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ORIGINAL RESEARCH

Anorexia, Hypertension, Pneumothorax, and Hypothyroidism: Potential Signs of Improved Clinical Outcome Following Apatinib in Advanced Osteosarcoma

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Aim: Apatinib, a specific tyrosine kinase inhibitor (TKI) that targets mainly vascular endothelial growth factor receptor-2 (VEGFR-2) as well as Ret, c-Kit and c-Src, has been assessed in patients with advanced osteosarcoma (phase II), the primary report of which has been published in PMID 30559126. This sub-study explored the potential signs of Adverse Events (AEs) for apatinib-treated osteosarcoma.

Methods: Participants with advanced osteosarcoma progressing upon chemotherapy received apatinib until disease progression or unacceptable toxicity. Toxicities, progression-free survival (PFS), and clinical benefit rate (CBR) following treatment were evaluated.

Results: Of the 41 patients recruited to the study, 37 received treatment and constituted the safety population. At data cut-off (December 30, 2017), median follow-up for safety was 7.37 (IQR, 6.33–11.07) months. The most common grade 3–4 AEs were pneumothorax (16.22%), wound dehiscence (10.81%), proteinuria (8.11%), diarrhea (8.11%), and skin reaction (8.11%). Only hypertension was an independent predictive factor for both PFS (hazard ratio [HR], 0.44; P = 0.07) and CBR (P = 0.07). Anorexia was also significantly related to a longer PFS in a Cox regression model (HR, 0.35; P =0.01). For CBR, pneumothorax and hypothyroidism showed more clinical benefit (P = 0.07 and 0.00, respectively).

Conclusion: The results of this study suggest that anorexia, hypertension, pneumothorax, and hypothyroidism might be markers for a favorable clinical outcome following apatinib-treated refractory osteosarcoma.

Keywords: apatinib, osteosarcoma, prognosis

Introduction

The process of angiogenesis is crucial for osteosarcoma growth, invasiveness, and metastasis.[1] Anti-angiogenesis tyrosine kinase inhibitors (TKIs) are effective in prolonging progression-free survival (PFS) for advanced osteosarcoma that has progressed upon first- or second-line chemotherapy.[2,3] In a prospective study on apatinib for advanced osteosarcoma after the failure of traditional multimodal therapy (NCT02711007), apatinib reached 4-month PFS rate of 56.8% for advanced osteosarcoma[4–7] with a tolerable and manageable safety profile.[5,8–10] The administration of apatinib induced tumor shrinkage and showed a high objective response (43.2%), but the toxic effects were severe with high rates of dose reduction

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(59.5%). Anti-angiogenesis TKIs have some common toxicities such as hypertension, hand-foot skin reactions, hypothyroidism, fatigue, and anorexia.[11–14] However, previous trials[15–17] on other tumors have indicated that some of these toxicities correspond to a favorable outcome with these drugs.

The goals of this study were to determine the types of adverse events (AEs) most commonly seen in apatinib-treated osteosarcoma patients; whether the development of these AEs may be potential signs for drug efficacy; if these toxicities are related to the activity of apatinib; and when and how the management of these AEs would lead to optimal drug efficacy. To this end, we describe the clinical course, management, and resolution of key AEs in patients treated with apatinib in this phase two study to evaluate potential apatinib-induced toxicities for efficacy prediction.

Methods

Patients and Treatment

This Peking University People's Hospital Sarcoma Group (PKUPH-sarcoma) study was a single-arm, non-blind, single institution, phase two study that evaluated the efficacy and safety of apatinib in patients ≥16 years with advanced osteosarcoma progressing upon chemotherapy. Patients were required to have measurable disease according to the response evaluation criteria for solid tumors version 1.1,[18] and had received prior treatment with high-dose methotrexate, doxorubicin, cisplatin, and ifosfamide in an adjuvant and/or advanced disease setting. Participants received 500 or 750 mg apatinib according to body surface area once daily until disease progression or unacceptable toxicity. The primary outcomes of this trial were Objective Response Rate (ORR) and 4-month PFS. However, the aim of this substudy was to explore the potential signs of Adverse Events (AEs) for apatinib-treated osteosarcoma. The study was approved by the Institutional Review Board of Peking University People's Hospital (Beijing, China), and was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All of the patients provided written informed consent.

Safety and Serological Assessments

In addition to standard safety evaluations and imaging assessment, physical examination was performed at each follow-up. Laboratory tests included full blood count, serum chemistry, electrocardiogram, measurement of thyroid and cortisol levels, and urinalysis, in which levels of protein in urine were quantitatively measured after 24 h. The first time point for evaluation was set at 1 month and then repeated every 2 months thereafter. During each evaluation, all of the patients underwent ophthalmic, cardiac, and dermatologic surveillance examinations. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[19] In cases of grade 3 or 4 toxicity, apatinib was reduced by one dose level (from 750 mg to 500 mg daily or from 500 mg to 250 mg) or by two dose levels (750 mg once daily to 250 mg). Whenever feasible, patients were returned to a higher dose. Safety evaluation was continued until 28 days after the last dose of apatinib or recovery to grade one or zero from any acute toxicity associated with apatinib. The European Organization for Research and Treatment of Cancer 30-item core Quality of Life (QoL) questionnaire[20–22] and Numerical Pain Rating Scale[23,24] were adopted to evaluate QoL. Before initiation of treatment, all participants should be in a state without obvious AE except for the disease. We excluded all those who had hypertension that could not be well controlled through antihypertensive drugs or those who had a previous hypertensive crisis or hypertensive encephalopathy. Here hypothyroidism was defined as abnormal thyroid function including serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4), all of which were assessed using the enzyme-linked immunosorbent assay.[25] Our institutional laboratory reference ranges were 0.35–4.94 mIU/L for TSH, 1.71–3.71 pmol/L for FT3, and 0.7–1.48 pmol/L for FT4. Subclinical hypothyroidism was defined as an increase in TSH above the upper limit of normal (>4.94 mIU/L) with normal FT3 and FT4 levels. However, for better analysis, we merged hypothyroidism and subclinical hypothyroidism into hypothyroidism.

Statistical Analysis

Patients who received at least 2 months of apatinib were included in the survival and safety analyses. The results used descriptive statistics. The data cut-off date was December 30, 2017. All of the statistical analyses were performed using SAS for Windows version 9.1.3. Statistical analysis of 2 × 2 contingency tables of categorical variables was conducted using the Fisher's exact test. Median durations of PFS were calculated using the

Kaplan–Meier method, and comparisons between cohorts were made using log rank tests. Correlations between parameters were evaluated with the Pearson's test. Factors with $P < 0.10$ in an univariate analysis were examined with multivariate analysis including the Cox proportional hazard model and logistic regression, which defined as independent predictive factors.[26] Most of the statistical tests were two-tailed, with significance defined as $P < 0.05$. This trial is registered with ClinicalTrials.gov, number NCT02711007.

Results

Summary of AEs

Of the 41 patients recruited, 37 received treatment and constituted the safety population. Baseline characteristics have been reported.[27] The overall incidence of apatinib-related AEs was 89.2%. In general, drug-related AEs were limited to grade one or two. With a median follow-up time of 7.37 months (interquartile range [IQR], 6.33–11.07) for the safety analysis, 22/37 (59.5%) patients had dose-reduced treatment, and 11/37 (29.7%) patients had temporary treatment interruption.[27] The frequency of apatinib administration was 40.5% of the planned administration dose. The mean temporary interruption duration was 8 days (95% confidence interval [CI], 4–10). The following grades 3 and 4 toxic effects impacted the dose reductions: pneumothorax (6 [16.2%] of 37 patients); wound dehiscence, (4 [10.8%]); proteinuria, (3 [8.1%]); diarrhea, (3 [8.1%]); palmar-plantar erythrodysesthesia syndrome, (3 [8.1%]); rash acneiform, (2 [5.4%]); abdominal cramps, (2 [5.4%]); anorexia, (2 [5.4%]); pleural infection, (1 [2.7%]); bladder perforation, (1 [2.7%]); hypertriglyceridaemia, (1 [2.7%]); weight loss, (1 [2.7%]); anemia, (1 [2.7%]); hypokalemia, (1 [2.7%]); palpitations, (1 [2.7%]); back pain, (1 [2.7%]); anorectal infection, (1 [2.7%]); cholecystitis, (1 [2.7%]); and fatigue, (1 [2.7%]).[27] All of these AEs were causally related to the study drug. No deaths were related to the experimental treatment; all of the deaths were attributed to disease progression. The most common any-grade AEs (reported in ≥15% of patients) included bilirubin increase (18.9%), diarrhea (18.9%), hypertriglyceridemia (27.0%), hypertension (18.9%), hypercholesterolemia (16.2%), hypothyroidism (21.6%), fatigue (32.4%), weight loss (32.4%), anorexia (35.1%), pneumothorax (32.4%), rash acneiform (16.2%), and palmar-plantar erythrodysesthesia syndrome (21.6%). Due to the small sample size, we did not observe some rarely seen AEs (overall incidence ≤5% of patients) and merged some of the AEs into one bigger group for more appropriate statistical analyses. For example, we merged hypertriglyceridemia and hypercholesterolemia into hyperlipemia and merged palmar-plantar erythrodysesthesia syndrome and rash acneiform into hand-foot skin reaction since this appeared to be different severity degrees of the same AE.

Time to Onset of AEs of Interest and Management

The most common AEs of clinical interest were anorexia, weight loss, fatigue, pneumothorax, hyperlipemia, and hypothyroidism. Time to initial occurrence of these AEs is summarized with a median AE onset of 20 to 165 days (Figure 1). For adolescents and young adults with advanced osteosarcoma, hand-foot skin reactions usually had an early onset, with majority of patients experiencing the AE within the first three cycles of treatment. During the trials, we actively used prophylactic measures such as emollients, protection of pressure-sensitive areas, urea cream and clobetasol cream, and analgesics if pain control was needed. We also used some traditional Chinese herbs to control hand-foot skin reactions, which is beneficial for restricting AEs within grades 1–2. These herbs included portulacaria, geranium wilfordii maxim, rhizoma, flos carthami, and cortex phellodendri, all of which have been formulated into medical treatments in some clinics in Beijing. The time to resolution clearly differed in our population with different management methods. Anorexia was the most common AE, with a median onset time of 90 days (95% CI, 36–185), for which methyl diprogesterone acetate tablets were our first treatment measure. Hypothyroidism with elevated TSH levels was observed in eight patients with a median onset time of 126 days (95% CI, 48–303); most cases were subclinical with abnormal hormone levels. Hypothyroidism can aggravate patient fatigue and anorexia and is usually treated with levothyroxine sodium supplementation. Weight loss was a frequently observed AE, accompanied by anorexia and hypothyroidism with a median onset time of 64 days (95% CI, 48–107). There was limited information on the weight maintenance strategies among patients receiving apatinib. A similar time to onset was observed for abdominal cramps, diarrhea, hypertension, fatigue, oral mucositis, and myalgia/arthralgia, with a median time to onset of 1–2 months after starting treatment, with the exception of proteinuria, hyperlipemia and pleuritic pain for which the median time to onset was slightly longer (4–5 months).

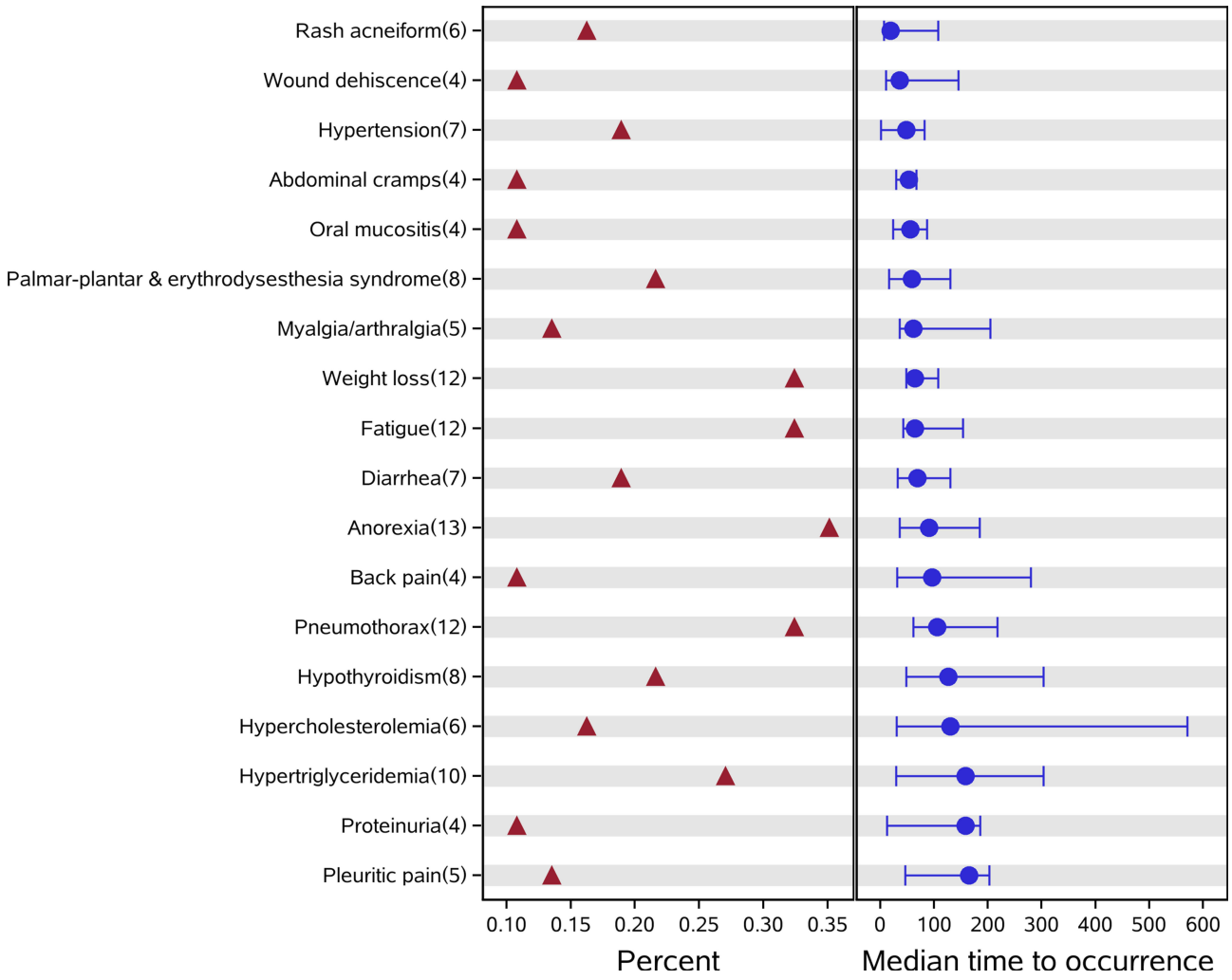

Figure 1 The percentage of participants who had AEs of interest and the median (95% CI) for the onset of first incidence of AEs of interest (any grade) in days.

Wound dehiscence usually occurred early in patients who previously had operations or wounds. Repetitive dressing changes and debridement should be required for these patients with interruption of apatinib for at least 3–4 weeks. Wound dehiscence generally occurred in patients again after apatinib treatment resumed, even if the wound had previously healed. Pneumothorax was particularly frequent for pulmonary metastatic lesions with a median occurrence of 106 days (95%, 61–218). Surgical intervention, such as thoracotomy, is usually not recommended to avoid the interruption of apatinib and further disease progression; rather, chest tube placement with chemical or mechanical pleurodesis is preferable. However, chest tube usually lasts for months because of the failure of mechanical pleurodesis and secondary infection develops afterwards. Thus, final progression is often inevitable because of dose reductions or interruptions of apatinib.

Toxicity as Signs for Antitumor Efficacy

We evaluated the relationship between AEs and drug efficacy in the 37 patients who had completed at least 2 months of apatinib treatment. Hypothyroidism or subclinical hypothyroidism at baseline was not observed in any patient. For ORR, the only AE that had some impact was anorexia ($P = 0.03$). However, the onset of abdominal cramps might predict a partial response ($P = 0.06$). For CBR, hypothyroidism obviously indicated a clinical benefit ($P = 0.00$), while hypertension and pneumothorax also had some relationship with more clinical benefit ($P = 0.07$ and 0.06, respectively) (Table 1).

Independent Factors That Predict Apatinib Efficacy

The Cox proportional hazards model was used to determine the HRs of the abovementioned parameters for predicting the

Table 1 The Effect of Adverse Event Which Arose in At Least Four Participants on Objective Response Rate (ORR) and Clinical Benefit Rate (CBR)

Adverse Event	PR N (%)	SD N (%)	PD N (%)	P	ORR N (%)	P	CBR N (%)	P
Proteinuria				0.518		0.618		0.601
No	13 (81.3)	8 (100.0)	12 (92.3)		18 (85.7)		11 (84.6)	
Yes	3 (18.8)	0 (0.0)	1 (7.7)		3 (14.3)		2 (15.4)	
Abdominal cramps				0.064		0.118		>0.999
No	12 (75.)	8 (100.0)	13 (100.0)		17 (81.0)		12 (92.3)	
Yes	4 (25.0)	0 (0.0)	0 (0.0)		4 (19.1)		1 (7.7)	
Diarrhea				0.320		0.012		>0.999
No	11 (68.8)	7 (87.5)	12 (92.3)		14 (66.7)		11 (84.6)	
Yes	5 (31.3)	1 (12.5)	1 (7.7)		7 (33.3)		2 (15.4)	
Hyperlipemia				0.488		>0.999		>0.999
No	14 (87.5)	8 (100.0)	10 (69.2)		18 (85.7)		11 (84.6)	
Yes	2 (12.5)	0 (0.0)	3 (30.8)		3 (14.3)		2 (15.4)	
Hypertension				0.198		0.675		0.072
No	11 (68.8)	8 (100.0)	11 (84.6)		16 (76.2)		8 (61.6)	
Yes	5 (31.3)	0 (0.0)	2 (15.4)		5 (23.8)		5 (38.5)	
Myalgia/arthralgia				0.251		0.364		>0.999
No	12 (75.0)	8 (100.0)	12 (92.3)		17 (81.0)		11 (84.6)	
Yes	4 (25.0)	0 (0.0)	1 (7.7)		4 (19.1)		2 (15.4)	
Hypothyroidism				0.171		0.104		0.001
No	10 (62.5)	7 (87.5)	12 (92.3)		14 (66.7)		6 (46.2)	
Yes	6 (37.5)	1 (12.5)	1 (7.7)		7 (33.3)		7 (53.9)	
Oral mucositis				0.811		0.296		>0.999
No	15 (93.8)	7 (87.5)	11 (84.6)		20 (95.2)		12 (92.3)	
Yes	1 (6.3)	1 (12.5)	2 (15.4)		1 (4.8)		1 (7.7)	
Fatigue				0.906		>0.999		0.476
No	10 (62.5)	6 (75.0)	9 (69.2)		14 (66.7)		10 (76.9)	
Yes	6 (37.5)	2 (25.0)	4 (30.8)		7 (33.3)		3 (23.1)	
Pneumothorax				0.233		0.166		0.067
No	9 (56.3)	5 (62.5)	11 (84.6)		12 (57.1)		6 (46.2)	
Yes	7 (43.8)	3 (37.5)	2 (15.4)		9 (42.9)		7 (53.9)	
Wound dehiscence				0.251		0.618		0.115
No	13 (81.3)	7 (87.5)	13 (100.0)		18 (85.7)		10 (76.9)	
Yes	3 (18.8)	1 (12.5)	0 (0.0)		3 (14.3)		3 (23.1)	
Hand-foot skin reaction				0.773		0.805		>0.999
No	16 (100.0)	7 (87.5)	11 (84.6)		17 (81.0)		10 (77.0)	
Yes	0 (0.0)	1 (12.5)	2 (15.4)		4 (19.1)		3 (23.1)	
Weight loss				0.206		0.726		0.476
No	10 (62.5)	4 (50.0)	11 (84.6)		15 (71.4)		10 (76.9)	
Yes	6 (37.5)	4 (50.0)	2 (15.4)		6 (28.6)		3 (23.1)	
Pleuritic pain				0.197		>0.999		0.638
No	13 (81.3)	6 (75.0)	13 (100.0)		18 (85.7)		12 (92.3)	
Yes	3 (18.8)	2 (25.0)	0 (0.0)		3 (14.3)		1 (7.7)	

(*Continued*)

Table 1 (Continued).

Adverse Event	PR N (%)	SD N (%)	PD N (%)	P	ORR N (%)	P	CBR N (%)	P
Anorexia				0.034		0.315		0.472
No	8 (50.0)	4 (50.0)	12 (92.3)		12 (57.1)		7 (53.9)	
Yes	8 (50.0)	4 (50.0)	1 (7.7)		9 (42.9)		6 (46.2)	
Back pain				>0.999		0.618		>0.999
No	14 (87.5)	7 (87.5)	12 (92.3)		18 (85.7)		12 (92.3)	
Yes	2 (12.5)	1 (12.5)	1 (7.7)		3 (14.3)		1 (7.7)	

risk of disease progression after covariates were adjusted for all participants (Figure 2). PFS was set as the dependent variable, and parameters for which $P < 0.10$ in the univariate analysis were examined by multivariate analysis, including the Cox proportional hazard model and logistic regression, were set as independent variables. Based on the univariate analyses of AEs on PFS (Figure 2), we found that anorexia and hypertension were associated with improved clinical outcomes (HR, 0.35; $P = 0.01$ and HR, 0.44; $P = 0.07$, respectively) and these two factors were further testified into multivariate analyses. Hypertension was defined as maximum systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg at least three-fold that at resting state after the first day of treatment. In patients with and without hypertension, the median PFS was 6.63 (95% CI: 5.67–7.59) and 4.30 (95% CI: 3.51–5.09) months, respectively ($P = 0.06$; Figure 3); and in patients with and without anorexia, the median PFS was 6.27 (95% CI: 5.78–6.76) and 3.23 (95% CI: 2.01–4.45) months, respectively ($P = 0.01$; Figure 4). All of the observed clinical outcomes were not related to hypertension grading, whereas anorexia seemed to be related to weight loss ($P < 0.00$). AEs correlation analysis showed that fatigue was also correlated with hypothyroidism and weight loss ($P = 0.07$ and 0.00, respectively). When included in the multivariate analysis

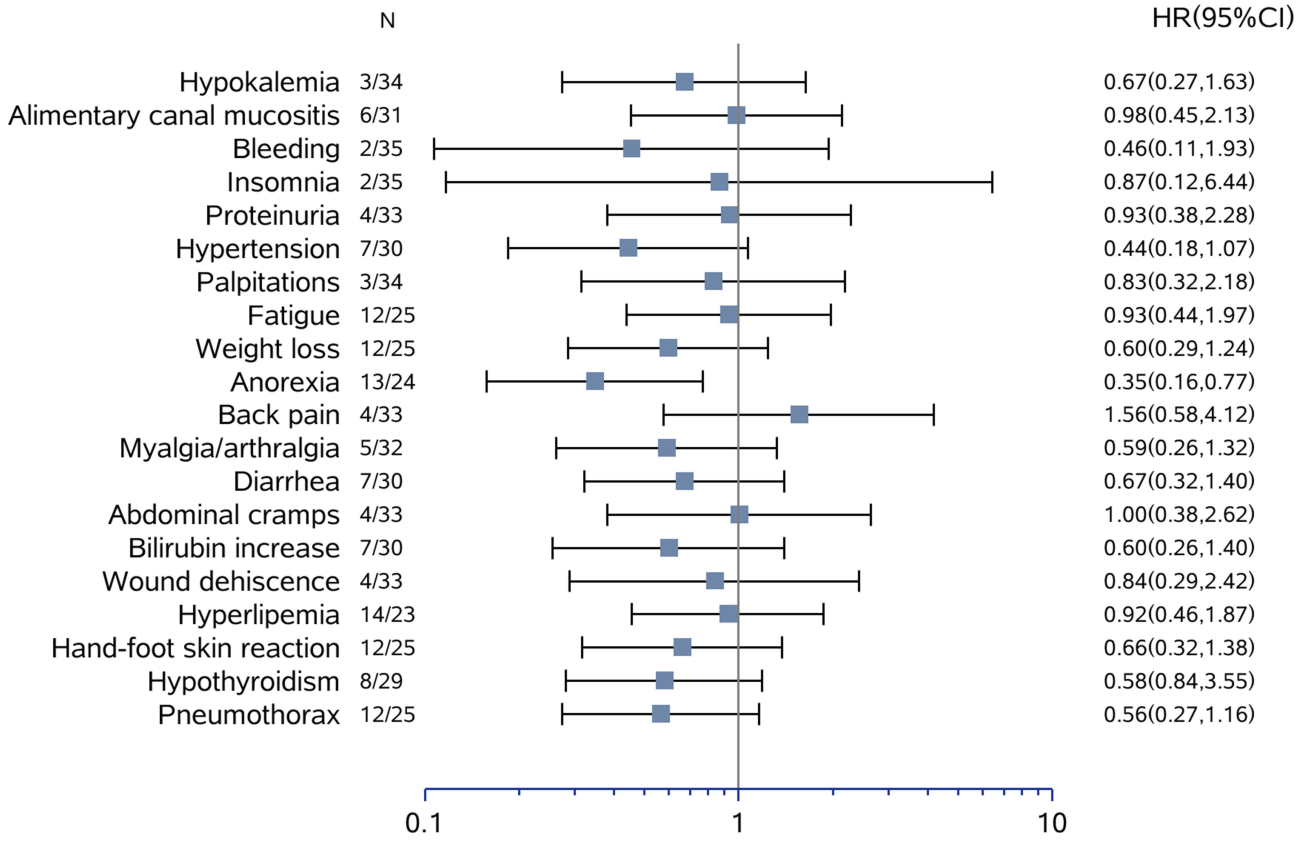

Figure 2 Forest plots of HRs for disease progression in different AE subgroups.

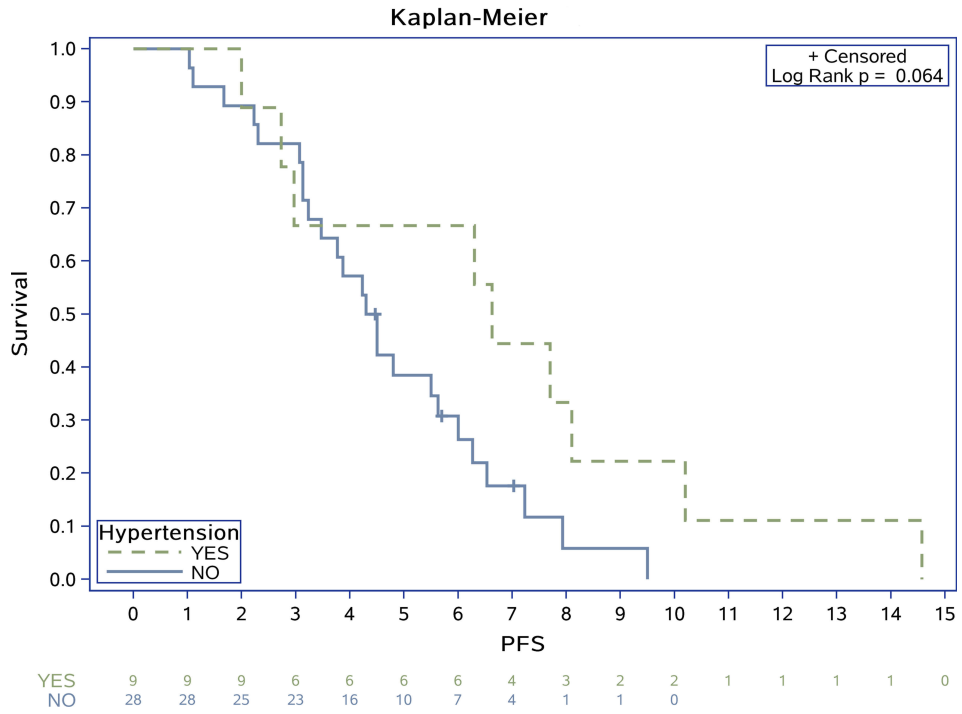

Figure 3 Kaplan–Meier curves for PFS from patients who did or did not have anorexia.

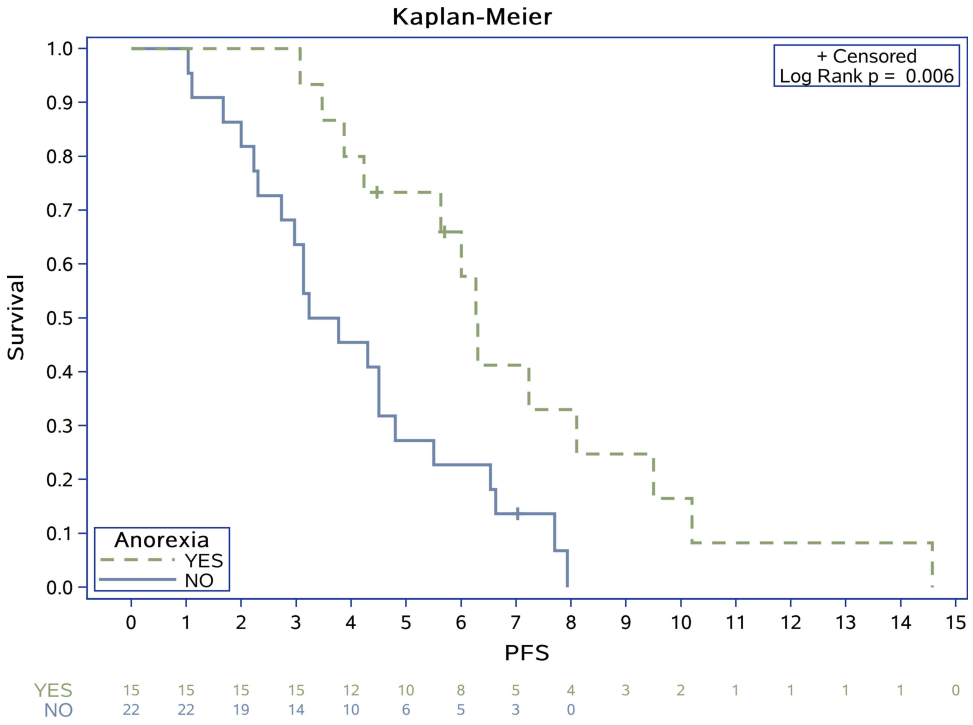

Figure 4 Kaplan–Meier curves for PFS from patients who did or did not have hypertension.

together with other clinicopathological factors that affected PFS,[27] only anorexia was found to be an independent factor for prognosis ($P = 0.04$). Although it did not appear to greatly impact the PFS, the HR was reduced for myalgia/arthralgia, bilirubin increase, hypothyroidism, pneumothorax, and bleeding (HR = 0.59, 0.60, 0.58, 0.56, 0.46, respectively), which suggests that the occurrence of these toxicities might benefit prognosis.

Discussion

Vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) play a critical role in angiogenesis in osteosarcoma.[1] All of the VEGFR-TKIs with a high specificity and strong affinity only had a median PFS of 4–6 months for refractory osteosarcoma,[2,3,5,27–29] suggesting an urgent need for a predictive marker that indicates benefits from VEGFR-TKI. The already explored potential predictive factors included patient-related factors, such as VEGFR gene polymorphisms;[30] tumor-related factors, such as microvascular density, serum VEGF level and VEGFR-2 expression;[31] and drug-related factors, such as treatment-induced hypertension and hand-foot syndrome.[32–34] Most of the AEs reported with apatinib can be ascribed to VEGFR inhibition and are consistent with the AEs observed with other VEGFR TKIs.[10,15,17,33] As tumor growth addiction to the specific pathway that is effectively targeted may be the link between a mechanism-based toxicity and efficacy, the biological basis of AEs might be pharmacological, with higher drug exposure being associated with greater toxicity and antitumor activity.[10,15] Some TKI-associated AEs correlate with improved patient outcomes.[17,33] An awareness of the mode of action can help the physician anticipate potential drug interactions, and an appreciation of the most common AEs but with appropriate management in case those AEs progressing into grades 3–4. The objectives of this single institution, phase two, open-label, single-arm study were to assess the efficacy and safety of apatinb in patients with heavily pretreated advanced osteosarcoma, and to evaluate the potential of apatinib-induced AEs for efficacy prediction.

To the best of our knowledge, this is the first study to demonstrate that commonly occurring AEs during the treatment with apatinib predicts clinical outcomes in osteosarcoma patients. In this expanded safety analysis of the PKUPH-sarcoma study, the reported incidence and severity of AEs for apatinib differed from those previously reported.[8–10] Some may think AEs were not predictive markers but just reflection of increased dose of apatinib.[10] However, most of the common AEs reported were grades 1–2 in our study and had not reached dose reductions yet. We had summarized apatinib-related similar study in Table 2 and realized that there had been abundant study investigating these toxicities as potential signs for clinical outcome in patients treated with apatinib. Our population was much younger than those participants in trials, which might influence the distribution of the side effects. Although the tumor burden was significantly reduced by this apatinib, the QoL did not improve, leading to declined physical, functional, emotional, cognitive, and social functioning. The pain was not greatly relieved and became more severe during the initial 1–3 months. Although hand-foot skin actions, hypertension, and hypothyroidism were also quite common toxicities (overall incidence of 32.4%, 32.4%, and 21.6%, respectively), they could usually be manageable. We noticed that hypertension was not as severe in adolescents. We also used some traditional Chinese herbs to control fatigue and hand-foot skin reactions, which might be beneficial for preventing those AEs from developing to severity.

As a potential sign for efficacy, with regard to ORR, the only AE that had some impact was anorexia ($P = 0.03$). However, the onset of abdominal cramps might predict a partial response ($P = 0.06$). This is in accordance with the independent factors used to predict PFS for anorexia ($P = 0.01$). However, multiple factors could influence anorexia, including patients' personal constitution, dietary habit, thyroid function, and oral stomatitis. In addition, anorexia is a subjective assessment that differs among patients. Thus, we could not objectively assess this AE, and as such, it may be difficult to use as a sign to assess drug efficacy.

For CBR, hypothyroidism indicated clinical benefit ($P = 0.00$) while hypertension and pneumothorax would also have some impact on the control of disease ($P = 0.07$ and 0.06, respectively). In this study, we merged hypothyroidism and subclinical hypothyroidism into hypothyroidism. The incidence of hypothyroidism was reported to be 18–85% during the use of sunitinib or sorafenib in metastatic renal cell cancer;[34–36] however, the precise mechanisms were not well clarified. It was proposed that the inhibition of VEGFR-1, VEGFR-2, and PDGFR induces thyroid ischemia via capillary regression and constriction.[37] VEGFR-TKI-mediated antiangiogenesis inhibition may impair thyroid activity and induce hypothyroidism, because these angiogenesis pathways play a role in the normal physiology of the thyroid gland.[37] Correlations between hypothyroidism during the treatment of VEGFR-TKIs and clinical outcomes were also investigated in several studies.[34,37] Hypothyroidism may serve as a predictive marker of VEGFR-TKI treatment outcome in multiple solid tumors.[3,13,34–36] In our study, several patients had tumor shrinkage and elevated TSH (>4.94 mIU/L) during apatinib treatment. Pneumothorax as a complication of antiangiogenesis therapy in children and young adults with refractory/recurrent solid tumors has been shown to be an indicator of a favorable prognosis.[17] Osteosarcoma tends to have pulmonary metastasis.[1] The pathophysiologic mechanisms of

Table 2 The Effect of Adverse Event Which Arose in At Least Four Participants on Objective Response Rate (ORR) and Clinical Benefit Rate (CBR)

Adverse Event	PR N (%)	SD N (%)	PD N (%)	P	ORR N (%)	P	CBR N (%)	P
Proteinuria				0.518		0.618		0.601
No	13 (81.3)	8 (100.)	12 (92.3)		18 (85.7)		11 (84.6)	
Yes	3 (18.8)	0 (0.0)	1 (7.7)		3 (14.3)		2 (15.4)	
Back pain				>0.999		0.618		>0.999
No	14 (87.5)	7 (87.5)	12 (92.3)		18 (85.7)		12 (92.3)	
Yes	2 (12.5)	1 (12.5)	1 (7.7)		3 (14.3)		1 (7.7)	
Abdominal cramps				0.064		0.118		>0.999
No	12 (75.)	8 (100.0)	13 (100.0)		17 (81.0)		12 (92.3)	
Yes	4 (25.0)	0 (0.0)	0 (0.0)		4 (19.1)		1 (7.7)	
Wound dehiscence				0.251		0.618		0.115
No	13 (81.3)	7 (87.5)	13 (100.0)		18 (85.7)		10 (76.9)	
Yes	3 (18.8)	1 (12.5)	0 (0.0)		3 (14.3)		3 (23.1)	
Myalgia/arthralgia				0.251		0.364		>0.999
No	12 (75.0)	8 (100.0)	12 (92.3)		17 (81.0)		11 (84.6)	
Yes	4 (25.0)	0 (0.0)	1 (7.7)		4 (19.1)		2 (15.4)	
Oral mucositis				0.811		0.296		>0.999
No	15 (93.8)	7 (87.5)	11 (84.6)		20 (95.2)		12 (92.3)	
Yes	1 (6.3)	1 (12.5)	2 (15.4)		1 (4.8)		1 (7.7)	
Hypertension				0.198		0.675		0.072
No	11 (68.8)	8 (100.0)	11 (84.6)		16 (76.2)		8 (61.6)	
Yes	5 (31.3)	0 (0.0)	2 (15.4)		5 (23.8)		5 (38.5)	
Diarrhea				0.320		0.012		>0.999
No	11 (68.8)	7 (87.5)	12 (92.3)		14 (66.7)		11 (84.6)	
Yes	5 (31.3)	1 (12.5)	1 (7.7)		7 (33.3)		2 (15.4)	
Hypothyroidism				0.171		0.104		0.001
No	10 (62.5)	7 (87.5)	12 (92.3)		14 (66.7)		6 (46.2)	
Yes	6 (37.5)	1 (12.5)	1 (7.7)		7 (33.3)		7 (53.9)	
Fatigue				0.906		>0.999		0.476
No	10 (62.5)	6 (75.0)	9 (69.2)		14 (66.7)		10 (76.9)	
Yes	6 (37.5)	2 (25.0)	4 (30.8)		7 (33.3)		3 (23.1)	
Weight loss				0.206		0.726		0.476
No	10 (62.5)	4 (50.0)	11 (84.6)		15 (71.4)		10 (76.9)	
Yes	6 (37.5)	4 (50.0)	2 (15.4)		6 (28.6)		3 (23.1)	
Palmar-plantar Erythron dysesthesia syndrome				0.673		0.705		>0.999
No	13 (81.3)	7 (87.5)	9 (69.2)		17 (81.0)		10 (77.0)	
Yes	3 (18.8)	1 (12.5)	4 (30.8)		4 (19.1)		3 (23.1)	
Pneumothorax				0.233		0.166		0.067
No	9 (56.3)	5 (62.5)	11 (84.6)		12 (57.1)		6 (46.2)	
Yes	7 (43.8)	3 (37.5)	2 (15.4)		9 (42.9)		7 (53.9)	
Anorexia				0.034		0.315		0.472
No	8 (50.0)	4 (50.0)	12 (92.3)		12 (57.1)		7 (53.9)	
Yes	8 (50.0)	4 (50.0)	1 (7.7)		9 (42.9)		6 (46.2)	

(*Continued*)

Table 2 (Continued).

Adverse Event	PR N (%)	SD N (%)	PD N (%)	P	ORR N (%)	P	CBR N (%)	P
Hypercholesterolemia				0.188		>0.999		>0.999
No	14 (87.5)	8 (100.0)	9 (69.2)		18 (85.7)		11 (84.6)	
Yes	2 (12.5)	0 (0.0)	4 (30.8)		3 (14.3)		2 (15.4)	

Note: Detailed data has been published in PMID 30559126.[27]

pneumothorax in this setting are not clearly known, but may include fistula formation between the lung parenchyma and pleural space due to necrosis of a subpleural tumor nodule, infarction and necrosis of tumor emboli, over distension, and subsequent rupture of alveoli following VEGFR-TKI therapy.[15,17] In our study, pneumothorax was reported far more frequently than other solid tumors and with appropriate management, the prognosis seemed to be far more better than those that did not have it.

Based on univariate analyses of AEs on PFS (Figure 1), we observed that anorexia and hypertension were associated with improved clinical outcomes (HR, 0.35; $P = 0.01$ and HR, 0.44; $P = 0.07$, respectively). Further Kaplan-Meier analysis of PFS (Figures 3 and 4) showed that these two groups of patients could be separated obviously, indicating people with these one or two AEs would benefit more from the drug. Hypertension is observed with all of the VEGF pathway inhibitors and is likely linked to a decrease in nitric oxide (NO) leading to vasoconstriction.[38] The VEGF pathway activates endothelial NO synthase (eNOS),[39] and the inhibition of the VEGF pathway was reported to reduce the endothelial expression of eNOS in the kidney.[40] Regular monitoring of blood pressure is essential for patients receiving apatinib, potentially with the aid of home monitoring. Although it was not an independent factor in our study according to multivariate analysis, hypertension indicated a longer PFS in previous studies.[15,16,40] We tend to monitor it during the whole apatinib-treatment course and manage it with combination drug therapy.

The major limitation of our trial is the relatively small sample size and absence of a control group. In addition, personal discrepancy could easily influence the distribution and report of these toxicities. Further, larger sample analysis with a multi-center phase three trial is undergoing and more solid data are expected to better optimize apatinib-base therapy in advanced osteosarcoma.

Conclusions

Our study indicated that the development of anorexia, hypertension, pneumothorax, and hypothyroidism might be potential signs for the efficacy following apatinib-treated refractory osteosarcoma. These AEs arising early in the treatment course, which are mild or moderate and are manageable by patient monitoring and supportive care, would predict better prognosis.

Trial Registration

Prospectively registered in the Medical Ethics Committee of Peking University People's Hospital. The trial registration number is 2015PHB176-01 and the date of registration is March 15th 2016.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board of Peking University People's Hospital (Beijing, China), and was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice.

Patient Consent for Publication

All of the patients provided written informed consent for publication of their data. However, because they were all in Chinese, the English version of their consents are not applicable.

Data Sharing Statement

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

Author Contributions

Lu Xie, Jie Xu, and Wei Guo designed and developed the trial. Wei Guo, Xiaodong Tang, Rongli Yang, and Taiqiang Yan were responsible for patient inclusion. Lu Xie, Jie Xu, and Xin Sun collected data. Lu Xie, Jie Xu, and Wei Guo analyzed and interpreted the data. Lu Xie wrote the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest.

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