Anlotinib, Vincristine, and Irinotecan for Advanced Ewing Sarcoma After Failure of Standard Multimodal Therapy: A Two-Cohort, Phase Ib/II Trial

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. Both protracted irinotecan and antiangiogenesis therapy have shown promising efficacy against Ewing sarcoma (EWS).

Methods. Patients diagnosed with recurrent or refractory EWS were enrolled and further categorized into cohort A (≥16 years) or cohort B (<16 years). In the dose-defining phase Ib portion, anlotinib was given daily at a fixed dose, while a 3+3 design with dose de-escalation was used to determine the dose of irinotecan. The next dose-expanding phase II portion employed a conventional two-stage study design model. The primary endpoint was objective response rate at 12 weeks (ORR$_{12w}$).

Results. A total of 41 patients finally received the treatment regimen, including 29 in cohort A and 12 in cohort B. For cohort A, the first five patients were treated at the initial level of 20 mg/m^2/d d × 5 × 2, and two of them subsequently a dose-limiting toxicity (DLT). An additional six patients were then treated at 15 mg/m^2 without any DLT, and the RP2D was determined. Notably, 23 out of 24 patients in cohort A were available for response evaluation at 12 weeks. ORR$_{12w}$ was determined to be 62.5%. For cohort B, no DLT was observed in the first six patients at the initial dose level. At last, 12 patients were included in cohort B. The ORR$_{12w}$ was 83.3%. The most frequently observed grade 3/4 adverse events were leukopenia (28.5%), neutropenia (24.4%), anemia (8.7%), and diarrhea (3.7%).

Conclusion. The combination of vincristine, irinotecan, and anlotinib demonstrated an acceptable toxicity profile and promising clinical efficacy in patients with advanced EWS. *The Oncologist* 2021;26:e1256–e1262

Implications for Practice: This is the first trial to evaluate an irinotecan-based regimen in combination with antiangiogenesis tyrosine kinase inhibitors in Ewing sarcoma (EWS). A 3+3 design with dose de-escalation was used to determine the most appropriate dose of irinotecan in each cohort. The next dose-expanding phase II portion employed a conventional two-stage study design model. The objective response rate was 62.5% for adults and 83.3% for children. Median overall survival was not matured. This study shows that the combination of vincristine, irinotecan, and anlotinib demonstrates an acceptable toxicity profile and promising clinical efficacy in patients with advanced EWS.

Background

Ewing sarcoma (EWS) is a small round blue cell tumor derived from primordial mesenchymal stem cells, which often originates in the bone marrow. The prognosis of patients with EWS refractory to first-line treatment or recurring after radical therapy is relatively poor [1]. Although numerous potential drugs, including targeted therapy and immunotherapy, have been tested over the past 15 years [2, 3], the best therapeutic response was

achieved by traditional irinotecan-based regimens [4]. Compared to single-bolus dose, a protracted administration of irinotecan for more than 5 days could lead to better outcomes in pediatric patients with sarcoma [4, 5].

Small molecular tyrosine kinase inhibitors (TKIs) targeting a broad spectrum of vascular endothelial growth factor receptor (VEGFR) have been introduced in patients with EWS, and promising results have been reported [6–8]. Anlotinib is a multikinase angiogenesis inhibitor that suppresses the activation of VEGFR2, platelet-derived growth factor receptor beta (PDGFRβ), and fibroblast growth factor receptor 1 [9] and exhibits antitumor activity in several soft-tissue sarcoma entities. According to previous reports in soft-tissue sarcomas, we noticed that anlotinib may have better tolerance [10, 11]. It has been demonstrated that irinotecan can synergistically enhance the antiproliferative and proapoptotic effects of multikinase angiogenesis inhibitors in preclinical models [12]. The combination of multikinase angiogenesis inhibitors and irinotecan has been applied to colorectal cancer [13] and pancreatic cancer [12], which shows good therapeutic efficacy and low toxicity. Based on the evidence of this synergistic effect, we designed a multicenter, two-cohort, phase Ib/II trial to evaluate the safety and efficacy of anlotinib, vincristine, and irinotecan (AVI) in patients with advanced EWS.

SUBJECTS, MATERIALS, AND METHODS

Study Design

This is a multicenter, two-cohort, phase Ib/II clinical trial (NCT03416517). Patients were enrolled into different cohorts according to age at enrollment: cohort A (≥16 years) and cohort B (<16 years). Dose-limiting toxicity (DLT) is defined by any of the following adverse events: (a) grade 4 neutropenia lasting >7 days or febrile neutropenia; (b) grade 4 thrombocytopenia (platelet <25,000/mm^3); (c) grade 3 or 4 nonhematological adverse effects with the specific exclusion of grade 3 nausea or vomiting, grade 3 diarrhea or abdominal pain, and grade 3 hypertension; (d) delay in starting the next treatment cycle within 7 days or treatment discontinuation due to adverse events; and/or (e) treatment-related death. Prophylactic use of granulocyte colony-stimulating factor was permitted.

In the dose-defining phase Ib portion, a 3+3 design with dose de-escalation was used to evaluate the recommended level of irinotecan in each cohort. Specifically, a fixed anlotinib level of 12 mg was given to cohort A and 8 or 12 mg to cohort B (12 mg if body surface area [BSA] is ≥1.0 m^2 or 8 mg if BSA is <1.0 m^2). Different dose levels of irinotecan were predesigned according to previous literature and experience [4]. Recommended phase II dose (RP2D) was defined as the highest dose at which no more than 30% patients experienced a DLT during the first two courses. In each cohort, the first three patients were treated at a standard dose level 0, and three additional patients were treated at this level if one or no DLT was noticed. If no more than one DLT was observed in all the six patients, this level was then adopted as RP2D. If two or more of these patients

experienced a DLT, the subsequent three patients were enrolled at a lower level.

In the next dose-expanding phase II portion, RP2D defined in the previous phase Ib was adopted. A conventional two-stage study design model was used to distinguish a favorable true response rate of 24% from a null rate of 5%. In stage 1, 12 patients were recruited. If one or more patients experienced objective responses, an additional 10 patients were enrolled into stage 2 to achieve a total population of 22 patients. Objective response rate (ORR) was defined as the proportion of patients with partial response (PR) and complete response (CR), ORR = CR + PR. If 3 or more of the 22 patients experienced objective responses, the regimen was considered effective. This statistical model assumed a null versus alternative response rate as 5% versus 24%, with a 9% type I error and 91% power. This design could reach a 54% probability of stopping early if the drug was ineffective. Patients who were initially treated at the RP2D level in phase Ib, with the presence of target lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, were directly transferred to the phase II portion.

This clinical trial was conducted after approval by the local institutional review board and independent ethics committee and done in accordance with the ethical principles derived from the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice Guidelines and locally applicable laws and regulations on January 22, 2018. Informed consent was obtained from each patient in Chinese.

Data available on request from the authors.

Inclusion and Exclusion Criteria

The inclusion criteria for phase Ib were as follows: (a) age ≥3 years; (b) histologically confirmed recurrent or refractory unresectable EWS, but EWS-FLI 1 translocation by fluorescence in situ hybridization was not required in this study; (c) prior treatment consisted of standard EWS chemotherapy agents such as doxorubicin, vincristine, cyclophosphamide, ifosfamide, and etoposide; (d) adequate organ function; (e) an Eastern Cooperative Oncology Group performance status of 0 or 1; (f) an estimated life expectancy of ≥3 months; and (g) time elapsed from previous therapy must be ≥3 weeks for systemic therapy and ≥2 weeks for radiation therapy or major surgery. For the phase II portion, the existence of an evaluable lesion according to the RECIST version 1.1 was required in addition to the general criteria of phase Ib.

Patients were excluded if they had (a) poorly controlled hypertension; (b) metastasis to the central nervous system; (c) persistent clinically significant toxicities caused by previous cancer therapy; and/or (d) active hepatitis B, hepatitis C, or HIV.

Treatment Regimen

Protocol treatment was defined as a regimen of AVI. Specifically, the treatment consisted of a 90-minute intravenous infusion of irinotecan at a dose of 20 mg/m^2/d for 5 days at weeks 1 and 2 every 3 weeks (d × 5 × 2), vincristine given at a dose of 1.4 mg/m^2 (maximum 2 mg) on days 1 and

8, and an oral administration of anlotinib once daily on days 1–14 within a 21-day cycle. The treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discretion of the investigators. The whole regimen was delayed if the laboratory results on the first planned day of each cycle were absolute neutrophil count <1,000/mm^3, platelets <75,000/mm^3, hemoglobin <8 g/dL, serum transaminase >3 upper limit of normal (ULN), total bilirubin >1.5 ULN, common terminology criteria for adverse events (CTCAE) grade >2, as well as the occurrence of proteinuria or symptomatic toxicity. Irinotecan was obtained from Jiangsu Hengrui Medicine, Lianyungang, China, whereas anlotinib was supplied by Nanjing Zhengda Tianqing Pharmaceutical Co., Ltd.

Assessment and Follow-Up

Pretreatment evaluation included a medical history; physical examination; complete blood cell count; serum biochemical tests; and chest, abdominal, and pelvic computed tomography (CT) scans or positron emission tomography CT (PET/CT). Clinical examination and laboratory tests were conducted before and during every treatment cycle. Tumor responses were evaluated every two courses according to the RECIST version 1.1. If PR was first recorded, it should be re-evaluated and confirmed after two more courses. All adverse events during chemotherapy were evaluated every course using the National Cancer Institute CTCAE version 4.0. The minimum follow-up period was 6 months for each patient.

Treatment Outcomes

For phase Ib, the aim was to determine the optimal RP2D of AVI in each cohort. For the phase II portion, the primary endpoint was ORR at week 12 in each cohort, and the secondary endpoints included OS, PFS, and FFS. PFS was defined as the time from study entry until documented progression, protocol violation determined at investigator's discretion, serious adverse effect, or death from any cause. FFS was defined as the time from study entry to first documented progression or death from any cause.

RESULTS

From March 5, 2018 to October 5, 2018, 41 patients received the AVI treatment regimen, including 29 patients in cohort A and 12 in cohort B. The median follow-up times were 18 months (interquartile range [IQR] 16–19) in cohort A and 20 months (IQR 18–22) in cohort B, respectively. A total of 36 patients were finally enrolled in the phase II portion (Table 1).

Phase Ib Trial

For adults in cohort A, the first five patients were initially treated with 20 mg/m^2 of irinotecan in phase Ib portion, and two of them subsequently experienced a DLT. Both of them had a delay in starting the next treatment cycle for more than 7 days or treatment discontinuation due to diarrhea. An additional six patients were then treated with a lower dose (15 mg/m^2) of irinotecan, and no DLT was

Table 1. Demographics and baseline characteristics

Patients	Cohort A (n = 24)	Cohort B (n = 12)
Age (years; mean ± SD)	28 ± 9	11 ± 3
Sex, n (%)		
Male	19 (79.2)	5 (41.7)
Female	5 (20.8)	7 (58.3)
ECOG performance status at enrollment, n (%)		
0	19 (79.2)	10 (100.0)
1	5 (20.8)	2 (16.7)
Presence of metastasis, n (%)		
No (local advanced disease)	1 (4.2)	2 (16.7)
Yes	23 (95.8)	10 (83.3)
Primary tumor location, n (%)		
Extremities	9 (37.5)	5 (41.7)
Axial skeleton	6 (25.0)	3 (25.0)
Other	9 (37.5)	4 (33.3)
Site of target and non-target lesions, n (%)		
Lung only	11 (45.8)	4 (33.3)
Other organs involved	13 (54.2)	8 (66.7)
Time from first diagnosis to enrollment, n (%)		
≤24 months	22 (91.7)	12 (100.0)
>24 months	2 (8.3)	0 (0.0)
Lines of previous chemotherapy, n (%)		
1	15 (62.5)	8 (66.7)
≥2	9 (37.5)	4 (33.3)
EWS-FLI1 translocation, n (%)		
No	1 (4.2)	1 (8.3)
Yes	11 (33.3)	9 (75.0)
Not available	12 (50.0)	2 (16.7)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EWS, Ewing sarcoma.

observed. These six patients were directly transferred to the phase II portion.

For children in cohort B, no DLT was found in the first six patients treated with a standard dose (20 mg/m^2) of irinotecan. All these patients were directly transferred to the phase II portion.

Phase II Trial

Patient Enrollment

A total of 27 patients and 12 patients were assigned to cohorts A and B, respectively. The median number of cycles received per patient was 8 (range, 1–16). For the 27 patients in cohort A, two withdrew informed consent before treatment, one was diagnosed with hepatitis B virus infection and thus excluded, and one withdrew informed consent after the first assessment following two treatment courses, which recorded as unconfirmed PR. In total, 23 patients were

available for response evaluation at week 12. For cohort B, subject recruitment was halted prematurely by the investigators because of slow enrollment. Six patients in phase Ib were transferred to phase II directly, and an additional six patients were enrolled. Table 1 summarizes the baseline demographics and treatment characteristics of the patients.

Objective Response

Of the 23 evaluable patients in cohort A, 1 CR, 14 PR, 2 stable disease (SD), and 6 progressive disease (PD) were observed (supplemental online Fig. 1). Although two patients with bone lesions showed complete resolution of 18F-fludeoxyglucose uptake within tumor volume, abnormal lesions were still noticed on MR scan. Both of them were recorded as complete metabolic response (CMR) and classified into PR. The value of ORR was calculated to be 65%.

For cohort B, evaluation was available in all 12 patients. As shown in Table 2, there were four CR, six PR (including one CMR), and two PD. The ORR was 82%, and no SD was found in this cohort (supplemental online Fig. 2).

Survival and Long-Term Treatment Compliance

Considering the unexpected high efficacy, patients appealed for further local treatment to achieve better oncological outcome and better quality of life after obtaining CR or PR. For the benefit of patients, they were encouraged to discontinue standard AVI in the following situations: (a) whole lung radiation (WLI) if all pulmonary lesions were less than 3 mm in two consecutive CT scans; (b) surgical resection or radical radiation when a primary unresectable lesion became resectable and slow or no reduction in size was observed during the last assessment; (c) CR or nearly CR for longer than 6 months, and patients appealed for better quality of life, increased family involvement, and social work. Although the standard stick-to-protocol AVI was discontinued, a less dose-intense regimen was adopted in the

Table 2. Efficacy of AVI in adult (*n* = 24) and child (*n* = 12) patients with advanced Ewing sarcoma

| Efficacy measurements	Adult (*n* =24)	Children (*n* = 12)
Response at 12 weeks		
Complete response	1 (4.2%)	4 (33.3%)
Confirmed partial response[a]	14 (58.3%)	6 (50.0%)
Stable disease	2 (8.3%)	0 (0.0%)
Progressive disease	6 (25.0%)	2 (16.7%)
ORR at 12 weeks	62.5%	83.3%
ITT failure-free survival		
KM median, months (95% CI)	10.2 (6.0, 14.2)	8.7 (5.1, 14.4)
ITT overall survival		
KM median	NR	NR
Patients' status at last follow-up		
NED	3 (12.5%)	3 (25.0%)
AWD	12 (50.0%)	5 (41.7%)
DOD	9 (37.5%)	4 (33.3%)

[a]One patient received only two cycles of AVI and was evaluated as unconfirmed PR.
Abbreviations: AVI, anlotinib, vincristine, and irinotecan; AWD, alive with disease; CI, confidence interval; DOD, died of disease; ITT, intention-to-treat population; KM, Kaplan-Meier; NED, no evidence of disease; NR, not reached; ORR, overall response rate.

following treatment. All these situations of protocol violation were recorded as censored in the calculation of PFS. The times of events were recorded accordingly.

The median OS and PFS were not reached in both cohort A and cohort B (Fig. 1; supplemental online Fig. 3). The median FFS was 10 months (95% confidence interval [CI] 6–14) in cohort A and 8 months (95% CI 5–14) in cohort B (supplemental online Fig. 4). All 36 patients discontinued stick-to-protocol AVI at last follow-up: (a) Nine patients were recorded as PD at week 12. (b) Two patients were determined as PR at week 12 and then got PD subsequently. One of them developed a new bone lesion after two more cycles, and another patient showed progression of the primary lung lesion after four more cycles and eventually discontinued AVI. (c) Two patients discontinued AVI because of severe adverse effects (diarrhea at cycle 7 and fatigue at cycle 5). (d) One patient discontinued AVI at cycle 8 when one lesion showed progression, while other lesions displayed significant shrink. (e) All the other 22 (61.1%) patients discontinued AVI as decided by the investigators when they were still classified as CR or PR. Ten patients received WLI when their pulmonary lesions became smaller than 3 mm. Two patients received surgical resection and five patients underwent radical radiation. The remaining five patients received a less dose-intense AVI after a median standard therapy of 8.8 months (Fig. 2).

Figure 1. Overall survival.
Abbreviation: OS, overall survival.

Toxicity in Phase II Portion

Table 3 summarizes the toxicities (>1.0%) attributed to AVI in all assessable patients. The top three most common
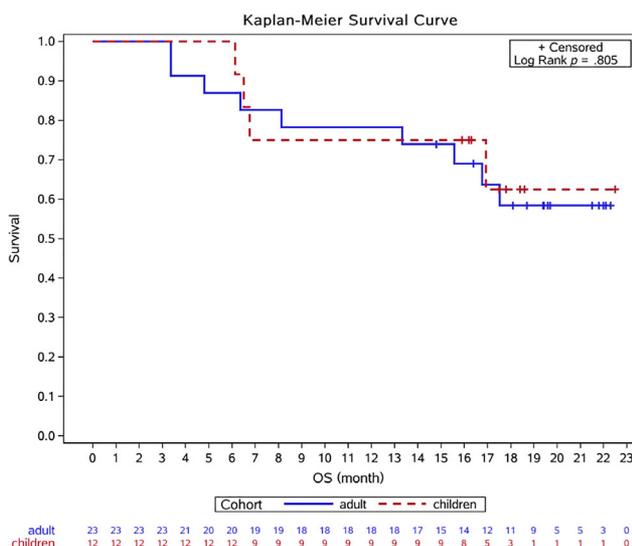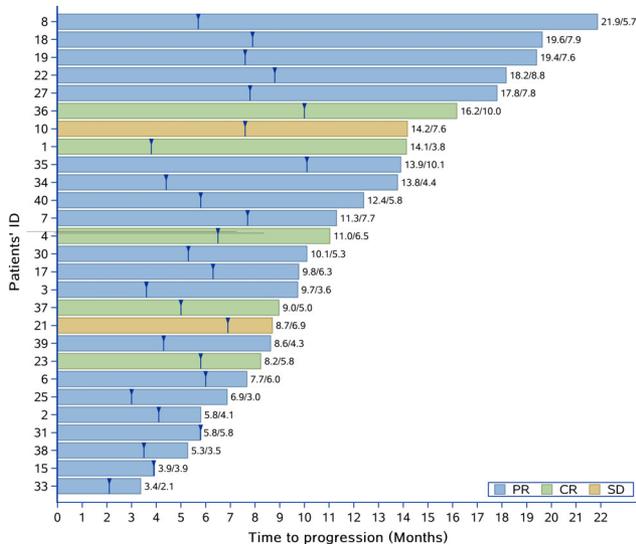
Figure 2. Duration of response for all patients (cohorts A and B). The numbers at the end of each line represent the duration of response. The number before the slant line means the whole period of time before progression, whereas the number after the slant line meansthe period of time from first evaluation of PR or CR to progression on treatment per protocol or the beginning of concurrent local treatment.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

toxicities were leukopenia (70.1%), anemia (53.7%), and neutropenia (51.0%), and the most commonly reported grade 3/4 adverse effects were leukopenia (28.5%), neutropenia (24.5%), and anemia (8.7%).

Table 3. Toxicities (>1.0%) attributed to therapy in assessable patients (n = 298 courses)

Adverse event	All, n (%)	Grade 3/4, n (%)
Leukopenia	209 (70.1)	85 (28.5)
Anemia	160 (53.7)	26 (8.7)
Neutropenia	152 (51.0)	73 (24.5)
Hypokalemia	79 (26.5)	1 (0.3)
Hyponatremia	79 (26.5)	0 (0.0)
ALT increased	75 (25.2)	0 (0.0)
Diarrhea	62 (20.8)	11 (3.7)
Hypoalbuminemia	61 (20.5)	0 (0.0)
Hypertriglyceridemia	51 (17.1)	0 (0.0)
Hyperbilirubinemia	40 (13.4)	0 (0.0)
AST increased	38 (12.8)	0 (0.0)
Proteinuria	32 (10.7)	0 (0.0)
Hypothyroidism	25 (8.4)	0 (0.0)
Thrombocytopenia	15 (5.0)	2 (0.7)
Fatigue	14 (4.7)	4 (1.3)
Dyspepsia	13 (4.4)	0 (0.0)
Myalgia	11 (3.7)	0 (0.0)
Anorexia	10 (3.4)	2 (0.7)
Weight loss	10 (3.4)	2 (0.7)
Abdominal pain	9 (3.0)	3 (1.0)
Hypertension	8 (2.7)	2 (0.7)
DIC	6 (2.0)	0 (0.0)
Fever	6 (2.0)	1 (0.3)
Skin ulceration	6 (2.0)	3 (1.0)
Bone pain	6 (2.0)	0 (0.0)
Epistaxis	5 (1.7)	0 (0.0)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DIC, disseminated intravascular coagulation.

DISCUSSION

The results of this phase Ib/II study indicated the feasibility and efficacy of the multi-targeted TKI anlotinib in combination with classical cytotoxic drugs irinotecan and vincristine in patients with recurrent or refractory EWS. In the phase Ib portion, dose de-escalation of irinotecan was achieved without any DLT in pediatric patients with EWS. A lower irinotecan dose was adopted in adult patients due to diarrhea, the most common adverse effect caused by irinotecan. As for the dose of anlotinib in both cohorts and irinotecan in the children cohort, the classical dose of each drug was still adopted [10, 14, 15].

The irinotecan-based regimen has been tested in patients with EWS in several prospective and retrospective trials. Several schedules of irinotecan administration have been studied. Compared with a high-dose compressed regimen [16, 17], a protracted infusion of low-dose irinotecan for more than 5 consecutive days showed better efficacy [18–20] in preclinical models [21] and clinical trials, especially in pediatric sarcomas. Frequent administration of low-dose irinotecan should be considered to increase response rates in the clinic. Based on this point of view, we adopted the original schedule of d × 5 × 2 q3w. The combination of irinotecan and temozolomide with or without vincristine has been used to treat patients with EWS, with an ORR of 29%–63% [15, 22–25]. In the recent rEECur trial, which is an international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma, the combination of irinotecan and temozolomide (d × 5 × 1, q3w) has shown an ORR of 20% versus 23% in topotecan/cyclophosphamide or ifosfamide group. However, 38% of patients discontinued before cycle 4 and were recorded as unevaluable, which may partly explain the relatively lower response rate [26]. In the phase II portion, compared with previously published data in the same group of heavily pretreated patients with EWS, we observed relatively high values of ORR in both cohorts. Although diarrhea was the main side effect of irinotecan, myelosuppression became a much more severe adverse effect of AVI regimen. The higher ORR and different spectrum of adverse events may be partly explained by the addition of anlotinib.

Antiangiogenic TKIs, such as cabozantinib [7], pazopanib [27], and apatinib [8], have shown meaningful activity in patients with EWS. As a multi-targeted TKI, the target molecules (e.g., VEGFR 1-3, EGFR, PDGFR-α and -β, FGFR 1–3, and stem cell factor receptor) of anlotinib can contribute to the inhibition of tumor angiogenesis and consequently affect tumor cell growth function [9, 28]. The antitumor

activity of anlotinib has been reported in many solid tumors, including non-small cell lung cancer [29], thyroid cancer [30], and soft-tissue sarcomas [10]. Previous studies showed that anlotinib was well tolerated in heavily treated patients [9, 10]. Synergistic effect of antiangiogenic TKI and irinotecan has been demonstrated in preclinical models [31], as well as in colorectal cancer, using sorafenib [13] or regorafenib [32]. However, an increased risk of diarrhea and neutropenia was observed in these trials. In this trial, we observed a higher ORR in the combination of AVI (65% in adults and 82% in children) compared with traditional irinotecan and vincristine (29%–63%) [15, 22–24].

In most trials, treatment will be continued unless there is disease progression or untolerated side effects. The eventual response rates in this trial were high, and the investigators attempted to cure more patients. To provide clinical benefits for patients, they were encouraged to receive WLI when all pulmonary lesions became too small to be evaluated, or surgical resection for primary unresectable lesions if surgeons feel confident regarding the adequacy of surgical margins. After local treatment (e.g., WLI), a less dose-intense schedule was adopted in the subsequent treatment to improve their quality of life. All these data were recorded as endpoints in the calculation of PFS when they received local treatment or WLI. In our study, PFS was defined as the time from study entry until documented progression, protocol violation determined at investigator's discretion, serious adverse effect, or death from any cause. Based on such a high rate of protocol violation determined at investigator's discretion, the PFS in our study may be largely dependent on investigators (22/36, 66.1%), instead of disease progression (11/36, 30.6%) or severe adverse effects (2/36, 5.6%). FFS, where local treatment and WLI were allowed in the calculation, was believed to be the result of a comprehensive sequential treatment. Unfortunately, as a result of different sequential therapy, neither FFS nor PFS could reflect the process of tumor evaluation or biological resistance to AVI. The impacts of sequential therapy on final oncological outcome and long-term prognosis will be discussed in our future article.

Given the high efficacy and good tolerance of AVI in patients with recurrent or refractory Ewing sarcoma, we believe it will become a promising choice in the future. The question is how to get long-term disease-free survival with good quality of life. In this study, we used WLI when all pulmonary lesions became too small to be evaluated and then stopped frequent chemotherapy or anlotinib. However, most of the patients experienced pulmonary recurrence later. We plan to design several maintenance tools, including anlotinib for at least half a year and stereotactic radiotherapy at an early stage rather than WLI at the end of chemotherapy, aiming at a longer recurrent-free survival.

Conclusion

The combination of vincristine, irinotecan, and anlotinib is well tolerated and provides meaningful clinical efficacy in patients with relapsed or refractory EWS after first-line chemotherapy. Future research is needed to establish the sequential treatment strategy for patients with advanced/recurrent EWS.

Author Contributions

Conception/design: Lu Xie, Jie Xu, Wei Guo
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