Incidence of cutaneous adverse events with PI3K-Akt-mTOR pathway inhibitors:

A Systematic Review and Network Meta-analysis

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Background

Phosphoinositide 3-kinase/Akt mammalian target of rapamycin (PI3K-Akt-mTOR) pathway is an intracellular signaling pathway that plays a pivotal role in the cell cycle control. It is an important target in malignancies that include PI3K inhibitors that contain three classes (Pan-class I, Isoform-selective and Dual PI3K/mTOR inhibitors), Akt inhibitors and mTOR inhibitors. Immune-mediated side effects are common with inhibitors of this pathway, but incidence of cutaneous adverse events is lacking.

Objective

To investigate the incidence of cutaneous adverse events with PI3K-Akt-mTOR pathway inhibitors from randomized clinical trials.

Methods

We performed a systematic review of the PubMed, Cochrane Central Register, Embase and clinical trial registries on September 9, 2021 on phase 2 or 3 randomized control trials (RCTs) studying PI3K/Akt/mTOR inhibitors. Data were extracted based on the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines. Network meta-analysis in frequentist framework using Mantel-Haenszel method (for sparse event data) was performed with R package "netmeta."

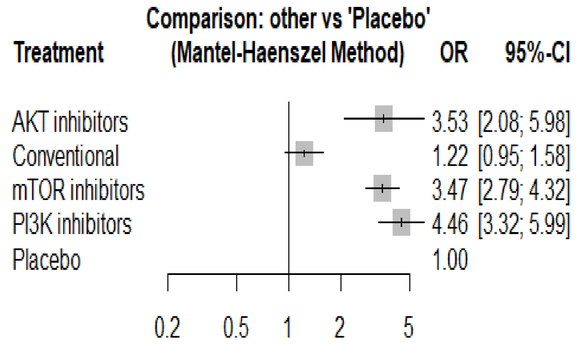

Figure 1. Pairwise comparisons presenting likelihood of development of cutaneous adverse events with PI3K-Akt-mTOR pathway inhibitors

Results

A total of 134 publications were initially identified and 58 registered trials. There were a total of 43 relevant RCTs examining 7 PI3K inhibitors, 4 Akt inhibitors, 3 mTOR inhibitors, conventional and placebo, with a cumulative sample size of 13,029 participants. Test of inconsistency yielded statistical non-significance (Q= 11.12, df= 6, p =0.08). Compared with placebo and conventional treatments, PI3K inhibitors, mTOR inhibitors and AKT inhibitors were more likely to develop rashes among the intervention group (Figure 1). Largest effect sizes were seen for PI3K inhibitors (OR = 4.46, 95% CI: 3.32 to 5.99), followed by AKT inhibitors (OR = 3.53, 95% CI: 2.08 to 5.98) and mTOR inhibitors (OR = 3.47, 95% CI= 2.79 to 4.32).

Conclusion

This study provides incidence of cutaneous adverse events with PI3K inhibitors, Akt inhibitors and mTOR inhibitors. Further studies to explore the predictive value of cutaneous adverse events on response to therapy and survival outcomes are warranted.

References