Glycomics and Lipidopics

Extended Abstract

The impact of Renin-angiotensin system blockers on lung cancers prognosis: A prisma-compliant systematic review and meta-analysis.

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Abstract:

The impact of antihypertensive medications angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on the clinical outcomes of lung cancer patients remains controversial. This meta-analysis was conducted to investigate the association between ACEIs/ARBs usage and survival of lung cancer patients. Eligible studies were identified by searching Pubmed, Embase and Cochrane library up to February, 2017. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for the effect of ACEIs/ARBs on survival of lung cancer. Heterogeneity and sensitivity were also analyzed. We finally included 9 eligible studies (8 articles) with the total number of 29,156 patients in this meta-analysis. Our results showed that ACEIs/ARBs usage was associated with favorable overall survival (OS) (HR, 0.86; 95% CI, 0.76–0.98) in lung cancer patients. Moreover, the significant association was found in subgroup of advanced clinical stage (IIIb to IV) (HR, 0.77; 95% CI, 0.64-0.92) and non-small cell lung carcinoma (NSCLC) (HR, 0.78; 95% CI, 0.65–0.93). However, no significant association was revealed between ACEIs/ARBs usage and progression-free survival (PFS) (HR, 0.84; 95% CI, 0.70–1.02). ACEIs/ARBs statistically significantly prolong OS of lung cancer patients, especially in advanced clinical stage or patients with NSCLC. However, it has no demonstrable impact on PFS. Lung cancer is the leading cause of cancer death among men and the second leading cause of cancer death (after breast cancer) among women worldwide, responsible for an estimated 1.6 million deaths a year. Despite of the advances in diagnosis and treatment in recent years, the prognosis of lung cancer patients is still unsatisfactory. In order to further palliate symptoms and prolong survival time, significant efforts have been taken to seek potentially effective agents. Recently, increasing attention has been paid to renin-angiotensin system blockers (RASBs) as potential factors influencing lung cancer progression and mortality.The renin-angiotensin system (RAS) has been found associated with tumor growth and its key signaling molecule is angiotensin II (Ang II). The tumor-promoting effect of Ang II seems to be mediated by a G-protein coupled receptor known as angiotensin type 1 receptor (AT1R), the expression of which has been reported to be increased in cancer tissues. Indeed, a positive correlation has been found between the expression level of AT1R in tumor tissues and the clinical stage of the cancer. Namely, higher level has been detected in advanced stage. Although the concrete mechanism behind the tumor-promoting process of Ang II remains unclear, several relevant aspects have been discussed: (1) Ang II binds with AT1R and then the G-protein pathway is activated, followed by enhanced expression of cell growth-related factors, such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF1) and basic fibroblast growth factor (bFGF). These factors can promote tumor proliferation and angiogenesis. (2) The interaction of Ang II and AT1R leads to some receptors transactivation, such as epidermal growth factor receptor (EGFR). The increased expression and activity of these receptors has already been demonstrated to be associated with angiogenesis and metastasis of tumor cells. (3) The inflammation and oxidative stress are also regulated by Ang II binding with AT1R, releasing a series of pro-inflammatory mediators like TNF-α, ROS and various prostaglandins. Furthermore, the inflammatory cytokines are connected to cancer cachexia. Collectively, Ang II and AT1R play crucial roles in tumor initiation and development by stimulating proliferation, angiogenesis and inflammation. The effects of Ang II can be inhibited by renin-angiotensin system blockers (RASBs), including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). ACEIs prevent the generation of angiotensin II by inhibiting angiotensin-converting enzymes (ACEs) while ARBs selectively block angiotensin II binding to the AT1R. In addition, as a kind of metalloproteinase inhibitors, ACEIs might prevent the progression of cancer directly since metalloproteinase is related to tumor metastasis. Therefore, ACEIs/ARBs hold great promise for antitumor activity. Preclinical studies have suggested that RASBs might decrease tumor growth, inhibit tumor-associated angiogenesis and improve cancer survival, but clinical data have been mixed Results from observational studies in lung cancer patients are controversial and the potentiality of ACEIs/ ARBs in cancer treatment is still not fully understood. In order to shed light on possible roles of ACEIs/ARBs in antitumor treatment, we conducted the meta-analysis to determine the impact of ACEIs/ARBs on progression-free survival (PFS) and overall survival (OS) in lung cancer patients. Systematic literature search and

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quantitative analysis were conducted and reported according to a predefined protocol following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines. A systematic literature search for eligible studies was conducted in Pubmed, Embase, and Cochrane library from inception to February, 2017. The following keywords and medical subject headings (MeSH) terms were used: anti-hypertensive, renin-angiotensin system blockers, RASBs, angiotensin-converting enzyme inhibitors, ACEIs, angiotensin receptor blockers, ARBs, angiotensin II type 1 receptor blockers, angiotensin receptor antagonists AND pulmonary neoplasm, lung neoplasm, lung cancer, pulmonary cancer, cancer of the lung, AND observational study, cohort study, case-control study, clinical trial. Reviews, case reports and editorials were considered unqualified. We also searched the reference lists of all relevant articles to identify any further potentially eligible articles. Two reviewers independently screened the articles by title and abstract based on pre-specified eligibility criteria. Studies were included if they met the following inclusion criteria: (1) the study design was cohort study or case-control study or randomized controlled trial; (2) the study assessed the usage of ACEIS/ARBs in the study population; (3) the study used clinically relevant outcomes such as PFS, OS, tumor recurrence or metastasis. Discrepancies between the two reviewers' lists of articles for inclusion were resolved with discussion. When two or more studies had overlapping study samples, only the most recent or the most complete study was involved in the analysis. Two authors conducted the data extraction independently with disagreements resolved by consensus or an experienced third author. Data extracted included the name of the first author, publication year, country, age, histology type, cancer stage, population according to the ACEIs and ARBs type, follow-up period, outcomes, hazard ratios (HRs) with corresponding 95% confidential intervals (95% CIs) and covariates adjusted. If multiple HRs were reported, we chose the one with the most comprehensive adjustment for our meta-analysis. If only Kaplan-Meier curves were available, data were calculated from survival curves and estimation of the HR was then performed by the method reported by Tierney et al.Quality assessment for studies included in this meta-analysis was evaluated by using the Newcastle Ottawa Scale (NOS) criteria. The higher score out of a total of nine points indicated the higher quality, and the studies that met 5 or more of the NOS criteria were considered of adequate quality for the meta-analysis. In this meta-analysis, we calculated pooled HRs with their corresponding 95% CIs to assess the prognostic significance of ACEIs/ARBs use in lung cancer patients, and the HR greater than 1 implied an inferior prognosis for patients with ACEIs/ ARBs use. We used a random effects model approach for our meta-analyses to account for both within and between study heterogeneity. Statistical heterogeneity of effect estimates was carried out using Cochran's Q test and Higgins I-squared statistic, and the I2 values ≥ 50% indicated significant heterogeneity. For additional analyses, subgroup meta-analysis was performed according to the histology (NSCLC or pan-lung cancer), medication type (ACEIs or ARBs) and the tumor stage (I-IIIa or IIIb-IV) respectively. Sensitivity analysis was performed by sequential omission of individual studies to examine the stability of the outcomes in this meta-analysis. Publication bias was evaluated by Egger's test and Begg's funnel plot. We performed all analyses using STATA software (version 12.0, Stata Corp, College Station, Texas, USA). A two-tailed P value less than 0.05 was considered significant in statistical tests.

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