INPLASY PROTOCOL

To cite: Cheng et al. Efficacy and safety of surufatinib: a system evaluation and meta-analysis. Inplasy protocol 202260026. doi: 10.37766/inplasy2022.6.0026

Received: 07 June 2022

Published: 07 June 2022

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Support: **National Natural Science Found.**

Review Stage at time of this submission: **Completed but not published.**

Conflicts of interest:
None declared.

Efficacy and safety of surufatinib: a system evaluation and meta-analysis

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Review question / Objective: **Population: Adult patients with solid tumors were eligible; Intervention: Surufatinib of 50mg/ 100mg/200mg/300mg/400mgqd ; 28-day cycle; Surufatinib of 300mg qd ; 28-day cycle; Comparison: Placebo; Outcome: The disease control rate (DCR), The objective response rate(ORR), The stable disease (SD), The progressive disease (PD), The partial response (PR), Safety outcomes. Study design: Randomized controlled trial, RCT.**
Study designs to be included: **Studies describing surufatinib in advanced solid malignancies, and studies reporting tumor response outcome measures and/or toxicity.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 June 2022 and was last updated on 07 June 2022 (registration number INPLASY202260026).

INTRODUCTION

Review question / Objective: **Population: Adult patients with solid tumors were eligible; Intervention: Surufatinib of 50mg/ 100mg/200mg/300mg/400mgqd ; 28-day cycle; Surufatinib of 300mg qd ; 28-day cycle; Comparison: Placebo; Outcome: The disease control rate (DCR), The objective response rate(ORR), The stable disease (SD), The progressive disease (PD), The partial response (PR), Safety outcomes.**

Study design: Randomized controlled trial, RCT.

Condition being studied: In recent decades, the incidence of various advanced solid malignancies (including neuroendocrine tumors; NETs) has gradually increased, while patients with advanced or recurrent metastatic disease have limited treatment options, thereby resulting in poor prognosis. The use of molecularly-targeted drugs is the most important treatment option for unresectable tumors; these drugs have been developing continuously in recent years, and several of these drugs (such as everolimus, sunitinib, and capecitabine) have received extensive attention. The vascular endothelial growth factor (VEGF) is a key mediator of tumor angiogenesis, and it is also an important therapeutic target on which the recent targeted molecular drug research focuses. Surufatinib (HMPL012; previously known as sulfatinib) is a potent, small-molecule tyrosine kinase inhibitor (TKI) that is selectively targeting VEGF receptors (VEGFR)-1, -2, and -3, the fibroblast growth factor receptor-1 (FGFR-1), and the colony-stimulating factor-1 receptor (CSF-1R). Previous studies have shown that surufatinib not only has a significant effect on pancreatic NETs, but also has a high objective response rate (ORR) for other solid tumors, such as the pancreatic NETs, cholangiocarcinoma, and thyroid cancer. However, the confirmation of the efficacy and safety of the drug requires high-quality evidence or verification by the results of randomized controlled trials. Therefore, we conducted a meta-analysis in order to evaluate the safety and efficacy of surufatinib in the treatment of various advanced solid tumors. The purpose of this study was to investigate whether surufatinib has a practical effect on various solid tumors (including NETs), and whether it is safe to use surufatinib in the treatment process, so as to explore a new way of tumor treatment.

METHODS

Participant or population: A total of 638 patients were available for the meta-analysis. Of these, 246 patients had pancreatic NETs (accounting for 42.6% of these patients), 253 had extrapancreatic NETs, 56 had biliary tract cancer, and 65 had other solid tumors (32 patients with differentiated thyroid cancer, 27 with medullary thyroid cancer, 3 with endometrial cancer and 3 with ovarian cancer). Moreover, 18 patients suffered from an unspecified solid tumor type.

Intervention: There were 510 patients assigned to treatment arms, and 35 patients that participated in a dose escalation study. These patients were equally divided into five groups, and were given surufatinib at doses of 50, 100, 200, 300, and 400 mg, once a day, for 28 days. An additional 475 patients received surufatinib at a dose of 300 mg, once daily, in 28-day cycles.

Comparator: There were 128 patients were assigned to the placebo or control arms.

Study designs to be included: Studies describing surufatinib in advanced solid malignancies, and studies reporting tumor response outcome measures and/or toxicity.

Eligibility criteria: Case reports, editorials, reviews, meta-analyses, review articles, as well as animal and experimental studies, and non-English articles.

Information sources: PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov.

Main outcome(s): All studies assessed the tumor response by using the Response Evaluation Criteria in Solid Tumors. The DCR was reported in four studies and ranged from 81% to 91%. The meta-analysis of the DCR revealed that surufatinib has a favorable DCR in patients with advanced solid tumors (ES = 0.86, 95% CI: 0.82–0.90; I2 = 34%; P = 0.208) in a random effect analysis . A pooled results of five studies suggested a beneficial ORR outcome (ES = 0.16, 95% CI: 0.12?0.21; I2 = 48%; P = 0.103) in a random effect analysis. Seven studies reported PR results regarding the surufatinib treatment for

advanced solid tumors. The pooled results suggested that the surufatinib treatment significantly improved the PR (ES = 0.15, 95% CI: 0.07–0.25; I2 = 94%; P = 0.000. Four studies reported data on SD: overall, a significant improvement in SD was observed for solid tumors (ES = 0.71, 95% CI: 0.66–0.75; I2 = 58.7%; P = 0.064). Five studies reported a PD outcome, and the results of the pooled analysis revealed that a treatment with surufatinib improved the PD (ES = 0.09; 95% CI: 0.05–0.15; I2 = 68%; P = 0.014). disease control rate (DCR); objective response rate (ORR); stable disease (SD); progressive disease (PD); partial response (PR).

Quality assessment / Risk of bias analysis: We used two quality assessment scales based on the specific content of the seven studies identified. Five of them were scored by using the Agency for Healthcare Research and Quality (AHRQ) scale, and two were scored by using the Newcastle-Ottawa Scale (NOS). The AHRQ scale is used as a quality evaluation standard for observational studies, and includes the existence of the following 11 items in each study: (i) a definition of the source of information (survey, record review), (ii) a listing of the inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or reference to previous publications, (iii) an indication of the time period used for identifying patients, (iv) an indication of whether all patients over a period of time were included in the study if not population-based, (v) an indication of whether the evaluators of the subjective components of each study were masked into other aspects of the status of the participants, (vi) a description of any assessments undertaken for quality assurance purposes (e.g., testing or retesting of primary outcome measurements), (vii) an explanation of any patient exclusions from the analysis, (viii) a description of how confounding was assessed and/or controlled, (ix) if applicable, an explanation of the way any missing data were handled in the analysis, (x) a summary of the patient response rates and of the completeness of the data collection, and (xi) a clarification of what follow-up, if any, was expected, and of the percentage of patients for which incomplete data or follow-up was obtained. Answers were provided in three forms: "yes," "no" or "unclear." On the other hand, the NOS scoring standard includes three aspects of evaluation: (i) selection, (ii) comparability, and (iii) outcome.

Strategy of data synthesis: The meta-analysis was performed by using Excel and the Stata software. Data were Freeman-Tukey double-arcsine-transformed, and we reported the treatment effect to adverse event ratios and their 95% confidence intervals (95% CIs) by using the DerSimonian-Laird random effects. In order to assess the heterogeneity of the results of the included studies, Higgins's I2 and Q-tests were used. A Q-test P-value 30% indicates significant heterogeneity. When there was little or no substantial heterogeneity between the tests, we used a fixed-effects model; otherwise, a random-effects model was used. Once a significant heterogeneity was identified, meta-regression, sensitivity analyses, and subgroup analyses were applied in order to identify the sources of that heterogeneity.

Subgroup analysis: We don't have subgroup analysis.

Sensitivity analysis: In an attempt to fully demonstrate our findings, we introduced two high-quality randomized controlled trials for analysis. These two studies refer to randomized controlled trials of surufatinib versus placebo, and have reported the relative risk (RR) of adverse events: increased ALT levels (RR = 0.84, 95% CI: 0.57–1.23; I2 = 0%; P = 0.886), increased AST levels (RR = 1.04, 95% CI: 0.54–2.02; I2 = 73.3%; P = 0.053), proteinuria (RR = 1.39, 95% CI: 1.13–1.69; I2 = 0%; P = 0.877), diarrhea (RR = 2.25, 95% CI: 1.57–3.23; I2 = 0%; P = 0.527), hypertriglyceridemia (RR = 4.2, 95% CI: 2.28–7.81; I2 = 0%; P = 0.886); hypertension (RR = 2.82, 95% CI: 2.02–3.94; I2 = 2.8%; P = 0.310), increased blood bilirubin levels (RR = 2.08, 95% CI: 1.39–3.11; I2 = 0%; P = 0.853), and increased thyroid hormone

levels (RR = 4.63, 95% CI: 2.58–8.30; I2 = 0%; P = 0.671).

Country(ies) involved: China.

Keywords: Surufatinib, Sulfatinib, Solid tumors, Efficacy, Safety, Meta-analysis.

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