

Original Article

Efficacy and safety of crizotinib for treatment of ALK-positive NSCLC: a meta-analysis

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Abstract: *Objectives:* The aim of this meta-analysis was to systematically evaluate efficacy and safety profiles of crizotinib in patients with ALK-positive NSCLC at first-line treatment. *Methods:* A comprehensive search was conducted of Pubmed, Embase, and Cochrane library databases up to September 2017, to identify clinical trials. Primary endpoints were overall survival (OS), progression-free survival (PFS), complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and adverse events (AEs). Severe adverse events (AEs) (grade ≥ 3) based on crizotinib were analyzed. *Results:* Four studies were included in this analysis. Pooled OR for CR and PR were 2.23 (95% confidence interval [CI] = 0.56-8.93; $P = 0.26$) and 4.89 (95% CI = 3.60-6.65; $P < 0.00001$), respectively. Patients receiving crizotinib at first-line treatment showed better SD (OR = 0.36, 95% CI = 0.26-0.51, $P < 0.00001$) and PD (OR = 0.19, 95% CI = 0.12-0.32, $P < 0.00001$). The pooled OR for PFS was 0.39 (95% CI = 0.27-0.57; $P < 0.00001$), indicating that there was improvement in progression-free survival and tumor response rates. However, the OR for treatment-related adverse events of grades 3 or 4 (vision disorder, diarrhea, nausea, vomiting, and fatigue) between patients that received crizotinib and chemotherapy did not show any safety benefits ($P > 0.05$). *Conclusion:* As a first-line treatment, crizotinib was superior to chemotherapy in patients with advanced ALK-positive NSCLC. It had a comparable safety profile with chemotherapy. Future investigation is necessary to analyze whether crizotinib improves OS efficacy.

Keywords: NSCLC, ALK-positive, crizotinib, meta-analysis

Introduction

Lung cancer is the leading cause of cancer-associated deaths, with non-small-cell lung cancer (NSCLC) accounting for 85-90% of cases [1]. Traditional first-line therapeutic approaches for advanced non-small-cell lung cancer have been based on chemotherapy. Recently, the understanding of mechanisms of molecular characterization of NSCLC has increased, leading to the development of targeted therapies [2-5].

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase target recently validated in a subset of non-small cell lung cancers (NSCLC) [6]. ALK-targeted small molecule inhibitors can efficiently enhance preferential effects, including promotion of tumorigenesis, tumor proliferation, and metastasis.

Crizotinib is a small-molecule, oral, and multi-targeted tyrosine kinase inhibitor that targets ALK, mesenchymal-epithelial transition (MET), and ROS1 [7, 8]. Previous clinical trials demonstrated that crizotinib treatment was associated with promising efficacy and well-tolerated toxicity with advanced ALK-positive NSCLC [5, 9, 10]. Based on these studies, crizotinib was approved by the US Food and Drug Administration (FDA) in 2011 for patients with ALK-positive advanced or metastatic NSCLC.

While the efficacy of crizotinib for treatment of NSCLC has been consistently reported, there remains a considerable amount of controversy regarding the comparison of crizotinib and standard chemotherapy as first-line treatment, especially differences in the toxicity profiles. The purpose of this study was to conduct a meta-analysis on clinical trials in which crizo-

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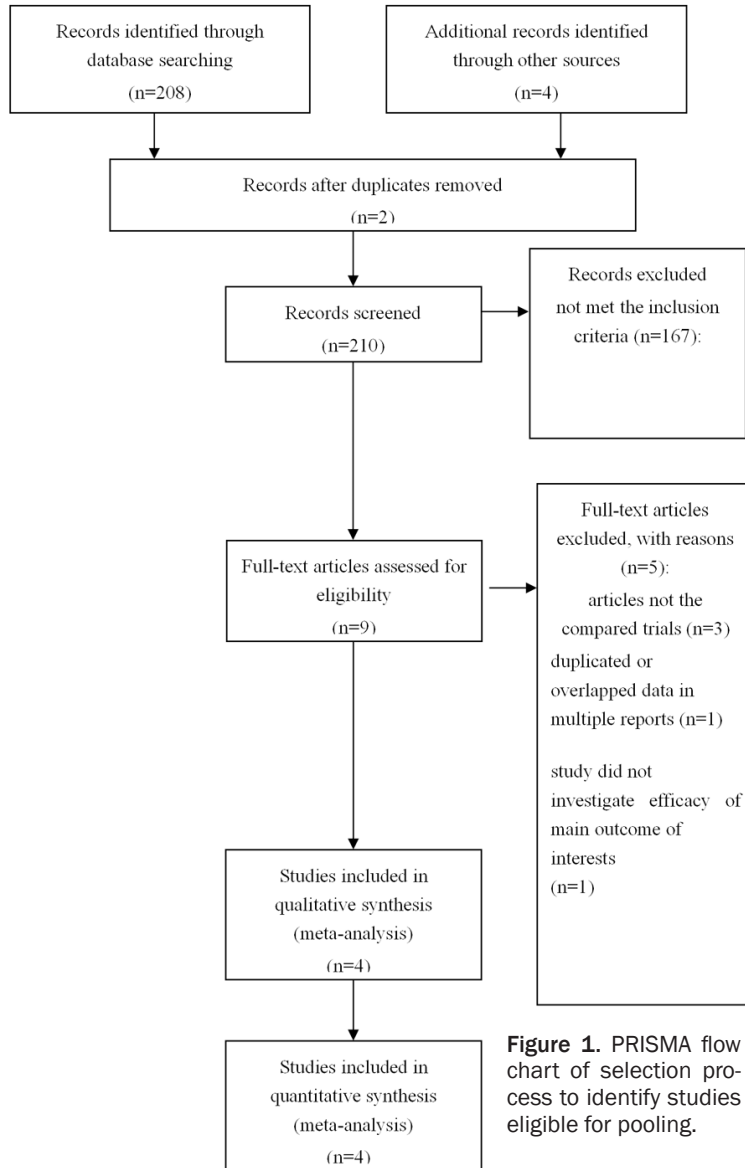


Figure 1. PRISMA flow chart of selection process to identify studies eligible for pooling.

searched to identify additional relevant publications.

Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: (1) Studies designed as trials comparing crizotinib with standard chemotherapy as first-line treatment; (2) Articles that enrolled NSCLC patients with locally advanced or metastatic anaplastic lymphoma kinase-positive; and (3) Outcomes of interest were efficacy (survival, tumor response) and toxicity (incidence of severe adverse effects (SAEs) and HRs with corresponding 95% CIs were provided. If duplicated or overlapped data were found in multiple reports, the one with the most complete information was included.

Quality assessment

Two investigators separately rated the quality of retrieved studies. Risk of bias items (ROBI) recommended by The Cochrane Handbook for Systematic Reviews of Interventions was chosen.

Data extraction

Two authors, independently, extracted relevant data from each trial. Disagreements were resolved by consensus. The main categories were as follows: first author family name, year of publication, study type, total number of cases, treatment regimen, and endpoint of interests. Corresponding hazard ratios (HRs) and risk ratios (RRs) were extracted to describe the strength of the association for survival (overall (OS) and progression-free survival (PFS)) and dichotomous (response rate (ORR, CR, PR, SD, PD) and adverse effect rate (vision disorder, piarrhea, nausea, vomiting, fatigue)) data, respectively, with corresponding 95% confidence intervals (CIs).

tinib was used to treat advanced ALK-positive non-small-cell lung cancer (NSCLC).

Methods and materials

Search strategy

Two investigators, independently, searched electronic databases Pubmed, Embase, and Cochrane library up to September 2017. This process was established to find all articles with the keywords: “non-small cell lung cancer” AND “ALK-positive” AND “crizotinib”. Relevant Medical Subject Heading (MeSH) terms were also utilized. Reference lists of all articles that dealt with the topic of interest were also manually

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Table 1. Primary characteristics of eligible studies in more detail

Study	Study type	Ceritinib (N)	Chemotherapy (N)	Treatment regimen
Benjamin J. Solomon 2015	RCT (PROFILE 1014)	172	171	Crizotinib at a dose of 250 mg twice daily or to receive intravenous chemotherapy (pemetrexed, 500 mg per square meter of body-surface area, plus either cisplatin, 75 mg per square meter, or carboplatin, target area under the curve of 5 to 6 mg per milliliter per minute) every 3 weeks for up to six cycles.
Quan Zhang 2016	Retrospective study	7	12	Oral crizotinib at a dose of 250 mg twice daily; 12 patients were administered standard chemotherapy (pemetrexed, paclitaxel, vinorelbine or gemcitabine plus either cisplatin or carboplatin) every three weeks for up to six cycles.
Shaohua Cui 2016	Retrospective study	30	50	Crizotinib, the dosage administered was 250 mg orally twice daily in 28-day cycles. standard chemotherapy, either pemetrexed (500 mg/m ² of body surface area), doc- etaxel (75 mg/m ²), or gemcitabine (1250 mg/m ² on days 1 and 8) plus either cisplatin (75 mg/m ²) or carboplatin (target area under the curve of 5-6 mg/mL per min) were administered intravenously in 21-day cycles.
Alice T Shaw 2013	RCT	173	171	Crizotinib (250 mg) twice daily or intravenous chemo- therapy with either pemetrexed (500 mg per square meter of body-surface area) or docetaxel (75 mg per square meter) every 3 weeks.

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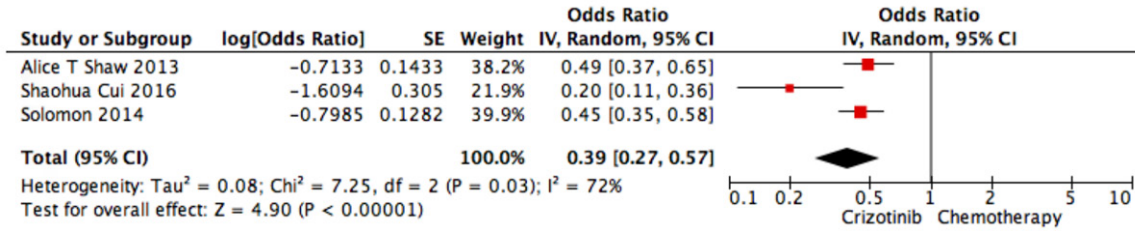


Figure 2. Pooled analysis of PFS comparing the addition of crizotinib with chemotherapy.

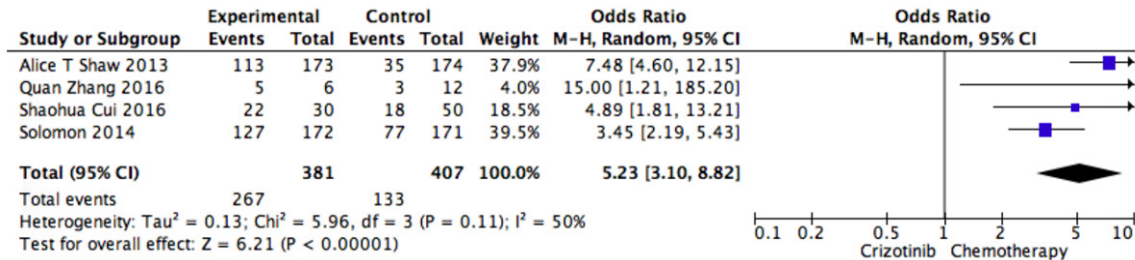


Figure 3. Pooled analysis of ORR comparing the addition of crizotinib with chemotherapy.

Statistical analysis

The safety of crizotinib was based on data from trials. Endpoints of interest in pooled analysis included OS, PFS, CR, PR, SD, PD, and SAE data. Endpoint outcome was considered as a weighted average of individual estimates of the HR in every included study, using the inverse variance method. If HRs and corresponding 95% CIs were reported, lnHRs and corresponding lnLLs and lnULs were used as data points for pooling analysis.

Sensitivity analysis was also performed to examine the impact on overall results, depending on the heterogeneity across included studies. Heterogeneity across studies was examined the I² statistic [11]. Studies with an I² of 25-50%, 50-75%, or > 75% were considered to have low, moderate, or high heterogeneity, respectively [12]. When there was low heterogeneity among studies, a fixed-effects model was used. Otherwise, a random effects model was used. P-values less than 0.05 indicate statistical significance. Statistical analyses were performed using Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom). Findings of this meta-analysis are shown in forest plots. Begg's and Egger's tests were conducted to evaluate publication bias.

Results

Overview of literature search and study characteristics

A total of 210 studies were retrieved initially for evaluation. Based on criteria described previously, 9 publications were evaluated in more detail, but some did not provide enough detail of outcomes of the two approaches. Therefore, a total of four trials (13-16) addressed the addition of crizotinib to chemotherapy. The search process is described in Figure 1.

All included articles in this study were based on moderate to high quality evidence. Table 1 describes the primary characteristics of eligible studies in more detail.

Clinical and methodological heterogeneity

Pooled analysis of PFS comparing the addition of crizotinib with chemotherapy: Pooling the PFS data from three studies (13-15) showed that crizotinib did prolong PFS (OR = 0.39, 95% CI = 0.27-0.57, P < 0.00001), compared to the chemotherapy group (Figure 2).

Pooled analysis of OS comparing the addition of crizotinib with chemotherapy: Only two studies reported available data on OS. Thus, it was not possible to perform meta-analysis. In

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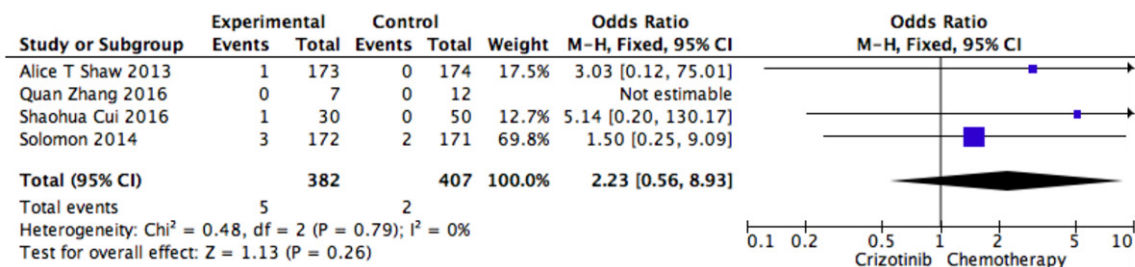


Figure 4. Pooled analysis of CR comparing the addition of crizotinib with chemotherapy.

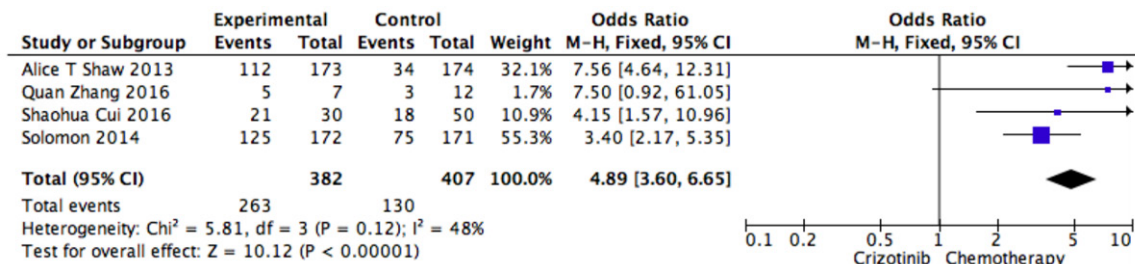


Figure 5. Pooled analysis of PR comparing the addition of crizotinib with chemotherapy.

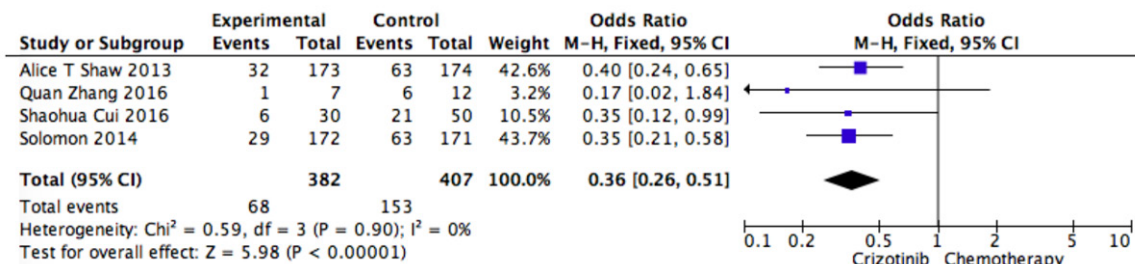


Figure 6. Pooled analysis of Sd comparing the addition of crizotinib with chemotherapy.

Solomon's study (14), median overall survival was not reached in either group (hazard ratio for death with crizotinib, 0.82; 95% CI, 0.54 to 1.26; P = 0.36). In Alice T Shaw's study (13), overall survival showed no significant improvement with crizotinib, compared with chemotherapy (hazard ratio for death in the crizotinib group, 1.02; 95% CI, 0.68 to 1.54; P = 0.54).

Pooled analysis of ORR comparing the addition of crizotinib with chemotherapy: Pooling ORR data (13-16) achieved an advantage in crizotinib agents (OR = 5.23, 95% CI = 3.10-8.82, P < 0.00001). In other words, the addition of nivolumab agents did increase the rate of ORR (Figure 3).

Pooled analysis of CR and PR comparing the addition of crizotinib with chemotherapy: The

four studies reporting data on CR and PR are shown in Figures 4 and 5. Pooled data showed that the addition of crizotinib with chemotherapy had significantly higher rates than the chemotherapy group, with pooled OR of 2.23 (95% CI 0.56-8.93, P = 0.26) and 4.89 (95% CI 3.60-6.65, P < 0.00001), respectively.

Pooled analysis of SD and PD comparing the addition of crizotinib with chemotherapy: SD and PD data are available for all four studies (Figures 6, 7). Aggregated results suggested that there were SD (OR = 0.36, 95% CI = 0.26-0.51, P < 0.00001) and PD (OR = 0.19, 95% CI = 0.12-0.32, P < 0.00001) benefits from the addition of crizotinib.

Pooled analysis of AEs comparing the addition of crizotinib with chemotherapy: Systematic

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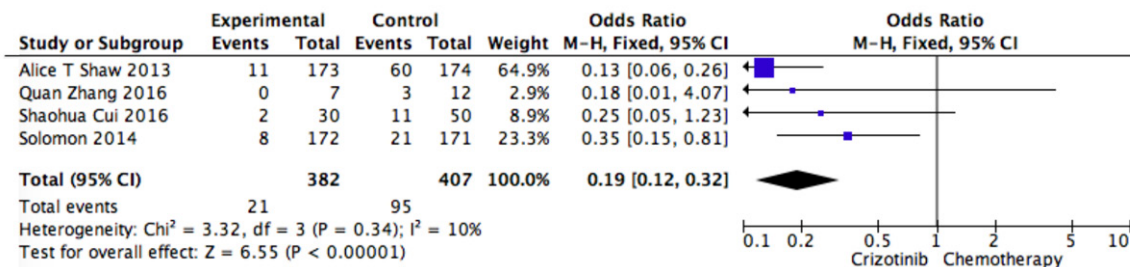


Figure 7. Pooled analysis of PD comparing the addition of crizotinib with chemotherapy.

Table 2. Pooled analysis of AEs comparing the addition of crizotinib with chemotherapy

	Crizotinib (N)	CT (N)	Vision disorder		Diarrhea		Nausea		Vomiting		Fatigue	
			Crizotinib	CT	Crizotinib	CT	Crizotinib	CT	Crizotinib	CT	Crizotinib	CT
Solomon 2014	171	169	1	0	4	1	2	3	3	5	5	4
Quan Zhang 2016	7	12	0	0	0	0	0	0	0	0	0	0
Alice T Shaw 2013	172	171	0	0	0	1	2	1	2	0	4	7
			P = 0.50		p = 0.46		p = 0.99		p = 0.99		p = 0.64	

evaluations of AEs data analysis are shown in Table 2. The most common treatment-related adverse events were vision disorders (OR = 2.98, 95% CI = 0.12-73.73, P = 0.50), piarrhea (OR = 1.79, 95% CI = 0.38-8.46, P = 0.46), nausea (OR = 0.99, 95% CI = 0.25-3.99, P = 0.99), vomiting (OR = 0.99, 95% CI = 0.30-3.26, P = 0.99), and fatigue (OR = 0.81, 95% CI = 0.33-1.97, P = 0.64). Differences between the two groups showed no statistical significance.

Discussion

Crizotinib is an oral small-molecule tyrosine kinase inhibitor targeting ALK, MET, and ROS1 tyrosine kinases [7, 8, 17]. Treatment with crizotinib has been associated with significantly higher response rates and prolonged progression-free survival, compared to chemotherapy [13-15].

In two single-group studies, crizotinib showed benefits in patients with advanced ALK-positive non-small-cell lung cancer, with an approximately 60% response rate with crizotinib and a median progression-free survival of 8.1 months in one of the studies and 9.7 months in the other [5, 18]. In contrast, standard single-agent chemotherapies in non-small-cell lung cancer patients have been associated with response rates of 10% or lower and median progression-free survival of 2 to 3 months [19, 20].

In the present analysis, the superiority of crizotinib therapy versus chemotherapy for treatment of ALK-positive NSCLC patients was revealed with PR, ORR, SD, PD and PFS, consistent with previous studies [13, 14]. The presence of an ALK rearrangement fulfills all the criteria for an oncogenic addiction, notably with a high response rate and durable tumor response with crizotinib. Based on the different results of PROFILE trials, the best strategy is to use crizotinib in a first-line setting, with probably a higher efficiency compared to subsequent lines.

However, overall survival did not differ significantly between crizotinib and standard chemotherapy groups [13, 14]. This finding is most likely attributable to the confounding effects of crossover treatment [21]. Crossover treatment has been associated with complicating the outcomes of overall survival in other randomized, phase 3 studies of EGFR kinase inhibitors in patients with advanced EGFR- mutant non-small-cell lung cancer [22-24]. Regarding these treatments, the addition of crossover treatment may contribute to survival. Moreover, previous studies have reported that pemetrexed-based chemotherapy was more efficient than other regimens in ALK-positive NSCLC [13], suggesting that patients with ALK-positive NSCLC achieved survival benefits, attributed to pemetrexed-based chemotherapy with NSCLC

[13, 25, 26]. A potential limitation of this study was that there was not enough data to perform subgroup analysis.

The present study found that, as a first-line treatment, crizotinib has a comparable safety profile with chemotherapy. Some factors may have contributed to this finding. First, the duration of study treatment with crizotinib was significantly longer than with chemotherapy and safety analysis was not adjusted to consider differences in treatment durations. Second, significantly more patients in the crizotinib group continued treatment beyond RECIST-defined progression of disease and the grade 3 or 4 elevations of patients in the crizotinib group and could be managed with dose interruptions or dose reductions. Third, immune response might be another source of differences. The pathogenesis and mechanisms of crizotinib-induced adverse events remain controversial. Dose reduction of crizotinib and subsequent administration of other ALK-TKIs might be a feasible method. In clinic, toxicity profiles are usually deciding factors for clinicians when selecting an effective regimen for ALK-positive NSCLC. Hence, it is important and necessary to choose a treatment with well-tolerated toxicological properties for patients, reducing the bad influence on patient quality of life (QoL), especially for palliating severe treatment related symptoms.

Regarding this systematic analysis, there were some limitations that should be noted. First, studies included both RCT and retrospective studies, which resulted in an imbalance between the two groups. Further random clinical trials are warranted to answer these questions. Second, as this study was a study-level meta-analysis, due to the lack of patient-level data, clinical heterogeneity among trials should be taken into consideration when interpreting the findings. Third, as the data of overall survival in included trials was limited, analysis of overall survival was not performed.

Conclusion

In conclusion, compared with chemotherapy, crizotinib treatment is superior with respect to progression-free survival, objective response rates, and improvement in quality of life in patients with ALK-positive NSCLC. The apparent lack of a survival benefit probably reflects

the confounding effects of crossover treatment, effects that have been observed in other randomized trials of molecularly targeted agents in patients with non-small-cell lung cancer. Additionally, the best treatment response with the lowest possible toxicity should be obtained in selecting patients with consideration for their complications and treatment regimen.

Disclosure of conflict of interest

None.

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