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Efficacy and safety of chiauranib in a combination therapy in platinum-resistant or refractory ovarian cancer: a multicenter, open-label, phase Ib and II study

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Abstract

Background Platinum-resistant or refractory ovarian cancer is a highly lethal gynecologic disease with limited treatment options. Chiauranib is a novel small-molecule selective inhibitor, which could effectively target multiple pathways including Aurora B and CSF-1R to inhibit cell cycle process and improve anti-tumor immune function, as long as VEGF pathway for tumor extinction.

Methods A phase II study was sequentially conducted after a phase Ib monotherapy study to evaluate the efficacy of chiauranib combined with chemotherapy. Chinese patients with recurrent ovarian cancer were enrolled. Eligible patients received chiauranib combined with a maximum of six cycles of chemotherapy: etoposide (CE group) or weekly-paclitaxel (CP group). Patients, who exhibited a complete or partial response, or stable disease following combo treatment, progressed to maintenance phase to receive chiauranib monotherapy. Primary endpoint was progression-free survival (PFS) according to RECIST v1.1.

Results From November 2017 to March 2019, 25 patients were enrolled in a phase 1b study and a median PFS of 3.7 months (95% CI 1.8–NE) was achieved by chiauranib monotherapy. From July 2019 to December 2020, a total of 47 patients were enrolled in the phase II study. One CP patient did not receive the study drugs, and three patients withdrew before the first tumor assessment. Thus, 43 patients (CE group: 22 patients; CP group: 21 patients) were included in the evaluation. The median PFS was 5·4 months (95% CI 2·8–5·6) and 5·6 months (95% CI 3·4–7·0), respectively.

Conclusions This was the first study to evaluate chiauranib, a novel multi-targeted kinase inhibitor in patients with ovarian cancer. The administration of chiauranib along with etoposide or weekly-paclitaxel significantly enhanced the efficacy with manageable adverse events. This warrants further clinical studies on this novel treatment. A phase III study is promising and ongoing.

Trial registration ClinicaTrials.gov identifier: NCT03901118 (phase II) and NCT03166891 (phase Ib).

Keywords Chiauranib, Ovarian cancer, Kinase inhibitor, Combo therapy, Clinical Trial

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Introduction

Ovarian cancer is a highly fatal gynecologic malignancy and ranks as the eighth most common cancer in women globally. In 2020, approximately 313,959 new cases were diagnosed, resulting in 207,252 deaths. The majority of patients are diagnosed with advanced-stage disease (stage III or IV). Treatment typically involves surgical debulking followed by chemotherapy. However, despite initial positive responses to platinum-based chemotherapy, over 75% of patients experience relapse. Eventually, nearly all patients become platinum resistant. Platinum resistance, defined as disease progression within six months of the last platinum-based chemotherapy, is common and carries a rather poor prognosis.

Despite its limited effectiveness, single-agent chemotherapy remains main treatment for recurrent platinum-resistant ovarian cancer [1]. From the mechanism, anti-angiogenic treatment can improve the treatment efficacy for the platinum resistant or refractory cancers. Several studies have investigated antiangiogenic-targeted therapies (e.g., VEGFR monoclonal antibody or tyrosine kinase inhibitor (TKI) therapy) for treating ovarian cancer, but the results obtained from these therapies alone were unsatisfactory [2–4]. Overall, vascular-targeted monotherapy has similar efficacy to that of non-platinum-based single-agent chemotherapy. Although bevacizumab was approved by the FDA for platinum-resistant ovarian cancer who received no more than two prior chemotherapy regimens, bevacizumab was not approved by NMPA because no clinical trials in platinum-resistant or platinum-refractory ovarian cancer had been conducted in China. Anti-angiogenic agents are neither licensed nor have they provided conclusive data based on critical phase III trials in China. The combination therapy involving bevacizumab is only approved in China as a first-line treatment following initial surgery. And no combination therapy of anti-angiogenic drugs with chemotherapy had been approved in platinum-resistant or platinum-refractory ovarian cancers. Therefore, there remains a significant unmet clinical need for treating platinum-resistant or platinum-refractory ovarian cancer.

Chiauranib, a multi-targeted kinase inhibitor of aurora kinase B (AURKB), colony-stimulating factor 1 receptor (CSF-1R), and vascular endothelial growth factor receptor (VEGFR)/platelet-derived growth factor receptor (PDGFR)/c-Kit receptor, is an oral active dual-pathway inhibitor of mitosis and neo-angiogenesis with highly selective binding to and inhibiting kinases related to mitosis, chronic inflammation, and angiogenesis. Based on the mechanism of multi-targeted kinase inhibitor, its anti-tumor effects are multiple, not just from inhibiting angiogenesis. Of particular note, it is unique among existing antiangiogenic TKIs due to its inhibition activity on AURKB, a member of the Aurora mitotic kinase family that monitors the normal function of several critical processes in the cell cycle and proliferation. Overexpression of Aurora B, a mitosis-related kinase, is associated with poor prognosis in epithelial ovarian cancer patients. One report revealed that targeting of Aurora B was an attractive way to increase cell sensitivity to chemotherapy, which could also display a synergistic effect in inhibiting cell proliferation and inducing apoptosis, especially in selected group of cisplatin-resistant ovarian carcinomas [5]. Chiauranib has also shown high antitumor efficacy in several human tumor xenograft models [6]. In its first-in-human clinical trial, chiauranib was administered to 18 patients with advanced solid tumors to determine the tolerability and pharmacokinetics of chiauranib, one of whom with ovarian cancer received 65 mg of chiauranib and showed a 23.5% decrease in the lesion size. Based on those data, 50 mg/day was determined as the maximum tolerated dose of chiauranib monotherapy, and it was hypothesized that it could be more effective when chiauranib was combined with chemotherapy in platinum-resistant or refractory ovarian cancer.

The phase II trial was conducted based on a pioneer phase Ib study to further evaluate therapeutic effects of chiauranib combined with chemotherapy in patients with recurrent ovarian cancer. In order to better demonstrate the results of combination therapy, we also introduced the results of phase Ib study in this article. Moreover, platinum-refractory ovarian cancer and clear cell carcinoma of ovarian cancer, which were known for poor prognosis, was not excluded from the study.

Methods

Study design and participants

A total of 47 patients from nine hospitals in China were enrolled in this phase II trial. Before this phase II trial, a pioneer phase Ib trial was conducted in 25 patients from four hospitals in China to evaluate the preliminary efficacy of chiauranib monotherapy. These two trials shared the same population. The eligibility criteria were as follows: (i) women (≥ 18 or ≤ 70 years old) with histologically or cytologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer; (ii) had measurable/assessable ovarian cancer that progressed after at least one platinum-based therapy and no more than two therapy lines for recurrent disease; (iii) Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, adequate organ function and hematological and biochemical parameters. Patients with platinum-resistant (defined as progression or recurrence of ovarian cancer within 6 months since the last administration of platinum-containing regimen) or platinum-refractory

(defined as progression during the first platinum-based treatment) ovarian cancer were permitted to be enrolled.

The main exclusion criteria were: (i) previous exposure to inhibitors of VEGF/VEGFR or Aurora kinases, etoposide, or weekly paclitaxel; (ii) had uncontrolled hypertension or significant cardiovascular diseases within 6 months before study initiation, including unstable angina, myocardial infarction, and New York Heart Association class III or IV congestive heart failure. Patients with at least one symptom were excluded: interstitial lung disease (ILD), deep vein thrombosis or pulmonary embolism, clinically significant gastrointestinal abnormalities, active bleeding, current thrombotic illness, or major surgery within the last six weeks.

Considering the phase II study was the first exploration of chiauranib combined with chemotherapy, a pretrail was taken to ensure the safety. Before the phase II trial, 3 subjects were enrolled in chiauranib with paclitaxel (CP) group and the other 3 were in chiauranib with etoposide (CE) group. A daily dose of 25 mg of chiauranib was taken orally to preliminarily evaluate the safety of the combination of chiauranib and chemotherapy. After all pre-trial subjects completed the first cycle of safety evaluation, the enrollment of formal phased II trial began. Among the 6 patients in the pre-trial, 2 requested to withdraw from the study due to own decision or disease progression in the first cycle. The other 4 patients were adjusted to 50 mg/day in the subsequent trial in order not to expose patients to ineffective doses. In the phase II trial, patients were randomly assigned to receive oral chiauranib with etoposide or weekly paclitaxel in a 1:1 ratio in a central manner. Patients received 50 mg of chiauranib daily alongside either 50 mg of oral etoposide for 21 days of a 28-day cycle or 60 mg/m^2 of paclitaxel (on days 1, 8, and 15) every 21 days. Etoposide and paclitaxel were limited to six cycles. Responders entered a maintenance phase with chiauranib. Dose adjustments were made as required per protocol. Patients were screened by CT or MRI of the chest, abdomen, and pelvis with head radiography for CNS symptoms four weeks before randomization and after every two cycles for each group until disease progression. Adverse events were recorded and graded as per guidelines. The primary endpoint was investigator-assessed PFS following RECIST v1.1. The secondary endpoints included overall survival (OS), the response duration, and time to progression and safety.

Statistical analysis

This trial was designed as a preliminary exploration. No statistical assumptions were made, and a sample size of 20–30 cases for each group was chosen only for exploratory purposes. The primary and secondary efficacy endpoints were assessed based on the intent-to-treat (ITT) patient group (i.e., all patients receiving at least one dosage of trial medication). All ITT patients who had filled out at least one safety case report form were included in the safety analysis. The ORR and its 95% confidence interval were calculated. The distributions of progression-free survival, duration of response, overall survival, and time to progression were evaluated using Kaplan–Meier curves. Based on the preliminary efficacy and safety results obtained in this phase II trial, the investigator discussed with the sponsor to determine whether to initiate a randomized controlled study comparing the treatment results of combination therapy (chiauranib and chemotherapy) and chemotherapy alone. Given that the efficacy data and median PFS of CP group were superior to those of the CE group. CP combination was chosen as the experimental group for future study in a phase III design.

Results

From Jul 03, 2019, to Dec 21, 2020, a total of 46 patients were enrolled to receive chiauranib combination therapy (CE group: 24 patients; CP group: 22patients). In the pioneer phase Ib trial, 25 patients were enrolled to receive the monotherapy. In the monotherapy stage, the median patient age was 50 years (34 to 69 years), and 88% of patients had received three or more previous systemic therapies, with none classified as platinum-refractory ovarian cancer patients. In the combination therapy or combo stage, the median patient age was 52 years (CE group) and 53 years (CP group). In the CE group, 29.2% of patients had three or more previous therapies; in the CP group, 27.3% had a similar history, including one platinum-refractory ovarian cancer patient (Table 1).

During the monotherapy stage, 25 patients received chiauranib alone. Two patients withdrew before the first tumor evaluation due to a lack of post-baseline efficacy assessment. Among the 23 patients evaluated, the ORR was 8.7% (95% CI, 1.1–28.0) (Fig. 1A, Supplementary Tab.1). In the combo stage, 47 patients were randomly assigned to the CE or CP group. One CP patient did not receive the study drugs, and three patients withdrew before the first tumor assessment. Thus, 43 patients (22 receiving chiauranib plus etoposide and 21 receiving chiauranib plus paclitaxel) were included in the evaluation. The ORR was 40.9% (95% CI, 20.7–63.7) in the CE group and 52.4% (95% CI, 29.8–74.3) in the CP group (Fig. 1B-C, Supplementary Tab.1).

Regarding PFS, the monotherapy group recorded 12 PFS events with a median PFS of 3.7 months (95% CI 1.8-NE) (Fig. 1D). In contrast, the CE and CP groups saw 18 and 17 PFS events with median PFS values of 5.4 months (95% CI 2.8–5.6) and 5.6 months (95% CI 3.4–7.0), respectively (Fig. 1E-F). The CE group exhibited

Table 1 Baseline characteristics of patients

	Chiauranib only (*n* = 25)	**Chiauranib with etoposide** (*n* = 24)	**Chiauranib with paclitaxel** (*n* = 22)
Age, years	50 (34, 69)	52 (43, 66)	54 (37, 69)
Duration, months	39.3 (23.1, 105.8)	12.3 (5.2, 41.0)	15.0 (7.5, 71.0)
Disease primary site			
Epithelial ovarian cancer	24 (96.0)	24 (100.0)	21 (95.5)
Carcinoma of fallopian tube	0	0	1 (4.5)
Peritoneal cancer	1 (4.0)	0	0
Histologic subtype			
High-grade serous carcinoma	17 (68.0)	17 (70.8)	18 (81.8)
Low-grade serous carcinoma	1 (4)	0	0
Clear cell carcinoma	0	1 (4.2)	1 (4.5)
Endometrioid carcinoma	5 (20.0)	1 (4.2)	1 (4.5)
Mucinous carcinoma	2 (8.0)	1 (4.2)	0
Unknown	0	4 (16.7)	3 (13.6)
ECOG performance status			
0	15 (60.0)	11 (45.8)	12 (54.5)
1	10 (40.0)	13 (54.2)	10 (45.5)
FIGO stage			
II	0	1 (4.2)	2 (9.1)
III	12 (48.0)	14 (58.3)	15 (68.2)
IV	11 (44.0)	8 (33.3)	5 (22.7)
Unkonwn	2 (8.0)	1 (4.2)	0
Platinum-free interval			
Refractory	0	0	1 (4.5)
Sensitive	3 (12.0)	0	0
Resistant	22 (88.0)	24 (100.0)	21 (95.5)
Previous treatment lines			
1	0	11 (45.8)	11 (50.0)
2	3 (12.0)	6 (25.0)	5 (22.7)
≥ 3	22 (88.0)	7 (29.2)	6 (27.3)
Radiotherapy	2 (8.0)	2 (8.3)	0
Operation	25 (100.0)	24 (100.0)	22 (100.0)

Data are median (range) or n (%)

a median OS of 14 months (95% CI 7.5-NE), while OS results were not mature for the other two groups at the data cutoff date (Supplementary Tab.2). The median follow-up time of CE group and CP group was 11.2 months and 12 months, respectively. The median follow-up time of monotherapy (phase Ib) study was 10.2 months. Notably, 7 of 25 patients (28.0%) in the chiauranib-only group, 5 of 24 patients (20.8%) in the CE group, and 3 of 22 patients (13.6%) in the CP group succumbed to disease progression.

In terms of adverse events (AEs), the most common Treatment-Related Adverse Events (TRAEs) in the monotherapy group were diarrhea, fatigue, decreased appetite, proteinuria, weight loss, abdominal pain, and hypertension, with most being grade 1 or 2. Grade 3 or 4 TRAEs included diarrhea (20.0%) and hypertension (16.0%) (Supplementary Tab.3). Meanwhile, there was one treatment-related deaths which was caused by multiple organ dysfunction syndrome. Five patients (20.0%) experienced treatment-related Serious Adverse Events (SAEs) (Supplementary Tab.4), and all patients experienced TRAEs (Supplementary Tab.5). Most toxicities were temporary and managed with dose adjustments or concomitant medications.

In the CE group, the most frequent TRAEs were hematological toxicities like neutropenia and leucopenia, along with non-hematological effects such as nausea and fatigue. Grade 3 or 4 TRAEs included neutropenia

(25.0%), leucopenia (25.0%), anemia (12.5%), and hypertension (12.5%). There was no treatment-related death in CE group. Four patients (16.7%) experienced treatment-related SAEs. In the CP group, hematological events like neutropenia, leucopenia, and non-hematological events like diarrhea and hypertension were predominant. Grade 3 or 4 TRAEs included neutropenia (54.5%), leucopenia (45.5%), lymphopenia (9.1%), and hypertension (27.3%). Overall, grade 3–4 AEs are more frequent in the CP group. Five patients (22.7%) experienced treatment-related SAEs (Supplementary Tab.3–4). 23 patients (95.8%) and 22 patients (100%) experienced TRAEs in the CE and CP group, respectively (Supplementary Tab.5).

In the chiauranib combination therapy group, 25.0% (CE group) and 31.8% (CP group) of patients experienced AEs necessitating chiauranib dose reduction. Additionally, 37.5% required etoposide dosage reduction and 13.6% required a one-dose-level decrease of paclitaxel, primarily due to adverse hematological events. However, one CP patient discontinued chiauranib and paclitaxel due to grade 3 interstitial pneumonia, while another CE patient discontinued etoposide due to grade 3 anorexia. SAEs occurred in 33.3% (CE group) and 27.3% (CP group) of patients (Supplementary Tab.5).

Discussion

Currently, targeted therapies for platinum-resistant/platinum-refractory recurrent ovarian cancer mainly include anti-angiogenic agents (VEGFR inhibitors), poly (ADP-ribose) polymerase (PARP) inhibitors, and immunotherapy. PARP inhibitors are recommended only for platinum-resistant/platinum-refractory patients with BRCA mutations, which constitute approximately 15% of patients. The majority of patients in platinum-resistant settings do not benefit from PARP inhibitors. Immunotherapy for ovarian cancer has not made significant breakthroughs. Limited by the efficacy of single-agent anti-angiogenic therapy and chemotherapy in platinum-resistant/platinum-refractory patients, there has been no substantial progress in recent years.

This clinical trial was the first to investigate the safety and effectiveness of chiauranib, a novel multi-targeted kinase inhibitor, in patients with recurrent ovarian cancer. Traditional anti-angiogenic drugs target the VEGF pathway only. Chiauranib inhibits Aurora B and CSF-1R, achieving inhibition of the cell cycle process and improvement of the body's anti-tumor immune function as long as targeting the VEGF pathway for tumor extinction. When chiauranib is used in combination with chemotherapy, it can play a synergistic lethal role.

In the monotherapy stage, most patients had platinum-resistant ovarian cancer. Among 23 patients, only two (8.7%) showed partial responses. The median PFS of 3·7 months was equivalent to the efficacy of standard chemotherapy, which has an ORR of 5 ~ 17% and a median PFS of around three months. Other anti-angiogenic medicines, such as pazopanib, sorafenib and bevacizumab, were previously found to have an ORR of 3 ~ 15·9% and a median PFS of 2·1 ~ 4·4 months [2–4]. Concerning chemotherapy combination, the combined treatment increased ORR to 40·9% in the CE group and 52·4% in the CP group, which was significantly higher than that after treatment with chiauranib alone and roughly double the value after treatment with etoposide or paclitaxel alone (ORR of etoposide was 27% and ORR of paclitaxel was 21%). The median PFS was 5·4 months in the CE group and 5·6 months in the CP group, which was similar to that in the recommended guidelines for pazopanib, sorafenib, and bevacizumab combined with chemotherapy.

As the number of previous lines of treatment increased, the clinical benefits patients received and their tolerance to the treatment decreased. One-third of the patients in our study received three or more lines of chemotherapy, which was higher than that in previous studies in which bevacizumab, pazopanib, and sorafenib were administered [7–9]. This study showed that combining chemotherapy with chiauranib might continuously benefit patients who have very limited treatment options. Among these patients, 2 of 46 (4.3%) were platinum-refractory and clear cell. As is well known, these two pathological conditions often represent poor prognosis.

In the monotherapy stage, the regular administration of chiauranib was manageable in ovarian cancer patients. It had a safety profile similar to that of other TKIs. The most common TRAEs were gastrointestinal reactions (diarrhea, loss of appetite, abdominal pain), fatigue, proteinuria, and hypertension. Among 25 patients, 13 (52%) had grade 3 TRAEs; diarrhea ($n=5$ [20·0%]) and hypertension ($n=4$ [16·0%])) were the most common TRAEs. Most patients discontinued because of disease progression and only 3 (12%) patients discontinued because of AEs.

The TRAEs were more common in patients treated with chiauranib combined with chemotherapy than in those who were administered either of the monotherapeutic agents. However, these events did not affect the treatment plan of the patients. Hematologic AEs were the most common, and non-hematologic AEs primarily consisted of gastrointestinal reactions and VEGFR target-related AEs. Hematologic AEs, such as neutropenia and leucopenia, were more common in the CP group than in the CE group and in studies with similar study populations where patients were administered anti-angiogenic medicines along with chemotherapy, such as AURELIA [7], MITO11 [8], TRIAS [9] and AEROC [10]. We suggest

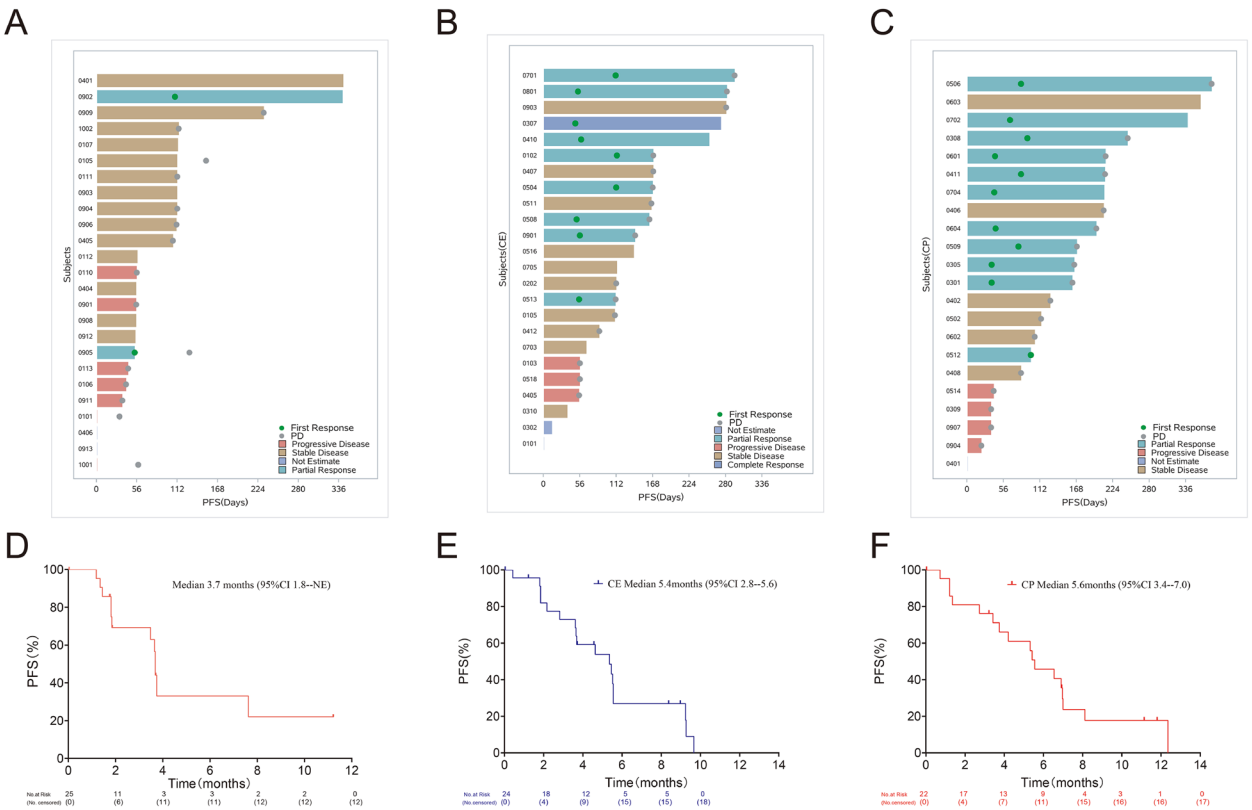

Fig. 1 Swimmer plot for response and Kaplan–Meier graph for PFS in patients. Chiauranib monotherapy group (**A**), 25 patients are shown, and 2 of 25 patients withdrew before the first tumor evaluation. Among the 23 patients evaluated, the ORR was 8.7% (95% CI, 1.1–2.80). Chiauranib with etoposide group (**B**), 24 patients are shown, 2 of 24 patients withdrew before the first tumor evaluation. Among the 22 patients evaluated, the ORR was 40.9% (95% CI, 20.7–63.7). Chiauranib with paclitaxel group (**C**), 22 patients are shown, 1 of 22 patients withdrew before the first tumor evaluation. Among the 21 patients evaluated, the ORR was 52.4% (95%CI, 29.8–74.3). Chiauranib monotherapy group (**D**), The monotherapy group recorded 12 PFS events with a median PFS of 3.7 months (95% CI 1.8-NE). Chiauranib with etoposide or paclitaxel group (**E** and **F**), The CE group saw 18 PFS events with a median PFS of 5.4 months (95% CI 2.8–5.6). The CP groups saw 17 PFS events with a median PFS of 5.6 months (95% CI 3.4–7.0)

that the dissimilarities observed may be due to the characteristics of combination chemotherapeutic drugs. Hypertension is a recognized adverse effect linked to the VEGFR pathway, and it was the most frequently reported grade 3 or 4 AEs in patients receiving chiauranib monotherapy, with three patients (12.5%) in the CE group and six patients (27.3%) in the CP group. The incidence of hypertension in both groups was higher than that in other similar studies cited above. Other target-related AEs included fatigue, proteinuria, and hand-foot syndrome, among others; these events occurred at a lower rate than that in other similar studies. The AEs caused by the combined chemotherapy regimens in this study were similar to those caused by chiauranib, etoposide, or paclitaxel monotherapy [11]. No new safety signals were recorded, and the treatment was well tolerated by most patients.

The toxicity caused by VEGFR TKIs has been reported as predictive factor for treatment efficacy [12, 13]. By conducting a post hoc exploratory analysis of toxicity and efficacy, we found that patients with hypertension had a higher objective response rate (45% vs. 23·1%) and a longer duration of overall response (4·5 months vs. 3·7 months) than patients without these conditions. We also found that patients with diarrhea had a higher ORR (42·3% vs. 20%) and longer PFS (6·5 months vs. 3·6 months) than patients without these conditions. Our results were similar to those of other studies, where the authors found that treatment-induced toxicities can be independent predictive biomarkers for the efficacy of VEGFR TKIs in other tumors [12, 13].

Although our study had a limited sample size, the efficacy within this population is currently being investigated in ongoing phase III trials. In addition to inhibiting the formation of tumor neovascularization through VEGFR, it also exhibits high selectivity in inhibiting Aurora B, uniquely affecting the tumor cell cycle progression and cellular proliferation. Meanwhile, reduction Aurora B phosphorylation is effective in reversing paclitaxel resistance in cancer cells [14]. The inhibition

of mitosis and angiogenesis is likely to contribute to the antitumor activity at well-tolerated doses in a variety of preclinical tumor models [15]. In addition, chiauranib can also inhibit the activity of CSF-1R, reducing the tumor infiltration and expansion of immunosuppressive cells. This improves the body's anti-tumor immune function. Through these actions, we believe that it can exert a comprehensive anti-tumor effect in stage III ovarian cancer patients resistant to conventional treatments in the future.

In summary, this was the first study to evaluate chiauranib, a novel multi-targeted kinase inhibitor in patients with platinum resistant ovarian cancer. The administrations of chiauranib along with etoposide or weekly-paclitaxel significantly enhance the treatment efficacy with manageable AEs. This warrants further clinical studies on this novel treatment. A phase III study evaluating the efficacy and safety of chiauranib in combination with weekly paclitaxel versus placebo with weekly paclitaxel in platinum resistant ovarian cancer (including platinum-refractory and clear cell carcinoma) is warranted. The outcomes of this ongoing phase III clinical trial (NCT04921527) and translational research are eagerly awaited.

Abbreviations

AURKB	Aurora kinase B
CSF-1R	Colony-stimulating factor 1 receptor
VEGFR	Vascular endothelial growth factor receptor
PDGFR	Platelet-derived growth factor receptor
ORR	Objective response rate
PFS	Progression-free survival
OS	Overall survival
TKI	Tyrosine kinase inhibitor
ECOG	Eastern Cooperative Oncology Group (ECOG)
TRAE	Treatment-Related Adverse Events
SAE	Serious Adverse Events
NMPA	National Medical Products Administration

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Xiaohua Wu designed and supervised the study; Jihong Liu, Rutie Yin, Dongling Zou, Hong Zheng, Junning Cao, Zhendong Chen, Wei Sun, Yunong Gao, Songling Zhang, Linjuan Zeng, Ruifang An enrolled and treated patients; Jin Li, Jihong Liu, Rutie Yin, Dongling Zou, Hong Zheng, Junning Cao, Zhendong Chen, Wei Sun, Yunong Gao, Songling Zhang, Linjuan Zeng, Ruifang An, Shuang Ye collected data. Jin Li analyzed data and wrote the first draft; Xianping Lu had reviewed this manuscript. All the authors approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics review board of Fudan University Shanghai Cancer Center and other sub-centers in accordance with the Declaration of Helsinki. Written informed consent was obtained from all individual patients included in the study. The study was conducted following good clinical practice, the Declaration of Helsinki, and relevant Chinese regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. NCCN clinical practice guidence in ovarian cancer/fallopian tube cancer/pimary peritoneal cancer (2024 Version 2.0). https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1453.
2. Friedlander M, Hancock K, Rischin D, et al. A Phase II, open-label study evaluating pazopanib in patients with recurrent ovarian cancer. Gynecol Oncol. 2010;119(1):32–7.https://doi.org/10.1016/j.ygyno.2010.05.033.
3. Matei D, Sill M, Lankes H, et al. Activity of sorafenib in recurrent ovarian cancer and primary peritoneal carcinomatosis: a gynecologic oncology group trial. J Clin Oncol. 2011;29(1):69–75. https://doi.org/10.1200/jco.2009.26.7856.
4. Cannistra S, Matulonis U, Penson R, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol. 2007;25(33):5180–6. https://doi.org/10.1200/jco.2007.12.0782.
5. Y Ma, H Cao, Lou, SiyueShao, et al. Sequential treatment with aurora B inhibitors enhances cisplatin-mediated apoptosis via c-Myc. J Mol Med (Berl). 2015;93(4):427–38. https://doi.org/10.1007/s00109-014-1228-0.
6. Zhou Y, Shan S, Li Z, et al. CS2164, a novel multi-target inhibitor against tumor angiogenesis, mitosis and chronic inflammation with anti-tumor potency. Cancer Sci. 2017;108(3):469–77. https://doi.org/10.1111/cas.13141.

7. Poveda A, Selle F, Hilpert F, et al. Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial. J Clin Oncol. 2015;33(32):3836–8.
8. Pignata S, Lorusso D, Scambia G, et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomised, open-label, phase 2 trial. Lancet Oncol. 2015;16(5):561–8.
9. Chekerov R, Hilpert F, Mahner S, et al. Sorafenib plus topotecan versus placebo plus topotecan for platinum-resistant ovarian cancer (TRIAS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2018;19(9):1247–58.
10. Lan C, Wang Y, Xiong Y, et al. Apatinib combined with oral etoposide in patients with platinum-resistant or platinum-refractory ovarian cancer (AEROC): a phase 2, single-arm, prospective study. Lancet Oncol. 2018;19(9):1239–46.
11. Gordon A, Fleagle J, Guthrie D, Parkin D, Gore M, Lacave A. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol. 2001;19(14):3312–22.
12. Rini BI, Cohen DP, Lu DR, Chen I, Motzer RJ. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst. 2011;103(9):763–73.
13. Donskov F, Michaelson M, Puzanov I, Davis MP, Rini BI. Sunitinib-associated hypertension and neutropenia as efficacy biomarkers in metastatic renal cell carcinoma patients. Br J Cancer. 2015;113:1571–80.
14. Liu M, Li Y, Zhang C, Zhang Q. Role of aurora kinase B in regulating resistance to paclitaxel in breast cancer cells. Hum Cell Mar 2022;35(2):678–93.
15. Zhou Y, Shan S, Li ZB, et al. CS2164, a novel multi-target inhibitor against tumor angiogenesis, mitosis and chronic inflammation with anti-tumor potency. Cancer Sci Mar 2017;108(3):469–77.

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