Original Article

Efficacy and safety of intermittent versus continuous dose apatinib plus docetaxel as second-line therapy in patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma: a randomized controlled study

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Background: Previous studies of the second-line treatment for advanced gastric cancer or gastroesophageal junction adenocarcinoma (GC/GEJAC) had reported that apatinib combined with chemotherapy improved the treatment outcomes. However, the benefits were sometimes limited due to the tolerance of continuous dose regimen. This randomized controlled study aimed to investigate the efficacy and safety of intermittent or continuous dose apatinib plus docetaxel as a second-line therapy in patients with advanced GC/GEJAC.

Methods: Advanced GC/GEJAC patients who failed first-line chemotherapy were recruited (enrollment time: from September 15, 2017 to July 21, 2019), and randomly assigned to either the intermittent dose group (IG group) or the continuous dose group (CG group) (1:1 ratio) using the block randomization method. In the IG group, patients received apatinib 500 mg/d for 5 consecutive days then held for 2 days plus docetaxel 60 mg/m^2 q3w, in a 3-week cycle. In the CG group, patients received apatinib 500 mg daily plus docetaxel 60 mg/m^2 q3w, in a 3-week cycle. The progression free survival (PFS) was evaluated every two cycles and follow-ups were performed monthly. The primary endpoint was PFS, and the secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety.

Results: In total, 76 eligible patients were enrolled and randomly assigned (1:1 ratio). The IG group exhibited similar PFS compared to the CG group [median PFS: 3.88 (95% CI: 1.72–6.03) months *vs.* 3.98 (95% CI: 1.06–6.90) months, P=0.546] and OS [median OS: 9.00 (95% CI: 5.31–12.70) months *vs.* 9.40 (95% CI: 5.20–13.59) months, P=0.310]. ORR (21.1% *vs.* 18.4%, P=0.773) and DCR (60.5% *vs.* 60.5%, P=1.000) were of not statistically different between the IG and CG groups. As for safety, the IG group exhibited less frequent hypoproteinemia (31.6% *vs.* 55.3%, P=0.037) and lactate dehydrogenase increased (18.4% *vs.* 44.7%, P=0.014), while no differences in other adverse events were observed between the two groups.

Conclusions: Intermittent dose apatinib plus docetaxel was equally effective and more tolerable than continuous dose apatinib plus docetaxel as a second-line therapy in patients with advanced GC/GEJAC.

Trial Registration: ClinicalTrials.gov NCT03334591.

Keywords: Apatinib; docetaxel; intermittent dose; continuous dose; gastric cancer or gastroesophageal junction adenocarcinoma (GC/GEJAC)

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Introduction

Gastric cancer (GC), as one of the most common and deadly cancers worldwide, accounts for 572,000 newly diagnosed cases and 311,000 cancer-related deaths annually, and has a high incidence and prevalence in East Asia, Eastern Europe, and South America (1). The etiology of GC is still unknown; however, Helicobacter pylori infection, environmental factors, and inheritance are considered to be important triggers (2,3). Although awareness and early screening programs have been improved to some extent, more than 80% of GC cases are initially diagnosed at an advanced disease stage, leading to a worse prognosis and a 5-year survival rate of less than 20% (4,5). Therefore, to improve the prognosis of patients, exploring treatment options is essential.

Recently, anti-angiogenic therapy has been introduced as an important treatment option for several cancers, including GC (6,7). Apatinib, as a recently developed small-molecule vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitor that inhibits endothelial cell viability and mobility, thereby blocking tumor angiogenesis, has been proposed to treat GC or gastroesophageal junction adenocarcinoma (GC/GEJAC), and has exhibited good efficacy with acceptable tolerance (8,9). A randomized, placebo-controlled, parallel-arm, phase II trial observed that apatinib prolongs progression-free survival (PFS) and overall survival (OS) in metastatic GC patients who experience treatment failure with at least two chemotherapeutic regimens (10). Another randomized, double-blind, placebo-controlled phase III trial discovered that apatinib significantly improves PFS and OS in advanced GC/GEJAC patients who failed to at least two lines of prior chemotherapy (9). As for the second-line treatment for advanced GC/GEJAC, previous studies have reported that apatinib or ramucirumab combined with chemotherapy improved the treatment outcomes in these patients (3,11,12). However, due to the relatively poor physical conditions and toxicity, the dose of apatinib is often tapered or discontinued during treatment, which limits its benefits to a certain degree. Therefore, better solutions, such as a lower dose strategy that lowers the administered dose each time, were proposed. And this lower dose strategy of apatinib had been applied in treatment of several cancers, for example, advanced non-small cell lung cancer, with good efficacy and tolerable adverse events (13). Although there were experience in continuous lower dose administration of apatinib in the real-world studies (14), no reports examining this lower dose strategy of apatinib, which could be briefly summarized as 5 days administration plus a 2-day gap per week, plus chemotherapy in treating GC/GEJAC as a second-line therapy.

Therefore, this randomized controlled study aims to investigate the efficacy and safety of intermittent or continuous dose apatinib plus docetaxel as a second-line therapy in patients with advanced GC/GEJAC. We present the following article in accordance with the CONSORT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-546/rc).

Methods

Patients

In this randomized controlled study, advanced GC/GEJAC patients who failed first-line chemotherapy were consecutively recruited. The inclusion criteria were as follows: (I) diagnosed as advanced GC/GEJAC; (II) aged ≥18 years; (III) failure of the first-line chemotherapy; (IV) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2; (V) patients with at least one measurable lesion; and (VI) those with a life expectancy >3 months. The exclusion criteria were as follows: (I) patients that were hypersensitive to medicine composition of apatinib or docetaxel; (II) contraindications to the study drugs, such as active bleeding, ulcers, intestinal perforation, intestinal obstruction, uncontrolled hypertension, within 30 days after major surgery, grade 3–4 cardiac insufficiency (NYHA standard), and severe hepatic and renal insufficiency (grade 4); (III) unable to take oral medicine; (IV) unable to be regularly followed up; (V) complicated with other primary cancers; and (VI) pregnant or breastfeeding females. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The First Affiliated Hospital of USTC (No. 2017-07) and informed consent was taken from all the patients.

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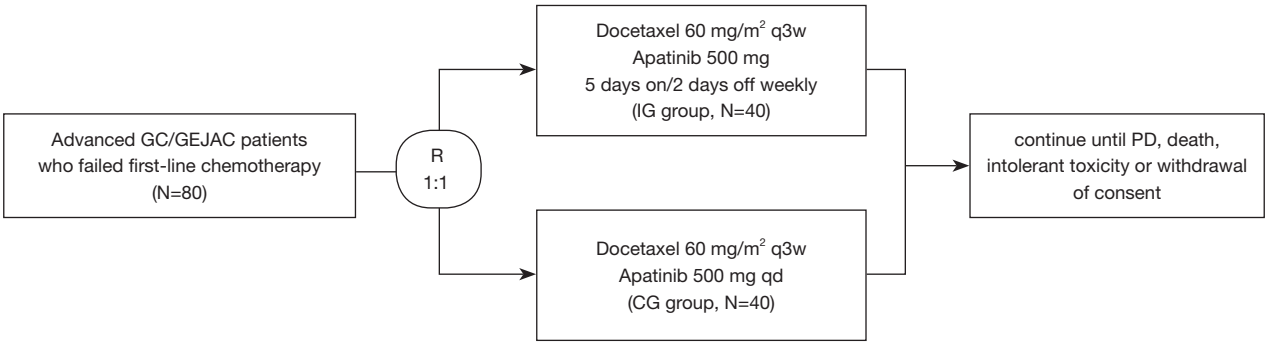

Figure 1 Study design flow chart. GC, gastric cancer; GEJAC, gastroesophageal junction adenocarcinoma; IG group, intermittent dose group; CG group, continuous dose group; PD, progressive disease.

Randomization and procedures

This study planned to enroll 80 patients and all enrolled patients were randomized to two groups by the ratio of 1:1 using block randomization method with block size 4. SAS 9.4 was used to generate the randomization list and MS EXCEL was used to conduct the randomization process.

After the eligibility of patients was confirmed, the patients were randomly assigned to either the intermittent dose group (IG group) or the continuous dose group (CG group). The trial oversight, database management, and quality assurance were performed at the Department of Medical Oncology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China. In the IG group, patients received an intermittent dose of apatinib for 5 consecutive days, then held for 2 days, combined with docetaxel 60 mg/m^2 ivgtt q3w; both apatinib and docetaxel were continued until the occurrence of progressive disease (PD), death, intolerant toxicity or withdrawal of consent. In the CG group, patients received a continuous dose of apatinib 500 mg/d p.o. daily combined with docetaxel 60 mg/m^2 ivgtt q3w; both apatinib and docetaxel were continued until PD, death, intolerant toxicity or withdrawal of consent (*Figure 1*). Safety assessments included blood pressure, ECOG performance status, blood pressure, laboratory examinations, and electrocardiogram (every 3 weeks), up to 30 days after treatment discontinuation.

Outcomes assessment

The primary outcome was PFS (the time from randomization to first disease progression, as assessed by central review according to RECIST, version 1.1, or death from any cause). The secondary outcomes included OS (the time from randomization to death from any cause), objective response rate (ORR), disease control rate (DCR), and adverse events. The PFS and OS were evaluated by monthly follow-up. Tumor response was examined by computed tomography (CT)/magnetic resonance imaging (MRI) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (15). The ORR was calculated as the percentage of patients who achieved complete response (CR) or partial response (PR). The DCR was calculated as the percentage of patients who achieved CR, PR, or stable disease (SD). The adverse events that occurred during the study were all recorded in detail and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 4.03 (16).

Statistical analysis

This study was a randomized, controlled clinical trial. The primary endpoint was the PFS evaluated by investigator per RECIST v1.1. A sample size of 80 patients (40 for each group), to achieve approximately 73 PFS events, would provide 80% power with an assumed PFS HR of 0.52 and a two-sided α value of 0.05.

Data were described as count with percentage or median with 95% confidence interval (CI). Comparison of the categorical variables between the two groups was determined by the Chi-square test, Fisher's exact test, or Wilcoxon rank-sum test (for categorical variables). Survival curves were constructed using the Kaplan-Meier method and determined by the Log-rank test. SPSS 20.0 statistical software (IBM Corp., Armonk, New York, USA) was used for data analysis. $P<0.05$ indicated statistical significance.

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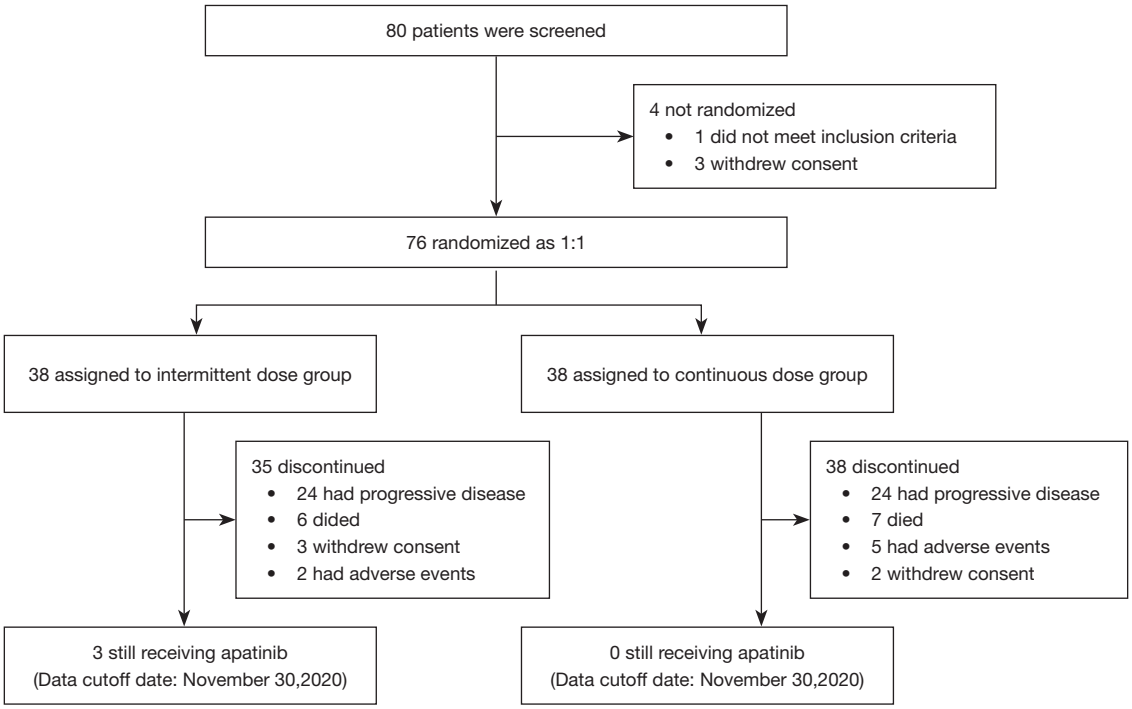

Figure 2 Study flow chart.

Results

From September 2017 to August 2019, a total of 80 patients were screened, among which four cases were excluded, and the remaining 76 eligible patients were randomly assigned into either the IG group (n=38) or CG group (n=38) in 1:1 ratio (*Figure 2*). And follow-ups were performed monthly until November 30, 2020. In the IG group, 35 patients discontinued treatment due to PD (n=24), death (n=6), withdrawal of consent (n=3), or adverse events (n=2), and three patients then still received the treatment until the last follow up. In the CG group, 38 patients discontinued due to PD (n=24), death (n=7), adverse events (n=5), or withdrawal of consent (n=2), and no patients continued to receive the treatment until the last follow up. The detailed baseline features of patients between the IG group and CG group are displayed in *Table 1*. No difference of age, sex, ECOG PS score, primary tumor site, metastatic lesion number, signet-ring cell carcinoma, history of surgery, or previous chemotherapy regimens was observed between the two groups (P>0.05).

Moreover, the mean, median, and range of the total actual dose of apatinib were 42,901.3, 32,000.0, and 12,000.0–177,000.0 mg in the IG group, respectively; and 49,980.3, 38,625.0, and 7,000.0–217,500.0 mg in the CG group, respectively.

Primary outcome

The IG group exhibited a median PFS of 3.88 months (95% CI: 1.72–6.03 months), which was of no different to that of the CG group (median PFS: 3.98 months, 95% CI: 1.06–6.90 months, P=0.546, *Figure 3*).

Secondary outcomes

The IG group achieved 21.1% PR, 39.5% SD, and 31.6% PD, resulting in an ORR of 21.1% and a DCR of 60.5%. As for the CG group, 18.4% PR, 42.1% SD, and 34.2% PD were achieved, resulting in an ORR of 18.4% and a DCR of 60.5%. Further comparison showed that there was no difference in the treatment response between the two groups (P>0.05, *Table 2*). Furthermore, the OS also showed no difference between the IG and CG groups [median OS: 9.00 (95% CI: 5.31–12.70) months *vs.* 9.40 (95% CI: 5.20–13.59) months, P=0.310, *Figure 4*].

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Table 1 Baseline characteristics of the included patients

Characteristics	Intermittent dose group (N=38)	Continuous dose group (N=38)	P value
Age, n (%)			1.000
<60 years	19 (50.0)	19 (50.0)	
≥60 years	19 (50.0)	19 (50.0)	
Gender, n (%)			0.454
Male	25 (65.8)	28 (73.7)	
Female	13 (34.2)	10 (26.3)	
ECOG PS score, n (%)			0.417
0	3 (7.9)	2 (5.3)	
1	35 (92.1)	35 (92.1)	
2	0	1 (2.6)	
Primary site, n (%)			0.435
Stomach	17 (44.7)	21 (55.3)	
Gastroesophageal junction	20 (52.6)	17 (44.7)	
Unknown	1 (2.6)	0	
Metastatic lesion number, n (%)			1.000
≤2	27 (71.1)	27 (71.1)	
>2	11 (28.9)	11 (28.9)	
Signet-ring cell carcinoma, n (%)			0.103
Yes	3 (7.9)	8 (21.1)	
No	35 (92.1)	30 (78.9)	
History of surgery, n (%)			0.490
Yes	16 (42.1)	19 (50.0)	
No	22 (57.9)	19 (50.0)	
Previous chemotherapy regimens, n (%)			0.082
Monotherapy	3 (7.9)	0	
Doublet chemotherapy	35 (92.1)	36 (94.7)	
Triplet chemotherapy	0	2 (5.3)	

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Adverse events

A total of 94.7% of patients in the IG group and 92.1% in the CG group presented with adverse events; meanwhile, 36.8% patients in IG group and 39.5% patients in CG group suffered from grade ≥3 adverse events.

Notably, hypoproteinemia (31.6% *vs.* 55.3%, P=0.037) and lactate dehydrogenase increased (18.4% *vs.* 44.7%, P=0.014) were less frequent in the IG group compared with the CG group (*Table 3*). In addition, hypertension (55.3% *vs.* 65.8%), anemia (55.3% *vs.* 63.2%), proteinuria (26.3% *vs.* 31.6%), and hand-foot syndrome (21.1% *vs.* 26.3%), as the common adverse events, were numerically lower in the IG group compared with CG group, although there was no statistical significance. Furthermore, seven cases experienced dose reduction to 250 mg in the IG group, while 13 cases received this dose reduction in the

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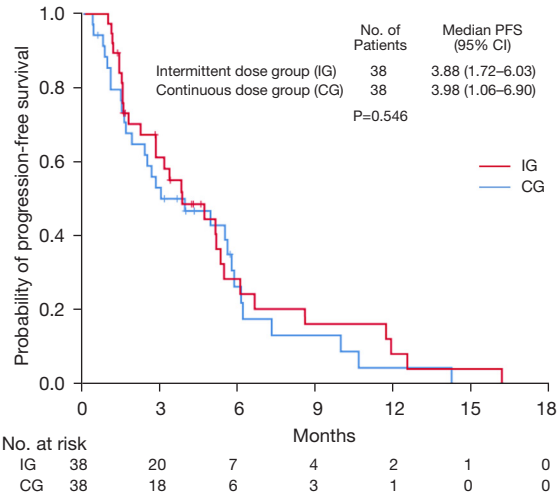

Figure 3 Progression-free survival analysis.

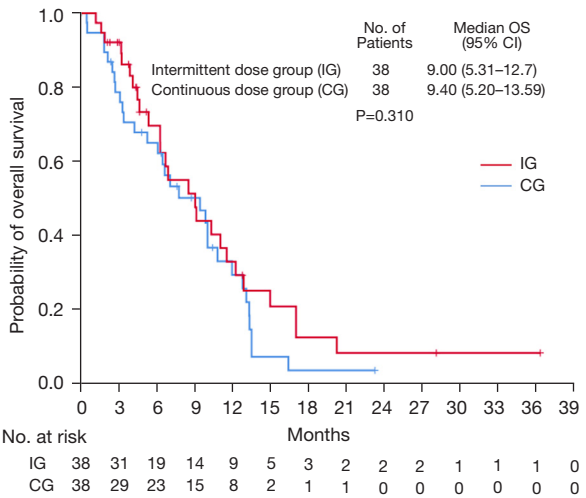

Figure 4 Overall survival analysis.

Table 2 Tumor responses

Best overall response	Intermittent dose group (N=38)	Continuous dose group (N=38)	P value
PR	8 (21.1)	7 (18.4)	0.773
SD	15 (39.5)	16 (42.1)	0.815
PD	12 (31.6)	13 (34.2)	0.807
UK	3 (7.9)	2 (5.3)	1.000
ORR	8 (21.1)	7 (18.4)	0.773
DCR	23 (60.5)	23 (60.5)	1.000

Data were presented as n (%). PR, partial response; SD, stable disease; PD, progressive disease; UK, unknown; ORR, objective response rate; DCR, disease control rate.

CG group.

Discussion

Several interesting findings were observed in the present study: (I) intermittent dose apatinib plus docetaxel achieved a similar treatment response, PFS, and OS compared to continuous dose apatinib plus docetaxel as a second-line therapy in patients with advanced GC/GEJAC; (II) less adverse events occurred in the IG group compared to the CG group in terms of increased hypoproteinemia lactate dehydrogenase, suggesting that an intermittent dose of apatinib might be safer than a continuous dose of apatinib in these patients.

Advanced GC/GEJAC is dismal regarding its quick progression and poor prognosis, it is now recommended that platinum and fluorouracil-based chemotherapy be used as first-line treatment for these patients, which improves the outcomes to some extent (17). However, there remains a proportion of patients who are refractory or fail first-line chemotherapy. For these patients, paclitaxel, docetaxel, or irinotecan is encouraged; however, recent options consider that monotherapy of paclitaxel, docetaxel, or irinotecan provides restricted benefits in these patients (3,17). In order to resolve this issue, great efforts never stop. Notably, increasing studies have reported that the addition of anti-angiogenic agents to chemotherapy as a second-line therapy would further facilitate the prognosis of advanced GC/GEJAC (11,12,18).

Since becoming commercially available, apatinib has been commonly used to treat GC/GEJAC under various disease conditions (19-22). In terms of second-line therapy

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Table 3 Adverse events

Items	Intermittent dose group (N=38)		Continuous dose group (N=38)		P value[a]	P value[b]
	Any event	Grade ≥3	Any event	Grade ≥3		
Hypertension	21 (55.3)	3 (7.9)	25 (65.8)	3 (7.9)	0.348	1.000
Anemia	21 (55.3)	3 (7.9)	24 (63.2)	4 (10.5)	0.484	1.000
Erythropenia	21 (55.3)	1 (2.6)	15 (39.5)	0	0.168	1.000
Alkaline phosphatase increased	15 (39.5)	3 (7.9)	13 (34.2)	0	0.634	0.240
AST increased	14 (36.8)	4 (10.5)	19 (50.0)	1 (2.6)	0.247	0.358
Appetite impaired	13 (34.2)	0	12 (31.6)	0	0.807	–
Creatinine decrease	13 (34.2)	0	11 (28.9)	0	0.622	–
γ-glutamyl transpeptidase increased	13 (34.2)	4 (10.5)	12 (31.6)	5 (13.2)	0.807	1.000
Diarrhea	12 (31.6)	1 (2.6)	9 (23.7)	0	0.442	1.000
Hypoproteinemia	12 (31.6)	0	21 (55.3)	0	0.037	–
Leukopenia	11 (28.9)	1 (2.6)	8 (21.1)	0	0.427	1.000
ALT increased	11 (28.9)	0	9 (23.7)	0	0.602	–
Total bilirubin increased	11 (28.9)	2 (5.3)	12 (31.6)	2 (5.3)	0.803	1.000
Asthenia	10 (26.3)	0	8 (21.1)	1 (2.6)	0.589	1.000
Nausea and vomiting	10 (26.3)	0	10 (26.3)	1 (2.6)	1.000	1.000
Proteinuria	10 (26.3)	0	12 (31.6)	1 (2.6)	0.613	1.000
Thrombocytopenia	10 (26.3)	2(5.3)	11 (28.9)	0	0.798	0.493
Urea nitrogen increased	10 (26.3)	0	10 (26.3)	0	1.000	–
Hand-foot syndrome	8 (21.1)	0	10 (26.3)	2 (5.3)	0.589	0.493
Neutrophil count decreased	8 (21.1)	2 (5.3)	5 (13.2)	0	0.361	0.493
Abdominal distension	7 (18.4)	0	9 (23.7)	0	0.574	–
Myelosuppression	7 (18.4)	2 (5.3)	7 (18.4)	3 (7.9)	1.000	1.000
Lactate dehydrogenase increased	7 (18.4)	0	17 (44.7)	0	0.014	–
Liver injury	6 (15.8)	0	5 (13.2)	0	0.744	–
Abdominal pain	5 (13.2)	0	5 (13.2)	0	1.000	–
Throat pain	5 (13.2)	0	1 (2.6)	0	0.200	–
Hypophosphatemia	5 (13.2)	0	3 (7.9)	0	0.711	–
Hypokalemia	5 (13.2)	0	8 (21.1)	0	0.361	–
Hematochezia	4 (10.5)	0	7 (18.4)	0	0.328	–
Hemorrhage	4 (10.5)	0	1 (2.6)	0	0.358	–
Blood urea	4 (10.5)	0	4 (10.5)	0	1.000	–
Headache/dizzy giddy	3 (7.9)	0	5 (13.2)	0	0.711	–
Constipation	3 (7.9)	0	1 (2.6)	0	0.615	–
Hoarse voice	3 (7.9)	0	0	0	0.240	–

Table 3 (*continued*)

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Table 3 (*continued*)

Items	Intermittent dose group (N=38)		Continuous dose group (N=38)		P value[a]	P value[b]
	Any event	Grade ≥3	Any event	Grade ≥3		
Back pain	3 (7.9)	1 (2.6)	4 (10.5)	0	1.000	1.000
Bowel obstruction	2 (5.3)	0	0	0	0.493	–
Dry mouth	2 (5.3)	0	2 (5.3)	0	1.000	–
Oral ulceration	2 (5.3)	1 (2.6)	3 (7.9)	0	1.000	1.000
Anasarca	2 (5.3)	0	0	0	0.493	–
Alopecia	2 (5.3)	0	1 (2.6)	0	1.000	–
Cough	1 (2.6)	0	3 (7.9)	0	0.615	–
Leg pain mass	1 (2.6)	0	2 (5.3)	0	1.000	–
Hyperthyroidism	0	0	1 (2.6)	0	1.000	–

Data were presented as n (%). [a], comparison of any event between the intermittent and continuous dose groups; [b], comparison of Grade ≥3 between the intermittent and continuous dose groups. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

for these patients, a previous retrospective cohort study discovered that apatinib plus chemotherapy improves the DCR and PFS compared with chemotherapy alone as second- or later-line therapy in GC/GEJAC, with good tolerance (12). Another prospective cohort study found that the addition of apatinib to chemotherapy promotes DCR and PFS compared with chemotherapy alone, and independently correlates with less disease progression after multivariate adjustment as a second- or later-line therapy in GC/GEJAC (23). Furthermore, a randomized controlled study showed that apatinib plus second-line chemotherapy achieved a better DCR, PFS, and OS, as well as fewer adverse events compared to chemotherapy alone in patients with advanced GEJAC (24). In our study, the numerical ORR, DCR, and PFS in both groups were in line with previous studies, while the OS was numerically longer (median OS of 9.0 months in the IG group and 9.4 months in the CG group) compared with that in previous studies that used chemotherapy alone [median OS of 5.2 months in the COUGAR-02 study (docetaxel), 7.4 months in the RAINBOW study (paclitaxel), and 8.3 months in the Keynote-061 study (paclitaxel)] (11,25,26). The possible explanations for this are as follows: (I) apatinib synergizes with chemotherapy drug as previously reported by two experiments (27,28), indirectly resulting in better treatment outcomes in the studied patients; and (II) apart from the synergistic effect, apatinib could directly repress angiogenesis, leading to a more satisfactory prognosis in the studied patients.

Despite the acceptable efficacy of apatinib plus chemotherapy in treating GC/GEJAC as a second-line therapy, the dose is commonly tapered or even stopped during the long-term treatment period, which mainly results from relatively poor physical conditions and toxicity. Therefore, it is essential to identify better solutions to this issue, such as a lower dose strategy that lowers the administered dose each time or reduces the amount of times that it is administered. Low-dose apatinib has been applied in the treatment of several cancers with good efficacy and tolerable adverse events, such as advanced non-small cell lung cancer, pulmonary, hepatic metastasis of nasopharyngeal carcinoma, etc. (13,29). In terms of GC/GEJAC, only two single-arm observational studies have revealed that low-dose apatinib is effective and tolerated for advanced GC patients (14,30). However, there are no reports examining the lower dose strategy of apatinib plus chemotherapy in treating GC/GEJAC as a second-line therapy. Encouragingly, our present study observed that intermittent dose apatinib plus docetaxel achieved a similar treatment response, PFS, and OS compared to continuous dose apatinib plus docetaxel as a second-line therapy in patients with advanced GC/GEJAC, which might be attributed to the fact that the 2-day dose gap of apatinib does not affect the long-term synergistic effect to chemotherapy, and thus, the intermittent dose apatinib plus docetaxel achieves an acceptable efficacy.

Safety data were also collected in detail in the present study, which was more comprehensive compared with

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previous studies. We found that less adverse events occurred with intermittent dose apatinib plus docetaxel compared to continuous dose apatinib plus docetaxel, especially in terms of hypoproteinemia (31.6% *vs.* 55.3%) and increased lactate dehydrogenase (18.4% *vs.* 44.7%). Furthermore, hypertension (55.3% *vs.* 65.8%), anemia (55.3% *vs.* 63.2%), proteinuria (26.3% *vs.* 31.6%) and hand-foot syndrome (21.1% *vs.* 26.3%), as the commonly occurring adverse events, were also numerically lower in the intermittent dose apatinib plus docetaxel group compared with continuous dose apatinib plus docetaxel group. Lastly, intermittent dose apatinib plus docetaxel also achieved a lower apatinib dose reduction rate compared with continuous dose apatinib plus docetaxel. The above results all suggested that intermittent dose apatinib was safer compared with continuous dose apatinib in these patients. This might be due to the fact that intermittent dose apatinib decreases accumulative drug-induced toxicity, thus leading to a relatively more tolerable safety profile.

Several limitations existed in this present study that should be noted. Firstly, the sample size of this study was relatively small, which might have resulted in selection bias. Secondly, intermittent dose apatinib (5 days administration plus a 2-day gap per week) was administered using a kind of lower-dose strategy. Therefore, the direct dose reduction strategy of apatinib plus chemotherapy in treating the studied patients needs to be explored in the future.

In conclusion, intermittent dose apatinib plus docetaxel is equally effective and more tolerable than continuous dose apatinib plus docetaxel as a second-line therapy in patients with advanced GC/GEJAC.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-546/rc

Trial Protocol: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-546/tp

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The First Affiliated Hospital of USTC (No. 2017-07) and informed consent was taken from all the patients.

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