International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

INPLASY202450104

doi: 10.37766/inplasy2024.5.0104

Received: 22 May 2024

Published: 22 May 2024

Effectiveness and Side Effects of Hedgehog Pathway Inhibitors for Advanced Basal Cell Carcinoma in the Patients with or without Previous Treatment: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202450104

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 May 2024 and was last updated on 22 May 2024.

INTRODUCTION

Review question / Objective Our objective is to report the efficacy or effectiveness and safety profiles of Hedgehog pathway inhibitors (vismodegib and sonidegib) in patients with advanced basal cell carcinoma with or without previous treatment.

Rationale Basal cell carcinoma (BCC) is the most common subtype of skin cancer, with main treatment modalities consisting of excision, radiotherapy, and systemic treatments. This included hedgehog pathway inhibitors (HHI), vismodegib and sonidegib, being approved by the Food and Drug Administration (FDA) in the past 10 years. Despite some current evidence showing the efficacy of HHI in advanced BCC, the efficacy and adverse events from this, when combined with other treatment modalities, are still lacking. The objective of this meta-analysis is to report the efficacy or effectiveness and safety profiles of Hedgehog pathway inhibitors (vismodegib and sonidegib) in patients with advanced basal cell carcinoma with or without previous treatment.

Condition being studied Advanced basal cell carcinoma, hedgehog pathway inhibitors.

METHODS

Search strategy Seven investigators will independently search articles from four databases, PubMed, EMBASE, Scopus, and Cochrane databases from inception to March 2024, using the keyword “basal cell carcinoma”, “vismodegib”, and “sonidegib”. We will conduct in patients with locally advanced basal cell carcinoma, or metastatic basal cell carcinoma.

Participant or population Patients with locally advanced basal cell carcinoma or metastatic basal cell carcinoma.

Intervention Vismodegib or sonidegib.

Comparator Vismodegib or sonidegib combined with other previous treatment, no treatment, placebo, or other treatments including surgery or radiotherapy.

Study designs to be included This systematic review includes randomized controlled trials and cohort studies that represent efficacy/effectiveness, which consists of an objective response rate, complete response rate, or duration of response to treatment and safety from vismodegib or sonidegib treatment.

Eligibility criteria The inclusion criteria are as follows: (i) the patients with advanced basal cell carcinoma, comprising locally advanced, or metastatic forms will be included. (ii) the patients received the medication treatment (hedgehog pathway inhibitors, including vismodegib or sonidegib) or combined with previous surgery and/or radiotherapy. (iii) the mean or median follow-up time is 7 to 17 months. (iv) the types of study are the prospective, retrospective cohorts, or randomized controlled trial.

Information sources PubMed, EMBASE, SCOPUS, and the Cochrane database.

Main outcome(s) – Objective response rate (ORR), defined by the percentage of patients who achieved complete response (CR) and partial response (PR).
Measures of effect
– ORR was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) or modified RECIST (mRECIST).

Additional outcome(s) – Efficacy/effectiveness outcomes:
Complete response rate (CRR), defined by the percentage of patients who achieved CR.
Progression-free survival (PFS), defined by the time from randomization or treatment initiation until the progression of the disease or death, whichever comes first.
Time to tumor response (TTR).
Duration of response to treatment (DOR), defined by the time from randomization or treatment initiation until the progression of the disease or death in patients who had CR or PR.
– Safety profiles: any grade ≥3 adverse events from the treatment.

Data management Seven investigators will independently search articles from inception to March 2024. We will independently screen the potentially eligible studies through Covidence. Any of the conflicts will be discussed by the senior investigators (PP) until receiving a final consensus.
Data extraction includes the last name of the first author, year of study, country of study, study type, number of patients in each treatment arm, treatment regimen, tumor staging, location, age, sex, and comorbidities. Data extraction was independently done by eight investigators. The conflicts will be resolved by the senior investigators (PP). In case of missing information, the corresponding author of the study will be contacted by the investigators via e-mail.

Quality assessment / Risk of bias analysis Three investigators (SU., WD., PS.) will independently do the quality assessment. For randomized controlled trial, the Cochrane risk-of-bias tool for randomized trials (RoB 2) will be used. For cohort studies, the Newcastle-Ottawa Scale (NOS) will be used.

Strategy of data synthesis The numerical data including the number of patients, outcomes, adverse effects, and death will be analyzed using IBM SPSS statistics version 26 (Armonk, NY). Discrete variables will be represented as raw number and percentage. Continuous variables will be represented as median and range.
For ORR, CRR, TTR, and DOR, “meta” package version 7.0.0 will be utilized for combining the effect estimates using generalized-inverse variance method.

Subgroup analysis Not performed.

Sensitivity analysis Not performed.

Language restriction English.

Country(ies) involved Thailand.

Other relevant information None.

Keywords Systematic review; vismodegib; sonidegib; basal cell carcinoma; treatment; Meta-analysis.

Contributions of each author
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