and OS time of patients with GIST, partial response (PR) and stable disease (SD) was documented in 54% of cases; however, ~28% of patients will develop advanced or metastatic GIST (5,6). The majority of patients with GIST will display drug resistance to imatinib and disease deterioration (12). A multi-target tyrosine-kinase inhibitor (TKI) that provides prolonged PFS time (27 weeks), compared with the placebo in a randomized phase III trial (13), was approved as the second-line targeted therapy for GIST after imatinib and

sunitinib; however, resistance to sunitinib also developed (14). Thus, novel TKIs are needed as an alternative option for patients with GIST, in the event that resistance to sunitinib resistance develops.

Regorafenib is another multi-kinase inhibitor that antagonizes various targets, including KIT, PDGFRA, vascular endothelial growth factor receptor, RAF1, BRAF, RET and fibroblast growth factor receptor, in *in vitro* analyses (15). An international, multicenter, randomized, placebo-controlled, phase III trial (GRID) (16) reported that the median PFS time was 4.8 months for the regorafenib-treated group and this was longer compared with placebo group by 0.9 months. Based on the GRID study, regorafenib was then approved by the Food and Drug Administration in February 2013 for metastatic or unresectable GIST after resistance to imatinib and sunitinib had developed. Asian patients enrolled in the phase III GRID trial were from Japan, Korea, China and Singapore, therefore the present study investigated the efficacy of regorafenib in a Taiwanese population.

The present prospective, non-randomized, single-center study aimed to assess the efficacy, prognosis and safety of regorafenib in inducing an objective response or SD in population of individuals with advanced inoperable/metastatic GIST, who either developed resistance to or could not tolerate the toxicity associated with imatinib or sunitinib. In addition, a literature review was conducted to elucidate the effect of regorafenib on GIST globally.

Materials and methods

Patients, study design and efficacy evaluation. Between April 2014 and December 2017, 40 patients were diagnosed with advanced inoperable/metastatic GIST histologically (17) and received regorafenib therapy. The clinical data was collected prospectively and reviewed retrospectively. Of note, regorafenib treatment has been reimbursed by National Health Insurance in Taiwan since August 2016 (16). While 18 patients were enrolled from the previous trial (18), 22 were enrolled from the health reimbursement program. In the present study, however, only 28 patients who were refractory or intolerant to imatinib and sunitinib and with measurable disease based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (19) were eligible for further analysis. There were 20 males and 8 females with a median age of 61 years (range, 36-71 years). In addition, these 28 patients had an Eastern Cooperative Oncology Group (ECOG) performance score of ≤3 and presented with adequate hepatic, renal and hematological functions. The dose of regorafenib was 160 mg daily in a 3-week on/1-week off schedule, every 4 weeks, orally. Regorafenib was not stopped, unless unmanageable toxicity or disease progression occurred or consent was withdrawn. Of note, regorafenib could be continued in spite of documented disease progression if a clinical benefit was evident to the treating physician. In contrast, postponement of treatment or lowering of the dose was considered in the event of adverse drug-associated side effect and dose re-escalation was allowed after these side effects were resolved. Regular monthly check-ups of participants included routine physical examinations and evaluations of their performance status, weight, complete blood count and serum chemistry, including aspartate aminotransferase, alanine aminotransferase and total bilirubin to measure hepatic function, creatinine for renal function, and T3, T4 and thyroid stimulating hormone for thyroid function. Standard computed tomography scans for each patient were performed every 3 months. Tumor size was determined by measuring the diameter of ≥5 target lesions and the largest dimension was used as a response evaluation indicator, according to the RECIST 1.1 criteria (19). Time to response (TTR=time point of the best response-time point of regorafenib administration) was defined as the interval for the best drug response during the treatment course. The time to progression (TTP=time point of disease progression-time point of regorafenib administration) was defined as the interval for the worse drug response with disease progression

Table I. Clinicopathological characteristics of patients with advanced GIST treated with regorafenib (n=28).

Characteristics	n	Range
Median age at time of, years		
Diagnosis of GIST	52	28-66
Diagnosis of metastasis	52	30-67
Start of imatinib	52	30-68
Start of sunitinib	58	35-68
Start of regorafenib	61	36-71
Sex, %		
Male/female	20/8	71.4/28.6
ECOG, %		
0-1/2-3	22/6	78.6/21.4
Genetic mutation, %		
Exon 9	5	17.86
Exon 11	6	21.43
Exons 11 and 17	10	35.71
Exons 11, 13 and 17	5	17.86
Wild-type	2	7.14
Median length of imatinib treatment, months	63.23	9.4-155.54
Median length of sunitinib treatment, months	21.91	2.69-67.91
Primary site, %		
Stomach	4	14.26
Small bowel	24	85.74
Metastatic site, %		
Liver	20	71.43
Peritoneum	18	64.29
Lung	3	10.71
Others	5	17.86
Prior failed TKI, %		
Imatinib	28	100.00
Sunitinib	28	100.00
Nilotinib	2	7.14

ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor; GIST, gastrointestinal stromal tumor.

Table II. Antitumor response of advanced gastrointestinal stromal tumor treated with regorafenib (n=24).

Response	n (%)	Sex, male/female, n	Median regorafenib duration, months	Median TTR/ TTP, months	Median OS, months
PR	4 (14.29)	3/1	15.21	6.16	21.05
SD	10 (35.71)	7/3	6.08	2.11	9.54
PD	10 (35.71)	8/2	3.09	2.46	11.69
N/A	4 (14.29)	2/2	0.46	N/A	N/A

PR, partial response; SD, stable disease; PD, progressive disease; N/A, not available; TTR, time to response; TTP, time to progression; OS, overall survival.

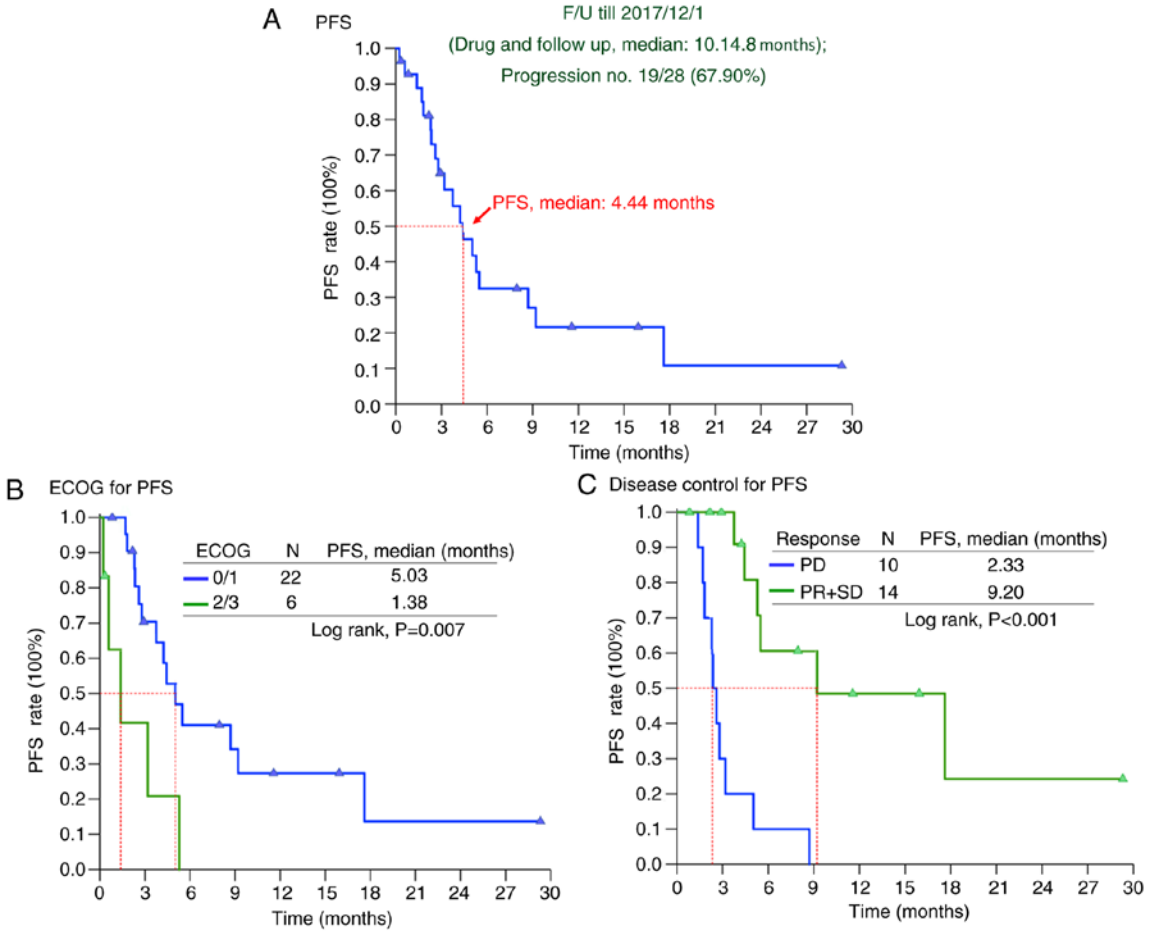

Figure 1. Survival analysis of PFS time. (A) Kaplan-Meier plot of the PFS time of 28 Taiwanese patients with advanced gastrointestinal stromal tumor treated with regorafenib, and in terms of (B) ECOG performance status and (C) response. PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; F/U, follow-up; PD, progressive disease; PR, partial response; SD, stable disease.

during the clinical course. PFS was defined as no disease progression after start of regorafenib treatment. OS was defined as the survival after regorafenib administration, and the endpoint of the present study was either GIST-associated death or December 2017. A total of 4 patients were excluded from the survival analysis due to 2 of them having received regorafenib <1 month prior to enrolment in the present study, 1 withdrew due to severe and intolerable adverse events, and 1 was lost to follow-up. The adverse events of regorafenib were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (20). The protocol of the present study was approved by The Institutional Review Board of the Chang Gung Memorial Hospital (approval no. 103-6044A3; Taoyuan, Taiwan), and written informed consent was provided by all patients for drug administration and analysis of tumor-associated genetic alteration.

Analysis of KIT and PDGFRA mutations. Sections (10-μm-thick) were prepared from formalin-fixed,

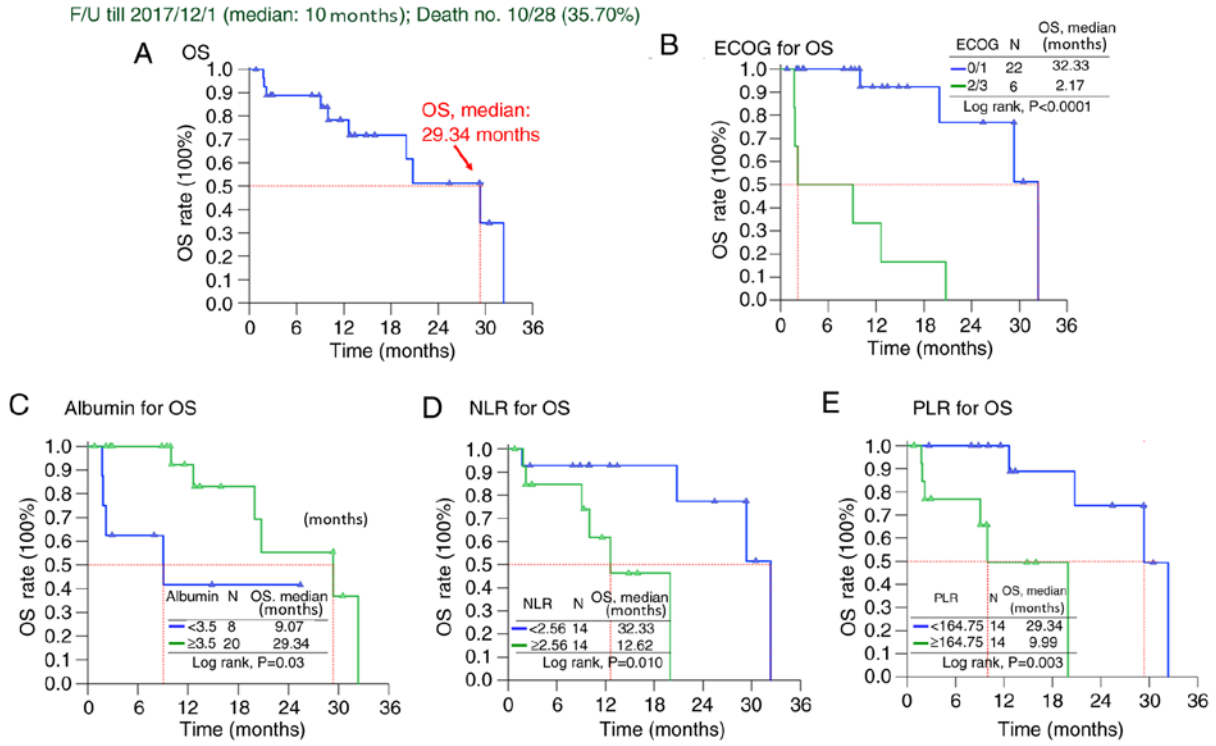

Figure 2. Survival analysis of OS time. (A) Kaplan-Meier plot of the OS time of 28 Taiwanese patients with advanced gastrointestinal stromal tumor treated with regorafenib, and in terms of (B) ECOG score, (C) albumin, (D) NLR and (E) PLR. ECOG, Eastern Cooperative Oncology Group; F/U, follow-up; NLR, neutrophil:lymphocyte ratio; PLR, platelet:lymphocyte ratio; OS, overall survival.

paraffin-embedded pretreatment specimens trimmed to enrich for tumor cells. Tissues were fixed with 10% formalin at room temperature for ≥24 h. Subsequently, PCR was performed as previously described (21) on the DNA isolated from these sections to amplify the genomic DNA sequences of *KIT* and *PDGFRA* by Professor CY Tzen at Cathay Memorial Hospital (Taipei, Taiwan). Sequences for mutations of *KIT* and *PDGFRA* were analyzed as described previously (21).

Statistical analysis. For descriptive statistics, all the data are presented as percentage of patients or mean. Kaplan-Meier and log-rank tests were performed for time-to-event analysis. Several potential variables impacting long-term outcomes, including PFS and OS time, were analyzed for significance, including age (<61 vs. ≥61 years), sex, ECOG performance status (score 0-1 vs. 2-3), mutational status (presence vs. absence exon 17 mutation), response [complete response + PR vs. SD vs. progressive disease (PD)], primary site and metastatic site of GIST, and parameters of the following: White blood cells with differential counts [neutrophil:lymphocyte ratio (NLR)], platelet counts, platelet:lymphocyte ratio (PLR), and hemoglobin and albumin levels. All aforementioned factors were analyzed using a Cox multivariate proportional hazard model if statistical significance was identified using univariate analysis. An 'enter-selection' procedure was used to select the most relevant prognostic factors and only factors that remained significant were included in the final model. All statistical analyses were performed using SPSS version 20.0 (IBM Corp). P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical features. Table I summarizes the demographic characteristics of 28 patients (20 males and 8 females; median age, 61 years; range, 36-71 years) with advanced inoperable/metastatic GIST treated with regorafenib. All patients had received imatinib and sunitinib treatment prior to regorafenib, and 2/28 (7.14%) had also received nilotinib. The median length of imatinib treatment was 63.23 months (range, 9.4-155.54 months) and that of sunitinib treatment was 21.91 months (range, 2.69-67.91 months). Most of the patients had a favorable ECOG score (22/28; 78.6%). While the small bowel was the leading primary site for GISTs treated with regorafenib (24/28; 85.74%), the liver was the leading metastatic site (20/28; 71.43%), followed by the peritoneum (18/28; 64.29%) and lungs (3/28; 10.71%). Out of the 28 patients with GIST with mutation data, exons 11 and 17 were the most common (n=10), followed by exons 11, 13 and 17 (n=5), exon 9 (n=5), exon 11 (n=6) and wild-type (n=2).

Treatment and outcomes. Regorafenib was administered to patients with pretreated metastatic GISTs, a starting dose of 160 mg/day was administered to all 28 patients. All patients were followed up after regorafenib administration at regular intervals until death or until December 2017. Table II summarizes the best antitumor response of regorafenib of all patients with pretreated metastatic GIST. Overall, 24/28 patients were available for the efficacy evaluation, four (14.29%) demonstrated a PR, 10 (35.71%) SD and 10 (35.71%) PD. In addition, 50.00% of patients with GIST exhibited a clinical benefit. Of 24 patients, the median TTR for four patients who presented PR and 10 SD were 6.2 and

Table III. Prognostic analysis for the PFS time for patients with gastrointestinal stromal tumor using the univariate and multivariate model.

	Univariate			Multivariate		
Variable	Total no.	Events no.	Median PFS (months)	Log-rank P-value	P-value	Hazard ratio (95% CI)
Age, years				0.378		
≤61	15	12	4.24			
>61	13	7	9.20			
Sex				0.125		
Male	20	13	5.29			
Female	8	6	2.33			
ECOG				0.007	0.009	4.330 (1.434-13.069)
0-1	22	14	5.03			
2-3	6	5	1.38			
Genetic status				0.422		
Non-exon 17	13	9	3.19			
Exon 17	15	10	5.30			
Metastatic site				0.136		
Non-liver	8	4	9.20			
Liver	20	15	3.75			
Total lymphocyte count				0.187		
<1,550	14	8	8.70			
≥1,550	14	11	3.19			
NLR				0.655		
<2.56	14	12	3.75			
≥2.56	14	7	5.29			
PLR				0.993		
<164.75	14	11	3.75			
≥164.75	14	8	5.29			
Albumin				0.403		
<3.5	8	5	4.24			
≥3.5	20	14	4.44			
Response				<0.0001	0.001	8.326 (2.513-27.588)
PR + SD	14	6	9.20			
PD	10	10	2.33			

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PLR, platelet:lymphocyte ratio; NLR, neutrophil:lymphocyte ratio; PR, partial response; SD, stable disease; PD, progressive disease.

2.1 months, respectively. The median OS time for four patients with PR and 10 with SD were 21.05 and 9.54 months, respectively. In 10 patients with PD, the median TTP was 2.46 months and the median OS time was 11.69 months (Table II).

Survival analysis of patients with pretreated metastatic GISTs receiving regorafenib. The median follow-up time after regorafenib treatment was 14.8 (range, 1.6-110.9) months and GISTs progressed in 19/28 patients (67.90%) during follow-up. All 28 patients had a median PFS time of 4.44 months and an OS time of 29.34 months (Figs. 1 and 2). Tables III and IV summarize the survival analysis regarding PFS and OS time, including clinical features, tumor size, mutational status and laboratory data. Both univariate and multivariate Cox's proportional hazard analyses revealed poor performance with ECOG 2 or 3, and primary resistance was associated with inferior PFS time for patients with GIST receiving regorafenib treatment (Table III and Fig. 1). Regarding OS time, ECOG 2 or 3, absence of exon 17 mutation, NLR ≥2.56, PLR ≥164.7 and albumin <3.5 were associated with a less favorable OS time in univariate analysis (Table IV and Fig. 2). However, multivariate Cox's proportional hazard analysis revealed that good performance status, lower

Table IV. Prognostic analysis for the OS time of patients with gastrointestinal stromal tumor using the univariate and multivariate model.

	Univariate			Multivariate		
Factors	Total, n	Events,n	Median OS, months	Log-rank P-value	P-value	Hazard ratio (95% CI)
Age, years				0.321		
≤61	15	6	32.33			
>61	13	4	29.34			
Sex				0.573		
Male	20	8	20.76			
Female	8	2	N/A			
ECOG				<0.0001	0.001	15.053 (3.024-74.929)
0-1	22	14	32.33			
2-3	6	6	2.17			
Genetic status				0.049	0.065	3.723 (0.92-15.056)
Non-exon 17	13	6	20.76			
Exon 17	15	4	32.33			
Metastatic site				0.117		
Non-liver	8	1	N/A			
Liver	20	9	19.94			
Total lymphocyte count					0.382	
<1,550	14	5	19.94			
≥1,550	14	5	32.33			
NLR				0.010	0.033	10.876 (1.217-97.211)
<2.56	14	4	32.33			
≥2.56	14	6	12.62			
PLR				0.003	0.019	13.543 (1.544-118.822)
<164.75	14	4	29.34			
≥164.75	14	6	9.99			
Albumin				0.03	0.045	4.221 (1.033-17.246)
<3.5	8	4	9.07			
≥3.5	20	6	29.34			
Response				0.172		
PR + SD	14	3	29.34			
PD	10	4	19.94			

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PLR, platelet:lymphocyte ratio; NLR, neutrophil:lymphocyte ratio; PR, partial response; SD, stable disease; PD, progressive disease; N/A, not available.

NLR and PLR (compared with high NLR and PLR) and good nutritional status with albumin ≥3.5 gm/dl were independent prognostic factors positively associated the OS time of patients with advanced inoperable/metastatic GIST after regorafenib treatment (Table IV and Fig. 2).

Literature review to compare the effect of regorafenib on GIST globally. For comparison with the present study cohort, a global literature review of patients with GIST who received regorafenib treatment was conducted (16,22-25). The literature review (Table V) revealed that regorafenib exhibited similar clinical efficacy compared with the GRID trial (16) comprising of Asian patients, including Korean and Japanese, with advanced GIST who experienced treatment failure with imatinib or sunitinib. While the PFS time ranged between 4.4 and 13.2 months, the OS time ranged between 12.2 and 29.3 months.

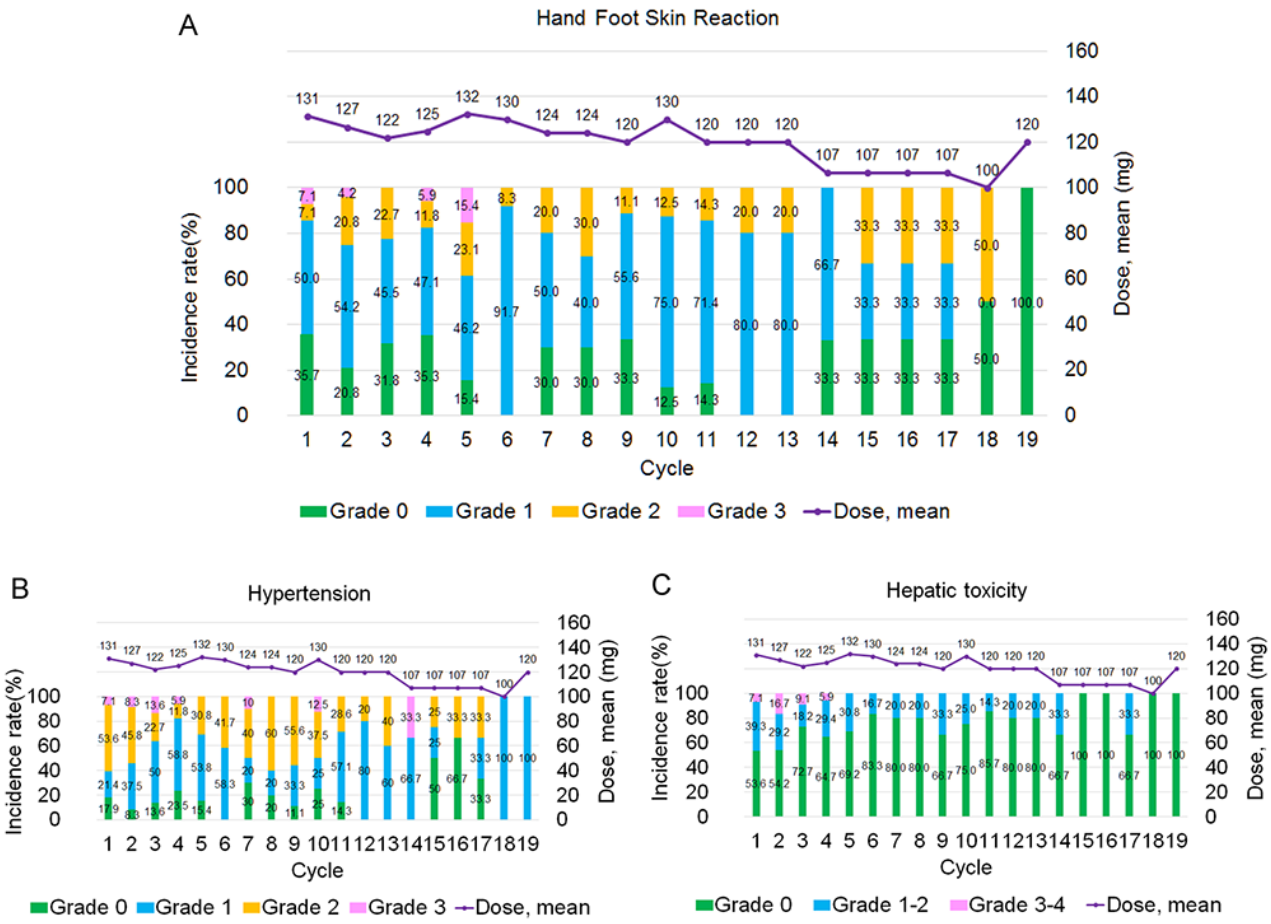

Figure 3. Toxicities of any grade (potentially associated with regorafenib) and mean dose of regorafenib occurring in the 12-month treatment period. (A) Hand-and-foot skin reactions. (B) Hypertension. (C) Hepatic toxicity.

Safety. The mean dose of regorafenib per day at 19 weeks was reduced to 120 mg, and 4/28 patients managed to re-escalate the dose (14.29%). Safety was assessed in all 28 patients. Despite the majority of patients requiring ≥1 dose reduction due to toxicity, some patients (4/28; 14.29%) subsequently had their regorafenib dose re-escalated without recurrence of unfavorable adverse effects. Particularly, the mean dose at 18 and 19 cycles of regorafenib per day was 100 and 120 mg, respectively, since 14.29% of patients re-escalated their dose. Table VI summarizes the hematological and non-hematological adverse events in patients. The leading grade 1-2 adverse events were hypertension (20/28; 71.43%), anemia (19/28; 67.86%) and hand-and-foot skin reactions (HFSRs; 18/28; 64.29%; Fig. 3A). The leading grade 3 adverse events were HFSRs (6/28; 21.43%), hypertension (6/28; 21.43%) and hepatic toxicity (5/28; 17.86%; Fig. 3A).

Discussion

The present single-center study investigated treatment outcomes for patients with pre-treated metastatic GIST treated with regorafenib. Several points of interest were observed. Firstly, the median PFS and OS time for all 28 patients were 4.4 and 29.3 months, respectively. Regorafenib exhibited similar clinical efficacy for Taiwanese patients compared with the GRID trial comprising of Asian patients, such as Korean and Japanese, with advanced GIST who experienced treatment failure with imatinib or sunitinib (23-25). Secondly, regarding regorafenib-induced adverse events, all patients exhibited similar treatment-associated toxicity profiles compared with those of the previous phase II (26) and III GRID trials (16), but with a lower incidence of grade III hypertension and diarrhea (23 and 5% in the phase III GRID trial vs. 21 and 0% in the present study, respectively). In addition, these adverse events corroborate with the toxicity profile of other kinase inhibitors with a similar target spectrum (27,28). Since the dose had to be reduced and was then re-escalated in some patients, it was not possible to draw any conclusions regarding the possible dose-response associations between regorafenib and adverse events in the present study.

HFSR was the most frequently observed adverse event and the most common reason for dose reduction in the present study. Although HFSRs are not lethal adverse effects, these conditions are associated with substantial unfavorable clinical symptoms, such as intractable pain and dose reduction and treatment may be stopping (18). Previous studies have demonstrated that Asian patients are particularly susceptible to regorafenib-induced HFSRs (18,25,29). The incidence of HFSR in the present study population (85.71%) was higher compared with that in the regorafenib group in the GRID trial (56%) (23) but was similar to Japanese subgroup (92%) in the GRID trial (29). Genetic polymorphisms of TNF-α, VEGF

Table V. Literature review concerning the treatment outcomes of patients with metastatic gastrointestinal stromal tumor treated with regorafenib.

Author, year	Area	No. of patients	PFS, months	OS, months	CBR, %	Grade 3 adverse events	Prognostic factors for PFS	Prognostic factors for OS	(Refs.)
Demetri *et al*, 2013	Global	133	4.8	17.4	52.6	HTN, HFSR, Diarrhea	N/A	N/A	(16)
Kollàr *et al*, 2014	UK	20	9.4	12.2	100	HTN, HFSR, Skin rash	N/A	N/A	(22)
Komatsu *et al*, 2015	Japan	17	7.1	NA	52.3	HTN, HFSR, Skin rash	N/A	N/A	(23)
Ben-Ami *et al*, 2016	USA	33	13.2	25	76	HTN, HFSR	Exon 11, SDH-deficient	N/A	(24)
Son *et al*, 2017	Korea	57	4.5	12.9	44	HTN, HFSR, Skin rash	Liver metastasis	ECOG Liver metastasis	(25)
Saito *et al*, 2018	Japan	11	7.4	N/A	N/A	HFSR, HTN	N/A	N/A	(29)
Present study	Taiwan	28	4.4	29.3	58.3	HTN, HFSR, Hepatic toxicity	ECOG, Disease control	ECOG, Albumin, NLR, PLR	-

PFS, progression-free survival; OS, overall survival; CBR, clinical benefit rate; AE, adverse event; HTN, hypertension; HSFR, hand-foot skin reaction; N/A, not available; ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil:lymphocyte ratio; PLR, platelet:lymphocyte ratio; SDH, succinate dehydrogenase.

Table VI. Adverse events and laboratory abnormalities of 28 patients with gastrointestinal stromal tumor following regorafenib treatment at a starting dose of 160 mg.

	Grade, n (%)		
Adverse effect	Any grade	Grade 1-2	Grade 3
Any event	28 (100.00)	13 (46.43)	15 (53.57)
Hypertension	26 (92.86)	20 (71.43)	6 (21.43)
Hand-and-foot skin reaction	24 (85.71)	18 (64.29)	6 (21.43)
Anemia	22 (78.57)	19 (67.86)	3 (10.71)
Hepatic toxicity	15 (53.57)	10 (35.71)	5 (17.86)
Thrombocytopenia	9 (32.14)	8 (28.57)	1 (3.57)
Fatigue	8 (28.57)	8 (28.57)	0
Diarrhea	7 (25.00)	7 (25.00)	0
Hypothyroidism	6 (21.43)	6 (21.43)	0
Hoarseness	4 (14.29)	4 (14.29)	0
Anorexia	3 (10.71)	3 (10.71)	0
Myalgia	3 (10.71)	3 (10.71)	0
Oral mucositis	2 (7.14)	2 (7.14)	0
Palpitation	2 (7.14)	2 (7.14)	0
Alopecia	1 (3.57)	1 (3.57)	0
Leukopenia	0	0	0

and UGT1A9 genes have been reported to be associated with the increased susceptibility of Asian patients to tyrosine kinase inhibitor-induced HFSRs, particularly in patients with hepatocellular carcinoma treated with sorafenib (18). Furthermore, the incidence of HFSRs in the present study was similar compared with that of Korean patients (82%) (25). Studies investigating the underlying molecular mechanisms of this increased susceptibility to regorafenib-induced HSFRs are required.

Good performance status and disease control mediated by regorafenib were independent factors for a favorable PFS time in the present study, supporting a previous study demonstrating that good performance status was consistently and independently associated with favorable PFS and OS time (12). Korean and Japanese patients with GISTs, who displayed good performance status, also had improved PFS and OS time with regorafenib treatment (23,25,29).

Regarding OS time, several novel prognostic factors were found in the present study, including liver metastasis, the pretreated albumin level, NLR and PLR. Similar to the Korean study (25), liver metastasis was a favorable factor for OS time, demonstrated by univariate survival analysis; however, liver metastasis was not an independent prognostic factor for OS time. Regarding the pretreated albumin level, a previous study reported higher pretreated serum albumin expression levels following two failed lines of TKIs in patients with pretreated metastatic GIST, and that these increased serum albumin expression levels were favorable factors associated with an improved OS time (30); however, in contrast with the present study, this previous study used nilotinib, sorafenib and imatinib as third-line TKIs, and therefore the results cannot be compared with those from the present study. In a meta-analysis including 29 studies investigating cancer of the gastrointestinal tract, 26/29 studies found that higher serum albumin levels were associated with improved survival using multivariate analysis (31). Therefore, further studies are required to resolve the molecular mechanisms underlying the aforementioned association so that increasing albumin levels may be used as a part of cancer treatment to improve OS time.

Previously, several studies demonstrated the association between the inflammatory and immunonutritional status and the prognosis of patients with cancer, including NLR and PLR (32-36). A high NLR was associated with poor prognosis in several malignancies, including pancreatic cancer, hepatocellular carcinoma, ovarian cancer and GIST (33-36). Although elevated NLR and PLR have been reported to be associated with poor treatment outcomes, including PFS and OS time, for primary GIST (37-41), to the best of our knowledge, the present study is the first study to demonstrate the association between lower NLR and PLRs to a more favorable OS time in patients with pretreated metastatic GIST receiving regorafenib.

The mechanism underlying elevated NLR and poor prognosis in GISTs is still unknown; however, elevated NLR usually indicates an imbalance between pro-tumor and the anti-tumor immune responses (42-44). Lymphocytes inhibit the proliferation and metastatic ability of cancer cells by inducing cytotoxic effects and cytokines production (45,46). Neutrophils have been demonstrated to induce tumor proliferation, invasion and vascularization by releasing proangiogenic chemokines (47-49), therefore increased neutrophils can inhibit the immune system by suppressing the cytolytic activity of immune cells, such as lymphocytes and nature killer cells (50,51). Thus, an elevated NLR directs the aforementioned imbalance in favor of the pro-tumor inflammatory status, which in turn causes an unfavorable outcome.

PLR has been reported as a poor prognostic factor in ovarian (52), colorectal (53), esophageal (54), pancreatic (55), endometrial cancer (56) and neuroendocrine tumors (57), as well as in primary GIST (40). A high PLR range between 150 and 300 is associated with less favorable outcomes, in terms of recurrence-free survival, cancer-specific survival or OS time (40). Inflammation has been recognized to be positively associated with PFS and OS outcomes of malignancy and is a contributor to the shutdown of the anti-tumor immune response by activating mediating T cells and chemokines release, facilitating tumor growth and metastasis (58). A non-specific response to cancer-associated inflammation was represented by the presence of neutrophilia and thrombocytosis (40). However, both the underlying mechanism, which links leukocytosis and neutrophilia to the progression of malignant tumors and explains the increase in platelets, and the biological pro-inflammatory behavior of cancer cells, remain unclear (47).

Overall, for Taiwanese patients with pre-treated GIST treated with regorafenib, poor performance status and poor disease control predicted an unfavorable PFS time; however, poor performance status, high NLR, PLR and low serum albumin levels predicted an unfavorable OS time.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

CHH collected the data and reviewed the literature. CNY designed the study, collected the data and wrote the manuscript. JSC, CYT, SYW, CTC and TSY interpreted the data and critically revised the manuscript for important intellectual content. CHH and CNY analyzed the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study protocol was approved by The Institutional Review Board of the Chang Gung Memorial Hospital (Taoyuan, Taiwan; approval no. 103-6044A3). Written informed consent was provided by all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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