Careful dose modification of apatinib as third or further-line treatment in advanced gastric cancer patients with poor performance status

Jianxin Chen, MDa, Junhui Wang, MDb,*, Qian Miao, MDa,∗

Abstract
The retrospective study was conducted to evaluate the efficacy and safety of careful dose modification of apatinib as third or further-line treatment in advanced gastric cancer (aGC) patients with poor performance status (PS = 2 or 3).

Patients with aGC of poor PS who had received at least 2 lines of chemotherapy were treated with apatinib at a dose of 250 mg initially and best supportive care (BSC). During the whole treatment, the dose of apatinib was adjusted according to the status of PS (group treatment). Meanwhile, patients of poor PS (PS = 2 or 3) with aGC who received BSC alone after second or further-line treatment in the recent 5 years in our institution have been investigated for their median overall survival (mOS) as control. Kaplan–Meier curve was adopted for the description of OS in the 2 groups. Univariate analysis was conducted with log-rank test between OS and the potential characteristics including gender, age, PS status, primary tumor lesion, Her-2 status, and previous lines of treatment. Toxicities were assessed with the criteria of National Cancer Institute Common Toxicity Criteria (NCI CTC) version 4.0.

A total of 23 patients who received apatinib plus BSC treatment and 41 patients treated with BSC alone were reviewed in the present study. Median exposure time of apatinib was 2.4 months ranging from 0.2 to 5.1 months. The median OS in the group treatment was 4.3 months (95% CI, 2.735–5.865) comparing to the control as 2.1 months (95% CI, 1.473–2.727, P = .0004). In addition, PS status was shown as the only independently significant factor to influence the OS (P = .049). Fatigue (82.6%), appetite decrease (73.9%), and anemia (69.6%) appeared to be the most common adverse events at any grade during the therapy of apatinib.

The outcomes of the present study revealed that therapeutic model of careful dose modification of apatinib therapy initiated with low dose plus BSC as third or further-line treatment might be more beneficial on survival time comparing to BSC alone in patients with aGC of poor PS, however, as well as apparent adverse events.

Abbreviations: aGC = advanced Gastric Cancer, BSC = best supportive care, FISH = Fluorescence in Situ Hybridization, Her-2 = human epidermal growth factor receptor 2, mOS = median overall survival, NCI CTC = National Cancer Institute Common Toxicity Criteria, NSCLC = non-small cell lung cancer, ONS = oral nutrition supplement, PFS = progression-free survival, PG-SGA = Patient-Generated Subjective Global Assessment, PS = performance status, TPN = total parenteral nutrition, VEGFR-2 = vascular endothelial growth factor receptor-2.

Keywords: advanced gastric cancer, apatinib, further-line, poor performance status

1. Introduction
Gastric cancer is one of the major causes which lead to cancer-related death all over the world, and becoming the third leading cause of cancer mortality in China.[1,2] Although with the development of the endoscopic techniques for early detection, patients were still always diagnosed as advanced or metastatic disease. In addition, high recurrence rate at 40% to 60% after surgery greatly limited the curative ratio in such patients.[3] Chemotherapy was recommended as the standard treatment in patients with advanced gastric cancer (aGC) according to the definite evidence from clinical trials.[4–6] Docetaxel, paclitaxel, irinotecan, and ramucirumab were emerged as standard second-line choices according to the established clinical data.[7–10] However, there still remains controversial on the third or further-line treatment in patients with aGC, especially in patients with poor performance status (PS = 2 or 3).

Apatinib, a novel small-molecule vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor, was considered significant value as further-line treatment in patients with aGC.[11,12] Results of the phase III trial indicated that the administration of apatinib could markedly improve progression-free survival (PFS, 2.6 months vs 1.8 months, P < .001) and
overall survival (OS, 6.5 months vs 4.7 months, \( P = .0149 \)) in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastro-esophageal junction as third or further-line treatment.\(^{[12]}\) Nevertheless, in China, the agent has been attempted as salvage therapy in multiple inoperable solid carcinomas including non-small cell lung cancer (NSCLC),\(^{[13]}\) metastatic triple-negative breast cancer,\(^{[14]}\) sarcomas,\(^{[15]}\) advanced esophageal squamous cell carcinoma,\(^{[16]}\) radiiodine refractory differentiated thyroid cancer,\(^{[17]}\) and advanced hepatocellular carcinoma.\(^{[18]}\)

Notably, the included patients, almost in majority of randomized, controlled clinical trials, were recruited with the criteria of good performance status (PS = 0 or 1). Patients with poor performance (PS = 2 or 3) were always considered as a contraindication for chemotherapy. However, the fact is, a majority of patients with aGC, especially in heavily pretreated patients, were capable of poor PS status. Such patients were always categorized as an unprofitable subgroup from cytotoxic drugs. In terms of reliable tolerance with mild toxicities of apatinib according to the reported clinical trials,\(^{[11,12]}\) salvage therapy with apatinib might be a potential candidate for patients with pretreated aGC. However, there were few researches conducted to investigate the efficacy and safety of apatinib in patients of poor PS status with aGC. Hence, we suggested the investigation on those patients might be more realistic and closer to clinical practice.

In the present study, we conducted a retrospective research, aiming to investigate the efficacy and safety of apatinib with dose-adjusted model in pretreated patients with aGC of poor PS status (PS = 2 or 3).

2. Patients and methods

2.1. Patients and eligibility

Patients of poor PS status (PS = 2 or 3) with aGC who received apatinib plus best supportive care (BSC) as third or further-line treatment in our institution from Oct. 1st 2015 to Nov. 31st 2017 were reviewed. Meanwhile, patients of poor PS with aGC who received BSC alone after second or further-line treatment in the recent 5 years in our hospital were reviewed for their median overall survival (mOS) as the control. Immunohistochemistry essay was adopted for the detection of Her-2 status. Results of (+++), (++++) were defined as positive mutation, while (+) and (-) were defined as negative ones. In addition, result of (+) was further identified with the method of Fluorescence in Situ Hybridization (FISH), results of which were considered as the final decision. ECOG PS status was classified as: Grade 0, Fully active, able to carry on all pre-disease performance without restriction; Grade 1, Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work; Grade 2, Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; Grade 3, Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; Grade 4, Completely disabled, cannot carry on any self-care, totally confined to bed or chair; Grade 5, Dead.\(^{[11]}\) Inclusion criteria for patients selection were listed below:

1. Histological or cytological diagnosis of gastric adenocarcinoma;
2. Advanced or metastatic disease which was not appropriate for radical operation;
3. Patients were unable or unwilling to receive any further chemotherapy after 2 lines of treatment at least due to poor PS status, serious cancer-related symptoms or any other reasons;
4. Without any anti-tumor treatment including local intervention or herbs during apatinib therapy;
5. Patients were willing to receive apatinib treatment plus BSC rather than BSC alone.

The research was approved by the institutional review board of Quzhou People’s Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

2.2. Treatment control

Apatinib tablet was administered initially at a dose of 250 mg (1 tablet) half an hour after breakfast once daily. PS status was evaluated every 2 weeks for dose adjustment of apatinib during the whole treatment. Criterion of PS status evaluation was listed as:

1. If PS upgraded from 2 to 3 or unchanged with 3, the dose of apatinib was increased to 500mg daily.
2. If PS status downgraded from 3 to 2 or unchanged with 2, the dose of apatinib was increased to 500mg daily.
3. Situation of hematological events ungraded to level 3 or non-hematological ones to level 2 according to the criteria of National Cancer Institute Common Toxicity Criteria version 4.0 (NCI CTC v4.0) after active supportive treatment was supposed to the symbol of drug discontinuation. One treatment cycle was set as 28 days.

As an essential part of BSC, nutritional interventions including oral nutrition supplement (ONS), and total parenteral nutrition (TPN) were administrated for selected patients which were evaluated as malnutrition according to the standard of Scored Patient-Generated Subjective Global Assessment (PG-SGA). Symptoms including pain, fatigue, anemia, and anorexia were managed with drugs or blood transfusion support.

2.3. Efficacy and toxicities evaluation

Tumor response evaluation was developed after two cycles of apatinib administration or treatment discontinuation due to any reasons. Clinical efficacy was evaluated with OS, which was defined as the duration from the time of the beginning of apatinib to the time of death or last follow-up in group treatment. OS of the control was defined as the duration from the last day of the last cycle of treatment to the death or last follow-up. Follow-up was up to March 31th 2018. Toxicities were assessed according to the NCI CTC version 4.0.

2.4. Statistics

Statistical analysis was performed with software SPSS version 17.0 (SPSS Inc., Chicago, IL). Survival data of OS was calculated with Kaplan–Meier curve by software Graphpad prism (USA). Univariate analysis of OS was conducted with log-rank test. \( P < .05 \) was regarded as statistically significant.
3. Results

3.1. Patient’s characteristics

A total of 23 patients with aGC or lesions in gastro-esophageal junction within measurable tumor lesions were reviewed. They had a median age of 53 years old, 15 patients of which were male and the other 8 patients were female. 73.9% of the included patients had a PS status as 2, 26.1% of which with PS as 3. There were 2 patients harboring human epidermal growth factor receptor 2 (Her-2) mutation type, 11 patients with wild type, and the other 10 patients remaining unknown. All patients in apatinib group received apatinib therapy as third or further-line treatment. The previously therapeutic regimens belong to all the patients in both of the groups were presented in the Appendix 1, http://links.lww.com/MD/D343. Clinical characteristics of the study population, as well as the control, were listed in the Table 1.

3.2. Drug exposure

Among patients treated with apatinib, median drug exposure time of all patients was 2.4 months within a range from 0.2 to 5.1 months. All the patients in group treatment received oral apatinib tablet at a dose of 250mg as initial, median dosage of which were 250mg ranging from 250mg to 500mg during the whole treatment. The variation of the mean dosage of apatinib intake among all the patients in the group treatment was shown in Figure 1. 22/23 patients suffered discontinuation of apatinib treatment at the time of March 31th 2018, 3 patients of which were due to progression disease, 7 patients due to severe symptoms related to disease, 10 patients due to adverse events caused potentially by apatinib, 2 due to poor economic status that could not afford subsequent treatment. There was 1 patient still receiving apatinib treatment in the last follow-up. With the beginning of 250mg apatinib administration initially, 14 patients (60.9%) received an increasing dose of apatinib with 500mg daily because of the stabilization of PS status (PS unchanged as 2). During the whole period of apatinib administration, there were two patients suffering the improvement of PS status downgraded from 3 to 2 (more than 50% of waking hours), with the dose of apatinib increasing from 250mg to 500mg daily (Patient 12 and 19 in the Appendix, http://links.lww.com/MD/D343). However, the dose of apatinib sustained only 2 weeks, and then decreased back to 250mg daily again in both of the 2 patients because of fatigue. The situation of drug exposure was presented in Table 2.

Table 1

| Variables                  | Apatinib + BSC (%) | BSC (%) | P value |
|----------------------------|--------------------|---------|---------|
| Gender                     |                   |         |         |
| Male                       | 15 (65.2)          | 24 (58.5)| .599   |
| Female                     | 8 (34.8)           | 17 (41.5)|         |
| Age                        |                   |         |         |
| Median (range)             | 53 (44–76)         | 58 (41–79)| .492   |
| <60                        | 16 (69.6)          | 25 (61.0)|         |
| >60                        | 7 (30.4)           | 16 (39.0)|         |
| PS                         |                   |         |         |
| 2                          | 17 (73.9)          | 21 (51.2)| .076   |
| 3                          | 6 (26.1)           | 20 (48.8)|         |
| Primary tumor lesion       |                   |         |         |
| Gastric                    | 20 (86.9)          | 36 (87.8)| .922   |
| Gastro-esophageal junction | 3 (13.1)           | 5 (12.2)       |         |
| Her-2 status               |                   |         |         |
| Mutation                   | 2 (8.7)            | 3 (7.3)   | .590   |
| Wild                       | 11 (47.8)          | 25 (61.0)|         |
| Unknown                    | 10 (43.5)          | 13 (31.7)|         |
| Lines of apatinib therapy  |                   |         |         |
| Third line                 | 15 (65.2)          | 28 (68.3)| .801   |
| Further line               | 8 (34.8)           | 13 (31.7)|         |

Her-2 = human epidermal growth factor receptor-2, N/A = not/applicable, PS = performance status.

Figure 1. Variations of mean dose of apatinib every 2 weeks.
3.3. Clinical efficacy

Among all the patients who received apatinib plus BSC as salvage treatment, 9 patients (39.1%) received 1 time evaluation at least. Fourteen patients (60.9%) did not receive image assessment because of the discontinuation of apatinib less than 2 months (n = 7), patients refusal (n = 4), refusal from family (n = 2), or economic status (n = 1). As a result, 6 patients were evaluated as stable disease, while 3 patients as progressive disease. No patients were evaluated as partial or complete response.

Among the 23 patients in the apatinib plus BSC group, and 41 patients treated with BSC alone, no patients were loss to follow-up. The median OS in group treatment was 4.3 months (95% CI, 2.735–5.865) comparing to the group control as 2.1 months (95% CI, 1.473–2.727, P = .0004) (Fig. 2). According to the results from the univariate analysis of OS in apatinib plus BSC group, there existed a statistical association of OS with PS status (P = .049), while no significant relevance with gender (P = .781), age (<60 P = .756, ≥60 P = .576), primary tumor lesion (P = .418), Her-2 status (P = .548) or lines of therapy (P = .412) observed. Detailed results of univariate analysis were presented in Table 3.

3.4. Clinical toxicities

All included patients treated with apatinib plus BSC were assessed for the toxicities. The most common events at any grade were fatigue (82.6%), appetite decrease (73.9%), and anemia (69.6%). The most common high-grade events (grade ≥3) were appetite decrease (47.8%), fatigue (39.1%), and anemia (30.4%). Grade 5 adverse event considered relative to treatment was not observed in the present retrospective study. The common adverse events at any grade and high grade were presented in Table 4.

4. Discussion

To the best of our knowledge, it might be the first study to evaluate the efficacy and safety of apatinib as dose modification therapy after standard treatment in patients of poor PS (PS = 2 or 3) with aGC, in spite of its nature of a retrospective one. The outcomes of the present study revealed that careful dose modification of apatinib therapy initiated from low-dose plus BSC as third or further-line treatment might be more beneficial on
mOS comparing to BSC alone in patients with aGC of poor PS status (median OS, 4.3 months, 95% CI, 2.735–5.865 vs 2.1 months, 95% CI, 1.473–2.727, \( P = 0.004 \)). However, the incidence of adverse events including appetite decrease, fatigue, and anemia in patients treated with apatinib plus BSC might be more frequent than patients treated with BSC alone.

Based on the superior efficacy to placebo, apatinib has been recommended for the third-line treatment in patients with aGC of good PS status in China (PS = 0 or 1).\(^{[12]}\) However, in view of the poor PS status in numerous patients after heavily treatment, it might be more practical to investigate the efficacy and tolerance of the agent in that population. Interestingly, the outcomes of the present retrospective study suggested that apatinib might be some of value with careful dose modification as third or further-line treatment in patients with aGC of poor PS status. At the first time of PS evaluation (first 2 weeks), more than half patients could maintain their PS status, and received an increasing dose up to 500mg apatinib intake. However, the dose of 500mg seems unsustainable according to the variation of mean dose of apatinib administration (Fig. 1). It suggested that the dosage of 500mg apatinib may not be appropriate for patients with poor PS status. K-M survival curve revealed that the difference of survival time between the 2 groups separated from approximately 1.5 months from the beginning (Fig. 2), which suggested that profit from apatinib might be emerged after 6 weeks administration. Patients’ tolerance to apatinib might play a significant role in the survival benefits of the patients with poor PS, which could be revealed from the results of survival curve and the variation of mean dose of apatinib. Though conducted with energetic supportive care, most patients suffered a deterioration of performance inevitably, whether caused by disease progression or adverse events. Even so, the significant difference of OS between apatinib plus BSC group and BSC alone still suggested that apatinib treatment with a model of careful dose adjustment might be effective for the patients with aGC of poor PS status.

In addition, univariate analysis of OS with clinical characteristics including gender, age, PS, primary tumor lesion, Her-2 status and lines of therapy was developed in the treatment group, outcomes of which suggested that PS status might be the only independently significant element to influence the final survival time (\( P = 0.049 \)). Similarly, as another antiangiogenic agent, ramucirumab was also revealed a significant benefit on OS compared to placebo (9.6 vs 7.4 months \( P = .017 \), and 5.2 vs 3.8 months, \( P = 0.047 \), respectively) in patients with previously treated advanced gastric or gastro-esophageal junction adenocarcinoma of good performance (PS = 0/1 or 0/1/2).\(^{[10,20]}\) However, patients with aGC of poor performance were not enrolled into any clinical trials on ramucirumab. Deficiency of the interesting data may lead to the confusion of the comparison between ramucirumab and apatinib. Nevertheless, few researches were conducted to investigate the evaluation of bevacizumab in gastric cancer patients with poor PS status. A case report showed that bevacizumab combined with S-1 as maintenance therapy might be effective and well-tolerated in a 64-year-old patient with heavily pretreated aGC, but results of which need additional clinical trials to evaluate further.\(^{[21]}\)

In the present study, apatinib tablet was administered at a dose of 250mg once daily initially, which was far less than the former reported researches (850mg daily or 425mg twice a day).\(^{[11,12]}\) The reasons for the adoption of the present dosage of apatinib in the present study were listed below. First, the patients included in the present study possessed a poorer PS status, which may also lead to a poorer tolerance to drug toxicities, regardless of hematologic toxicities or non-hematologic toxicities. In addition, the dosage of apatinib in the most of the ongoing clinical trials was administrated as 250mg or 500mg daily due to the potential severe adverse events including hypertension, fatigue, and hand-foot syndrome (ClinicalTrials.gov). Lastly, the specification of apatinib in China varies from 250mg to 500mg a tablet, which is convenient for taking in clinical practice. Exactly during the treatment, more than a half patients (16/23) suffered a dose adjustment either upgraded to 500 mg or downgraded to 250mg according to the variation of PS status and adverse events, as described in section methods, which revealed that apatinib administration with careful dose modification model as third or further-line treatment might be more reasonable and individualized for patients with poor PS status.

The most common adverse events at high grade within apatinib treatment were appetite decrease (47.8%), fatigue (39.1%), and anemia (30.4%), which were different from the data of phase III trial.\(^{[12]}\) In that research which enrolled patients with good PS status (PS = 0, 1), the most common adverse events were hand-foot syndrome (8.5%), elevated transaminase (8.0%), and anemia (6.3%). However, symptom of hand-foot syndrome was noticed in only 3 patients in the present study, all of which were observed in ones who were treated with apatinib more than 2 months. In addition, symptoms such as appetite decrease and fatigue were observed in 3 days after management of apatinib in earliest, which were also supposed to be the most common symptoms that lead to the therapy discontinuation in the present study. Besides, intestinal obstruction was observed in 1 patient, but not considered related to drug according to the consultation of surgeon.

There were several limitations in the present study. The major limitation was its retrospective nature and small size of sample, outcomes of which may bring with controversies. In addition, the study was an explorative 1 to assess the clinical application value of apatinib in patient with poor performance (PS = 2 or 3), which was short of a simultaneous group treated with BSC alone. Although patients of poor PS with aGC who received BSC alone after in the recent 5 years in our institution were reviewed for its OS as a control, temporal and supportively therapeutic bias seems inevitable for the final analysis of OS, which may limited the valuation of the results in the present study. Lastly, rather than 850mg in former study, the efficacy and safety of apatinib at a dose of 250mg and 500mg adopted in the present research should be further investigated in the future.

In conclusion, the outcomes of the present study revealed that low dose apatinib treatment with a model of careful dose adjustment as third or further-line treatment might be more beneficial compared to BSC alone, in patients with aGC of poor PS, however, may also be accompanied with adverse events including appetite decrease, fatigue, and anemia.

Author contributions

Conceptualization: Jianxin Chen.
Data curation: Jianxin Chen.
Formal analysis: Jianxin Chen.
Funding acquisition: Jianxin Chen.
Investigation: Jianxin Chen.
Methodology: Jianxin Chen, Qian Miao.
Project administration: Jianxin Chen, Junhui Wang, Qian Miao.
Resources: Jianxin Chen, Junhui Wang, Qian Miao.
Software: Jianxin Chen.
Supervision: Jianxin Chen.
Validation: Jianxin Chen, Junhui Wang.
Visualization: Jianxin Chen, Qian Miao.
Writing – original draft: Jianxin Chen.
Writing – review & editing: Jianxin Chen, Qian Miao.

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