Critical Reviews in Oncology / Hematology 125 (2018) 41–47

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Metformin for non-small cell lung cancer patients: Opportunities and pitfalls

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ARTICLE INFO

Keywords:
Biguanide
Targeted therapy
Radiotherapy
Irradiation
Thoracic oncology

ABSTRACT

Despite exciting advances of the anticancer armamentarium in the recent years, mortality of non-small cell lung cancer (NSCLC) remains high and novel treatments are requisite. Therapy intensification is explored with promising, but expensive and potentially toxic new compounds. Repositioning already existing drugs for cancer treatment could save money and improve patient outcomes in specific contexts. Observational data suggest that use of the standard antidiabetic agent metformin decreases lung cancer incidence and mortality. Several basic researches have shown various anticancer effects of metformin, acting both on the glycolytic metabolism and on the tumoral immune microenvironment. Synergistic actions of metformin with antitumoral agents in preclinical NSCLC models have then been highlighted. Recent retrospective studies advocated improved outcomes in NSCLC diabetic patients receiving metformin with chemoradiotherapy or systemic compounds (including conventional platinum-based chemotherapy and EGFR tyrosine kinase inhibitors). Several prospective randomized trials are therefore currently assessing the addition of metformin to standard therapy in non-diabetic lung cancer patients. This article reviews promises and possible limitations of concurrent metformin used as an anticancer agent in NSCLC patients.

1. Introduction

Lung cancer is the most frequent cancer worldwide and remains the leading cause of cancer death (1.6 estimated million deaths/1.8 million estimated new cases per year) (Brambilla and Travis, 2014). Non-small cell lung cancer (NSCLC) represents approximately 80–85% of all lung cancers, and close to 70% of patients present with stage III or IV disease. Standard treatment for patients with a good performance status and unresectable stage III NSCLC is platinum-based doublet chemotherapy with concomitant radiotherapy (RT) administered with curative intent. Overall survival (OS) and progression free survival (PFS) of patients with stage III NSCLC remain however poor (50–60% and 30%, respectively at 2 years) after platinum-based chemoradiotherapy (RTCT) (Bradley et al., 2015), and without major improvement during the last decade. At the opposite of metastatic patients, targeted therapies (including antiangioneic, mTOR inhibitor, and anti-EGFR [epidermal growth factor receptor]) have led to substantial toxicities without better outcomes (Bradley et al., 2015; Socinski et al., 2012; Deutsch et al., 2015; Ready et al., 2010; Levy et al., 2017a) in unselected locally advanced patients. In metastatic patients, personalized, genotype-directed therapy (main oncogenic drivers mutations in adenocarcinomas include *EGFR*, *HER2*, *KRAS*, anaplastic lymphoma kinase [*ALK*], *BRAF*, *PIK3CA*, and *ROS1* genes), and recent immunotherapies (mainly programmed cell death protein-1 or -ligand 1 [PD-1 or PD-L1] inhibitors) have revolutionized the management of NSCLC. Median OS has then reached 2 years in the subset of adenocarcinomas patients with molecular alteration (Herbst et al., 2016; Reck et al., 2016; Solomon et al., 2014; Rosell et al., 2012). Therapy intensification still continues to be explored in an attempt to prolong a favourable clinical state with promising, but expensive and potentially toxic (Michot et al., 2016; Antonia et al., 2017), new immunotherapies/targeted compounds.

Meanwhile, repositioning non-cancer standard therapies offer the possibility of saving money, time and potentially improving outcomes. Metformin is an oral antidiabetic drug considered as the first choice for oral treatment of type 2 diabetes. This hypoglycaemic compound of the biguanides class improves insulin action by increasing insulin-mediated glucose utilization in peripheral tissues. Improvements in glycaemic control get along with a reduction in serum insulin concentrations (Inzucchi et al., 2015). Surprisingly, observational data suggest that use

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https://doi.org/10.1016/j.critrevonc.2018.03.001
Received 6 November 2017; Received in revised form 17 January 2018; Accepted 1 March 2018
1040-8428/

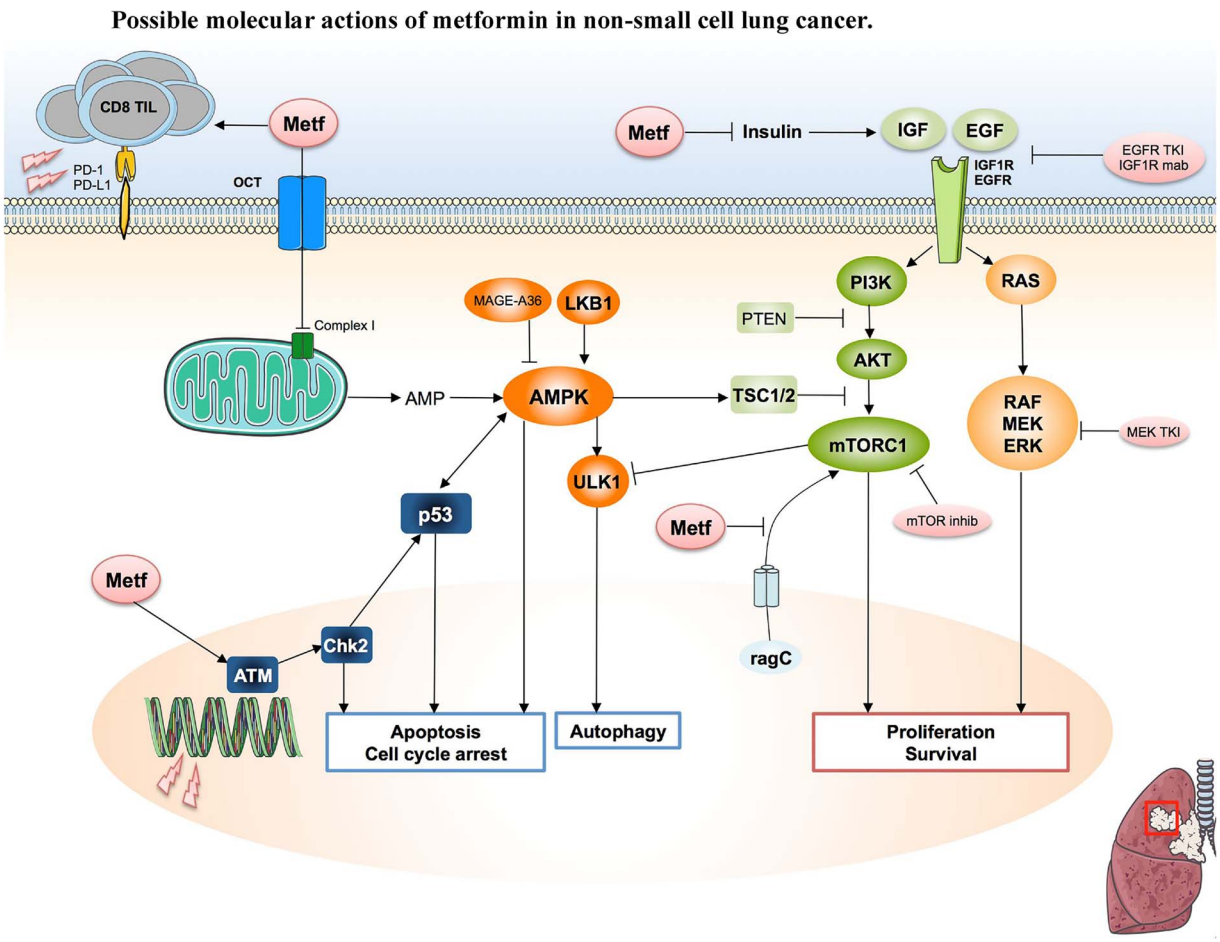

Fig. 1. Possible molecular actions of metformin in non-small cell lung cancer.
Metformin activates the AMP-activated protein kinase (AMPK) and repress the insulin-like growth factor-1 receptor (IGF-1R) pathway. This lead to phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and MAPK/ERK (both pro-oncogenic) pathways inhibition. Activated-AMPK trigger p53 and ULK1, then inducing several anticancer actions (apoptosis, cell cycle arrest, and autophagy). Metformin could also inhibit mTORC1 by the inhibition of the tuberous sclerosis 1 and 2 (TSC2) or nuclear pore complex restriction of the transport of the RagC GTPase. In cancer cell, AMPK may be deregulated through p53 or Lkb1 mutation/deletion (*e.g.* by the MAGE-A3/6-TRIM28 E3 ligase complex). At high doses metformin disrupts aerobic glycolysis through inhibition of the mitochondrial complexe I. Lastly, metformin could increase the number of CD8+ tumour-infiltrating lymphocytes (TILs) or activate the ATM (ataxia telangiectasia mutated)-checkpoint kinase 2 (Chk2) pathway, which can arrest the cell cycle, allowing DNA repair. This can explain how ionizing radiation or targeted therapies (Anti-EGFR/IGF-1R or mTOR inhibitors) can synergize with anticancer actions of metformin.

of metformin decreases lung cancer incidence (Tian et al., 2016). It has subsequently been advocated that metformin could exert anticancer actions and also enhances tumour response to ionizing radiation (IR) and/or systemic agents in several experimental models (Koritzinsky, 2015). Retrospective analyses in NSCLC patients have shown that diabetic patients receiving concurrent metformin and RT, and/or cisplatin-based chemotherapy, or EGFR-tyrosine kinase inhibitors (TKI) had improved outcomes, suggesting that this drug should be tested in non-diabetic patients (Wink et al., 2016; Chen et al., 2015; Tan et al., 2011). While prospective studies goes on, this paper re-examines the basic rationale and the current clinical evidence for combining metformin as an anticancer agent in NSCLC patients.

2. Methods

A literature search using Embase (Scopus) and Medline was performed with date restriction up to September 2017 using the following "lung cancer", "non-small cell lung cancer", "metformin", "biguanides" and "concurrent".

There were 255 articles first identified. When abstracts and letters were excluded, 208 articles were available for further analysis. We excluded articles dealing with sequential treatments, and other cancer types. Finally, 45 relevant articles were included for the main analysis.

2.1. Observational data on metformin in NSCLC patients

2.1.1. Overviews and cohort studies

Large cohort studies have shown that metformin may reduce both cancer incidence and mortality (Libby et al., 2009; Landman et al., 2010). Similar results have been suggested in lung cancer patients (mainly database-based studies and a limited number of cohort studies). In a meta-analysis based on the literature including 566,435 diabetic patients, metformin therapy was associated with significantly lower risks of cancers of the lung (pooled relative risk = 0.71; p = 0.02 (Zhang et al., 2014)). The chemo-preventive effect of metformin was moreover dose-dependent in a nationwide population-based study which analysed 47,356 diabetic patients (n = 19,074 metformin users). Authors indicated there, a > 50% risk reduction of lung cancer incidence in the patients who used metformin with a cumulative dose of > 730 cumulative defined daily dose (DDD) or an intensity of > 10 DDD/month (Tsai et al., 2014).

Lung cancer survival outcomes in diabetic patients receiving metformin have also been addressed. In a study using data from the SEER (Surveillance, Epidemiology, and End Results), 750 patients with diabetes (61% on metformin) and stage IV NSCLC were included. The survival was higher in metformin treated patients after controlling on sociodemographics, cancer characteristics, and treatment (Lin et al.,